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Title: Phase 1 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Revlimid (VIPOR) for Diffuse Large B-cell lymphoma involving the Central Nervous System

NCI Principal Investigator: Rahul Lakhotia, M.B.B.S.
Lymphoid Malignancies Branch (LYMB)
Center for Cancer Research (CCR)
National Cancer Institute (NCI)
Building 10, Room 4N115
National Institutes of Health (NIH)
Bethesda, MD 20892
[redacted]
Email: rahul.lakhotia@nih.gov

Drug Name:	Venetoclax (Venclexta®)	Obinutuzumab (Gazyva®)	Lenalidomide (Revlimid®)	Ibrutinib (Imbruvica®)	Prednisone
IND Number:	134937				
Sponsor:	CCR				
Manufacturer:	AbbVie, Inc.	Genentech, Inc.	Celgene Corporation/ Bristol Myers Squibb	AbbVie, Inc.	Generic
Supplier:	CC Pharmacy				

PRÉCIS

Background:

- Primary diffuse large B-cell lymphoma of the CNS (PCNSL) and aggressive B-cell lymphomas with secondary CNS involvement (SCNSL) have a poor prognosis
- Most CNS lymphomas (CNSL) exhibit molecular biology features of activated B cell diffuse large B-cell lymphoma (ABC DLBCL)
- We developed VIPOR (venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide [Revlimid®]) treatment in systemic lymphomas as a platform most effective for ABC DLBCL
- All agents in the VIPOR combination achieve meaningful CNS penetration and clinical activity for lymphomas involving the CNS

Objective:

- To determine the safety and tolerability of VIPOR in participants with PCNSL and SCNSL

Eligibility:

- Primary diffuse large B-cell lymphoma of the CNS (PCNSL) or non-germinal center B-cell (non-GCB) diffuse large B-cell lymphoma with secondary involvement of the CNS (SCNSL)
- Relapsed/refractory after prior therapy or ineligible for standard frontline therapy
- Age ≥ 18 years
- No pregnant individuals
- Adequate organ function

Study Design:

- A safety study of 10 evaluable participants with PCNSL or SCNSL treated with VIPOR (the original study protocol enrolled 4 participants to Cohort 1, Arm 1 consisting of VIPOR plus nivolumab which is now closed).
- Participants will receive VIPOR in 21-day cycles for a maximum of 6 cycles to collect data on safety and efficacy.
- Accrual ceiling will be set at 16 participants to allow for a few inevaluable participants or screen failures.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine the safety and tolerability of VIPOR in primary DLBCL of the CNS (PCNSL) and secondary CNS lymphoma (SCNSL)

1.1.2 Secondary Objectives

- To determine the overall response rate (CR + PR) of up to 6 cycles of VIPOR in CNSL
- To determine the complete response (CR) rate of up to 6 cycles of VIPOR in CNSL
- To determine the duration of response (DOR) after VIPOR in CNSL
- To estimate the 10-year progression-free survival (PFS) after VIPOR in CNSL
- To assess 10-year overall survival (OS) after VIPOR in CNSL

1.1.3 Exploratory Objectives

- To perform comprehensive molecular profiling of CNSL tumors and explore correlations with clinical response
- To genotype circulating-tumor DNA (ctDNA) from plasma and cerebrospinal fluid (CSF) and correlate to tissue genotyping
- To assess the pharmacokinetics (PK) of venetoclax and ibrutinib in the plasma and CSF
- To study cytokine changes across VIPOR therapy

1.2 BACKGROUND AND RATIONALE

1.2.1 Primary CNS Lymphoma

Primary diffuse large B-cell lymphoma of the CNS is a rare disease representing less than 3% of all non-Hodgkin lymphoma. It refers to lymphomas that arise exclusively within the brain parenchyma, spinal cord, eyes, cranial nerves, and meninges without systemic involvement.[1] Epidemiological studies show an increased incidence of PCNSL over recent years particularly in those with advanced ages.[2] PCNSL occurs in both human immunodeficiency virus (HIV) negative and positive participants, but HIV-associated PCNSL is virtually always associated with Epstein Barr Virus (EBV) and is biologically distinct from EBV-negative PCNSL.

1.2.2 Treatment of Primary Diffuse Large B-cell Lymphoma (DLBCL) of the CNS

Compared to participants with systemic DLBCL, the outcome for subjects with PCNSL is worse. Treatment of PCNSL differs significantly from systemic DLBCL because many chemotherapy agents do not adequately penetrate the blood-brain barrier. Historically, whole brain radiation (WBRT) has been a mainstay of treatment because it is effective, and side stepped the limitations of chemotherapy in penetrating the CNS. However, when used alone, responses are typically short-lived and virtually all subjects relapse.[3] The development of the chemotherapy-based treatments relied heavily on strategies used for solid brain tumors and was not optimized for the treatment of DLBCL. High dose methotrexate (HD-MTX), an agent with good CNS penetration, has been the centerpiece of PCNSL treatment for years; however, when used alone it produces a progression-

free survival of only 7 months.[4] When HD-MTX was followed by whole brain radiotherapy, it produced a high complete remission rate, but no evidence of cure.[4-6] Further, combined modality treatment that includes WBRT is associated with severe long-term neurotoxicity.[4-7] For this reason, there has been much interest in developing regimens that obviate the need for radiation. Most promising in this regard are combinations of high dose methotrexate with systemic agents that cross the blood brain barrier, such as cytarabine and ifosfamide, particularly in subjects under 60 years of age.[8] The Bonn group and others have adopted such an approach and have reported promising results with chemotherapy and deferred radiation in younger subjects.[8, 9] In their trial, 9% died of treatment related toxicity. Overall, the median time to treatment failure was 21 months with a median follow-up of 26 months; for those over 60 years of age, the time to treatment failure (TTF) was 15 months and for those under 60 years old, 60% were free from progression at 4 years. These results show that current strategies have a poor outcome with an unacceptably high treatment related mortality, and low rates of cure. Thus, there is an important need to develop more effective and less toxic strategies based on the molecular biology of PCNSL.[10, 11] We have developed a novel chemotherapy regimen for subjects with relapsed and refractory PCNSL that combines ibrutinib with temozolomide, etoposide, liposomal doxorubicin, dexamethasone, and rituximab (TEDDI-R).[12] Although this regimen is highly effective for subjects with relapsed and refractory PCNSL, it can be associated with hematologic toxicities and may not be tolerated by all subjects. Further, some subjects relapse after TEDDI-R, and effective salvage therapies are needed.

1.2.3 Molecular Biology of Primary Diffuse Large B-cell Lymphoma of the CNS

PCNSL has a high load of somatic mutations. Approximately, 30-40% have mutations of BCL6. In addition, aberrant hypermutation in the following proto-oncogenes and tumor suppressor genes are found: PIM1 (50%), c-MYC (60%), TTF (70%), PAX5 (60%), and Fas (CD95) (20%).[13] Interestingly, PCNSL almost never leaves the CNS and though many theories have been hypothesized, the reason for this neuro-tropism is not well understood. Theories that may explain this phenomenon include the following: 1) the brain is an immune sanctuary and the malignant B-cells are eliminated in the periphery by a specific antitumor immune response; 2) the malignant B-cells are dependent on a chemokine that is present in high concentrations within the brain such as BCA-1 – B-cell attracting chemokine encoded by CXCL13; 3) the malignant B-cells are dependent on specific adhesion signals; 4) the malignant B-cells are dependent on an antigen that is only found in the CNS.

Accessing tissue to better understand the biology of PCNSL has been very challenging due to the rarity of the disease and the technical challenges of obtaining tissue from the CNS. In addition, interpretation and analysis of CNS tissue have been impeded by the architecture of the CNS – characteristically there is variable cell density, neovascularization, and many infiltrating immune cells. However, four molecular profiling studies have been performed and they all revealed different messages about the biology of PCNSL. In the first of these, Rubenstein et al. looked at 23 cases of PCNSL and contrasted PCNSL with systemic DLBCL.[14] They showed that the oncogenes PIM1 and MYC were highly expressed in PCNSL relative to systemic DLBCL and there was also evidence of high expression of IL4 genes. They also demonstrated high expression of STAT 6 – which is important in interleukin-4 (IL4) signaling - and high levels of this were associated with poor survival, albeit in a small series. In the second of these studies, Tun et al., evaluated 13 cases of PCNSL.[15] They described a characteristic signature that was composed of

extracellular matrix and adhesion-related genes. A third study, by Montesinos-Rongen et al. looked at 21 cases and demonstrated a signature of a late germinal center B-cell and finally Booman et al looked at 9 cases and described a signature that was enriched in genes that were involved in apoptosis and the immune response.[16]

Most PCNSLs that arise in immunocompetent hosts originate from an activated B-cell (ABC) based on molecular biology analyses. In a limited series, PCNSL was shown to have deregulation of the NF-kappa B pathway, which is a defining molecular feature of ABC DLBCL.[17] Other studies have found coiled mutations of the signaling cascade protein – CARD11 – in 16% of PCNSL, activating L265 mutations of MYD88 in 36% of PCNSL, and mutations of CD79B (L. Staudt personal communication), all mutations that are almost exclusively found in ABC DLBCL.[17, 18]

1.2.4 Secondary CNS lymphoma

Secondary involvement of the CNS is an infrequent but often fatal complication of diffuse large B-cell lymphomas (DLBCL) and other aggressive B-cell lymphomas[19]. The term secondary CNS lymphoma (SCNSL) needs to be distinguished from PCNSL. SCNSL involves the brain, eyes, or CSF but either has concurrent systemic involvement of non-Hodgkin lymphoma (NHL) or has relapsed in the CNS after treatment for systemic NHL (isolated CNS relapse). Involvement of the CNS at the time of diagnosis for DLBCL occurs in ~5% of subjects and usually presents as leptomeningeal disease with involvement of the CSF[20]. Risk factors for the development of SCNSL after therapy have been identified and include a high International Prognostic Index (IPI), age > 60 years, elevated serum lactate dehydrogenase (LDH), advanced disease stage, ECOG performance status > 1, extensive extranodal involvement, and involvement of specific extranodal sites (kidney, testes and possibly uterus or breast).[21] A specific clinical predictor algorithm known as the CNS-IPI has been developed and validated based on these risk factors to identify subjects at greater risk of SCNSL after therapy for DLBCL. In a landmark retrospective study, subjects with all 6 of the risk factors (N=13) included in the CNS-IPI had a 32.5% risk of developing SCNSL, while those without any risk factor (N=235) had a 0.0% risk. The CNS-IPI tool is used in routine practice to identify subjects with newly diagnosed DLBCL who should be treated with CNS prophylaxis to prevent late recurrences in the CNS. Furthermore, the occult leptomeningeal disease can be detected by flow cytometry and identifies subjects with low volume involvement who should receive active treatment. However, CNS prophylaxis and/or active initial treatment of CNS disease does not eliminate the risk of developing SCNSL at a later time, as either a component of the systemic relapse or an isolated CNS relapse.

Compared to subjects with systemic DLBCL, the outcome for subjects with SCNSL is worse. The treatment of SCNSL differs significantly from systemic DLBCL because many chemotherapy agents do not adequately penetrate the blood-brain barrier and have been modeled on studies from PCNSL. In a large, international study of 291 subjects with SCNSL, the majority of subjects (87%) developed SCNSL as part of their first relapse, and 39% had a concurrent systemic relapse.[20] These subjects often developed debilitating symptoms and the post-relapse survival was only 3.9 months for the entire cohort. On multivariable analysis of the subjects who were deemed eligible for second-line therapy with curative intent (59% of cohort), subjects aged < 60, with an ECOG PS 0-1, and without parenchymal involvement had a 2-year OS of 62% (95% confidence interval (CI) 36-80). Overall, however, there are few effective treatments for most subjects and SCNSL, and this complication represents a major unmet clinical need. Prospective phase II and III studies

have established the role of high-dose antimetabolites and consolidative therapy, including WBRT or with autologous stem cell transplantation (ASCT), in subjects with PCNSL, but similar data in SCNSL is lacking with only a few small phase II studies suggesting a role for autologous transplantation.[22, 23] Indeed, this strategy is limited in population-based settings due to limited generalizability to most subjects, failure of salvage treatment, toxicity and unsuccessful stem cell harvest.

The molecular biology that confers CNS tropism for aggressive B-cell lymphomas is largely understudied, but recent studies have suggested that certain subsets of DLBCL have a greater risk of CNS spread, and that these tumors may be reliant on chronic active B-cell receptor signaling. Subjects with DLBCL who express both MYC and BCL2 by immunohistochemistry (i.e. 'dual expressors') have a greater risk of CNS relapse than a patient without (9.4% vs. 2.4% p=0.001)[24]. Although "dual expressor" DLBCL is not a specific biologic entity recognized by the World Health Organization (WHO) Classification of Lymphoid Malignancies, these subjects most commonly are ABC DLBCL. Subjects with ABC DLBCL are most commonly associated with chronic active BCR signaling and the likeliest to respond to inhibitors of Bruton tyrosine kinase (BTK) such as ibrutinib and acalabrutinib.[25, 26] Additional evidence of the underlying biology of SCNSL tumors comes from a recent paper from the Staudt lab who studied 574 DLBCL biopsies and comprehensively analyzed them using exome and transcriptome sequencing, DNA copy-number analyses and targeted amplicon resequencing. In this study, they identified four prominent genetic subtypes of DLBCL based on the underlying genetic aberrations.[27] One genetic subtype was termed MCD based on this striking co-occurrence of both *MYD88*^{L265P} mutations and *CD79B* mutations. Importantly, these mutations frequently co-occur in PCNSL, and the MCD subtype was associated with extensive extranodal involvement and had additional acquired mutations that are recurrently mutated in primary extranodal lymphomas. These observations suggest a biologic link between nodal MCD and extranodal lymphomas, including PCNSL. A recent study of SCNSL tumors confirmed that most cases of DLBCL that secondarily involve the CNS are of the MCD genetic subtype.[28]

1.2.5 Scientific Rationale and Clinical Activity of VIPOR in systemic ABC DLBCL

Insights into the molecular pathogenesis of lymphoid tumors have identified abnormalities in key survival pathways. Regulation of apoptosis by BCL-2 family proteins is a central regulator of normal B and T cells and lymphoid tumors have acquired multiple mechanisms of deregulation including translocation, amplification, and elevated gene expression from loss of endogenous MiRs that repress BCL-2 expression and gene hypomethylation. More recently, pathogenic B-cell receptor signaling has been identified in B-cell lymphomas and targeting BTK has shown clinical activity across B-cell lymphomas. In particular, mutations affecting the BCR receptor and downstream signaling molecules have been identified in ABC DLBCL where they lead to enhanced NFκB activation. Lenalidomide inhibits NFκB through its effect on IRF4. Furthermore, lenalidomide affects expression of multiple other proteins through its effect on cereblon E3 ubiquitin ligase and has immune-modulatory properties.

In the development of venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide (Revlimid), we hypothesized that inhibiting multiple pathogenic survival pathways would leverage the efficacy of targeted agents in systemic lymphomas. To help address this hypothesis, we first assessed if combinations of these agents were synergistic in vitro and in murine tumor models and showed synergy between BTK and BCL-2 inhibitors and lenalidomide. Further, in vitro studies

indicated that venetoclax inhibits the development of ibrutinib resistance in ABC DLBCL (unpublished data from the Staudt lab).

A major limiting factor for targeted therapy in lymphomas is the need for continuous dosing, which precludes the ability to give multiple agents. Hence, we developed VIPOR (NCT03223610) in relapsed/refractory B-cell lymphomas with a fixed-duration schedule [29]. The regimen was found to be safe with no unexpected toxicities and no maximum tolerated dose identified. The main toxicities are hematologic with grade 3/4 neutropenia, thrombocytopenia, and anemia occurring in 50%, 38%, and 15% of subjects and 27%, 16%, and 3% of cycles, respectively. Importantly, this study excluded subjects with CNS involvement.

1.2.6 Scientific Rationale for VIPOR in CNS lymphomas

The CNS penetrance and pharmacokinetics of the individual components of VIPOR have been evaluated in several clinical trials. A phase 1 study (NCT01542918) of lenalidomide with or without intraventricular rituximab for relapsed/refractory CNSL included time-matched plasma-CSF sample pairs to determine CSF penetrance. Among 14 subjects treated with doses of 10, 15, or 20 mg of lenalidomide, the 16-hour (trough) plasma concentration was 0-220 ng/mL, and the intraventricular CSF concentration was 0-16.68 ng/mL, with a mean CSF trough concentration of 4.9 ng/mL. The CSF/plasma ratio, calculated on time-matched pairs where the CSF lenalidomide concentration was >0, was 0-49%. Further, this group found that there is a dose-dependent increase in CSF concentration with lenalidomide, with higher CSF/plasma partition coefficients at the 15 or 20 mg lenalidomide dose.[30]

For ibrutinib CNS penetrance, in a phase 1b trial (NCT02315326) by Grommes et al., 15 subjects with recurrent/refractory CNS lymphoma including PCNSL and SCNSL were given ibrutinib at doses from 560-840 mg orally daily and had CSF samples drawn at 2 hours post the cycle 2, day 28 dose. Mean CSF ibrutinib concentration was 3.105 ng/mL (equivalent to 7.05 nM; range, 0.305-9.22). In subjects receiving 560 mg of ibrutinib, the mean CSF concentration was 1.553 ng/mL (range 0.991-2.62). The mean CSF levels in subjects receiving 840 mg of ibrutinib was 3.992 ng/mL (range 0.305-9.22).[31] In our TEDDI-R study (NCT03964090) for PCNSL, subjects were treated at ibrutinib dose levels of 560 mg (6), 700 mg (4), and 840 mg (8). In these 18 subjects, the time to max concentration in the CSF was approximately 2 hours and the $T_{1/2}$ was 18.1 (4.1-31.2) hours. In the 560 mg, 700 mg, and 840 mg ibrutinib cohorts, the median max CNS concentration was 1.4, 1.98, and 1.33 nM, respectively, and the median corrected area under the curve (AUC) AUC_{csf}/AUC_{plasma} was 43.4%, 35.1%, and 28.7%, respectively. These cohorts showed that there was not a proportional dose dependent increase in max CSF concentration or the areas under the curve at the 700 mg or 840 mg ibrutinib doses.[12] In relapsed/refractory CNSL, 2-hour-post mean CSF concentrations of ibrutinib monotherapy at doses of 560 to 840 mg daily was 0.77ng/ml (1.7nM) and 1.95ng/ml (4.4nM), respectively, and higher when checked at 2-hour-post at day 28 of therapy, 1.65ng/ml and 3.18ng/ml, respectively.[32]

In a case report of a patient with CLL with CNS involvement treated with venetoclax, time-matched plasma and CSF concentrations of venetoclax were obtained. The max and minimum concentrations at 2 hours and 23 hours post venetoclax were 1.2 and 0.52 µg/mL in plasma, respectively, and 2.8 and 1.5 ng/mL in CSF, respectively. The plasma to CSF concentration ratio was 0.1%.[33] In unpublished data collected at the NCI on two subjects treated with off-label use of VIPOR for relapsed/refractory PCNSL using 800 mg venetoclax daily, the mean 2-hour post

dose CSF concentration was 2.35 ng/mL (2 samples) and the 24-hour post-dose CSF mean was 1.83 ng/mL (3 samples).

Given that most CNSL share biologic features with ABC DLBCL and that VIPOR demonstrates the most clinical activity in ABC DLBCL, a formal study including the VIPOR platform for CNSL is highly rational.

1.2.7 Clinical experience with VIPOR in refractory PCNSL

At the time of this writing, we have had 5 subjects with PCNSL who relapsed after treatment with TEDDI-R that we have treated off-label with the VIPOR regimen due to their limited treatment options, and all 4 achieved at least a partial response.

The first patient was a 48-year-old man with primary refractory PCNSL who was treated on our TEDDI-R study (14-C-0157, NCT03964090). After 6 cycles, he was in complete remission, but he relapsed only 3 months later. Given that these subjects have a dismal prognosis, we offered him off-label use of VIPOR as a potential bridge to CAR-19. After only 1 cycle of VIPOR, he had an 80% decrease in his brain lesion. He was given a second cycle of VIPOR and successfully transitioned to CAR T-cell therapy on clinical trial at Massachusetts General Hospital. Interestingly, he achieved a complete response to CAR-19 that lasted 13 months before another clinical relapse. We then re-challenged him with VIPOR and after 1 cycle, he is again in complete remission. He continues on VIPOR with a plan to bridge to transplant.

The second patient was a 34-year-old woman with primary PCNSL who progressed on a high-dose methotrexate regimen and was referred for our clinical trial of TEDDI-R. The study was on administrative hold at the time of referral, so we treated her with off-label TEDDI-R. She was one of the few subjects who only achieved a partial response to TEDDI-R. She was also offered off-label use of VIPOR and achieved a partial response after 2 cycles. She was also successfully transitioned to CAR T-cell therapy on clinical trial at Massachusetts General Hospital and remains in remission 13 months after infusion.

The third patient was a 67-year-old man with relapsed PCNSL who was treated on our TEDDI-R study (14-C-0157) and achieved a complete response. He relapsed a few months after remission and was treated with off-label VIPOR for 2 cycles. He achieved a partial response to VIPOR and was a 3rd patient who was successfully transitioned to CAR T-cell therapy on clinical trial at Massachusetts General Hospital after the use of VIPOR. Unfortunately, this patient did not respond to CAR-19 and died of disease progression.

A fourth patient was a 67-year-old woman with primary refractory PCNSL who was treated on our TEDDI-R study (14-C-0157) and achieved a complete response. She relapsed a few months after remission and was treated with off-label VIPOR for 2 cycles and achieved a partial response. She was offered a referral to the CAR-19 clinical trial but did not want to be referred. She currently continues therapy with VIPOR with a plan for 6 cycles.

A fifth patient was a 78-year-old man with primary refractory PCNSL who was also treated on our TEDDI-R study (14-C-0157) but did not achieve a clinical response. This patient was treated with 1 cycle of VIPOR off-label but did not achieve a response. He did not have any adverse effects of the VIPOR treatment.

1.2.8 Safety Summary of VIPOR-based therapy in B-cell lymphoma

This study will utilize a novel combination of targeted agents and two important safety aspects will apply as part of the primary objective. First, the safety of VIPOR in patients with lymphoma involving the CNS. The safety of the combination has been established in over 58 patients with relapsed aggressive and indolent B-cell lymphomas without CNS involvement who were treated on an ongoing study at the NCI [NCT03223610]. The preliminary results have been presented at the 2020 Annual Meeting of the American Society of Hematology [34]. In these patients, most toxicity was hematologic and 16% and 7% of cycles were associated with G3 or G4 thrombocytopenia, respectively. Further, 15% and 7% of cycles were associated with G3 or G4 neutropenia which resulted in an amendment to ensure that all patients receive growth factor support. The most common G3/G4 non-hematologic toxicities were hypokalemia (17%), increased LFTs (9%), diarrhea (7%), and atrial fibrillation (5%). Other serious but rare toxicities that occurred included intracranial hemorrhage (N=1), tumor lysis syndrome (N=1), and pneumoperitoneum (N=1). Dose reductions were required on only 7% of cycles. We hypothesize that the toxicity of VIPOR will not be different in the participants included on this study.

1.2.9 Preliminary Safety of VIPOR-Nivo in CNSL

The original study design of this protocol added the PD-1 inhibitor nivolumab to VIPOR therapy. There were 4 participants enrolled to this treatment arm before the study was stopped for safety reasons and that treatment arm was closed to accrual. The safety concern was a participant who developed grade 4 hepatotoxicity during the nivolumab/lenalidomide window alone. Also, a multicenter study of nivolumab in PCNSL demonstrated an overall response rate of only 6% and these data became available after we initiated our original study design.

Regarding the toxicity, an older male participant with relapsed/refractory PCNSL enrolled following front-line treatment with high-dose methotrexate-based combination therapy with rituximab as well as ibrutinib monotherapy. On day 5 of window therapy with nivolumab and lenalidomide alone, he presented with a low-grade fever and increased confusion. Laboratory evaluations revealed ALT and AST elevations in the 2000 range and a slightly elevated bilirubin. Study treatment was held and the participant was treated with high-dose corticosteroid therapy which rapidly improved the hepatitis. Liver biopsy revealed acute hepatitis with zone 3 necrosis most consistent with drug-induced toxicity from PD-1 inhibition. The study was suspended from further enrollment and amended to remove nivolumab from the treatment regimen.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Participants must have histologically or cytologically confirmed primary diffuse large B-cell lymphoma of the CNS (PCNSL) or non-GCB diffuse large B-cell lymphoma with secondary involvement of the CNS (SCNSL). **NOTE:** Participants with B-cell lymphomas that were previously indolent but now involve the CNS (i.e., transformed

from previous follicular lymphoma, chronic lymphocytic leukemia, marginal zone lymphoma, and mantle cell lymphoma) **are eligible**.

2.1.1.2 Participants must have a disease that is relapsed or refractory after initial systemic treatment or be considered ineligible for standard frontline therapy with high-dose methotrexate due to one of the following criteria:

- Age≥ 70 years
- Estimated glomerular filtration rate < 60 ml/min/1.73m^2
- Presence of ascites or pleural effusion

2.1.1.3 Participants must have evaluable disease by clinical exam (i.e., palpable lymphadenopathy, measurable skin lesions, etc.) and/or imaging (measurable lymph nodes or masses on CT or MRI and/or evaluable FDG-avid lesions on PET).

2.1.1.4 Participants with second malignancies not requiring active systemic therapy or pre-malignant conditions such as monoclonal B-cell lymphocytosis (MBL) or monoclonal gammopathy of undetermined significance (MGUS) are eligible.

2.1.1.5 Participants that are positive for hepatitis B core antibody (HBcAb), hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative hepatitis B and/or C viral load by polymerase chain reaction (PCR). See Section **4.1.2**.

2.1.1.6 Age ≥18 years

2.1.1.7 ECOG performance status ≤2 (see **Appendix A**). **NOTE:** In participants with neurologic deficits caused by CNS lymphoma any ECOG status is acceptable to be eligible.

2.1.1.8 Participants must have adequate organ and marrow function as defined below:

absolute neutrophil count	≥ 1000 cells/mcL (1 × 10^9/L)
platelet count	≥ 50,000 cells/mcL (50 × 10^9/L)
hemoglobin	> 8.0 g/dL (transfusions permitted)
total bilirubin	≤ 1.5 × upper limit of normal (ULN) (unless Gilbert's syndrome or disease infiltration of the liver is present)
Aspartate Aminotransferase or serum glutamic-oxaloacetic transaminase/ Alanine Aminotransferase or serum glutamic pyruvic transaminase AST(SGOT)/ALT(SGPT)	≤ 3.0 × institutional ULN for those without lymphoma involvement OR ≤ 5.0 × institutional ULN for those with lymphoma involvement
Serum Creatinine OR creatinine clearance (Cr Cl)	≤ 1.5 mg/dL OR ≥ 40 ml/min/1.73m^2
NOTE: Cr Cl will be calculated with the use of the 24-hour creatinine clearance or eGRF in the clinical lab	

Laboratory assessments to determine eligibility may be performed at CLIA (or equivalent) certified laboratories outside the NIH and results forwarded to the study team for review and management. Given that the methodologies utilized are similar across all laboratories, no significant variability is expected and there is no anticipation that study data will be affected. However, as different laboratories use slightly different kinds of equipment, each laboratory must determine/validate its own reference ranges. Therefore, on this protocol, normal ranges from each lab will be used in reference to terms such as ULN, except in cases where absolute values are appropriate and are specified as such

2.1.1.9 Prothrombin time (PT) and activated partial thromboplastin time (aPTT) must be < 1.5 x the ULN; except if, the aPTT is prolonged because of a positive Lupus Anticoagulant.

2.1.1.10 Participants must agree to use certain methods of birth control. A "highly effective method of birth control" for participants of childbearing potential is defined as a method that has a low failure rate (i.e., less than 1% per year) when used consistently and correctly and includes implants, injectables, birth control pills with two hormones, some intrauterine devices (IUDs). Participant who can father children are required to use barrier. The specific guidelines are as follows:

- Individuals of childbearing potential (IOCBP), defined as a sexually mature individual who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months), must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting Revlimid®, as well as for the duration after the last dose of study drug as listed below. For more details see **Appendix C.**
- Individuals who can father children must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures as outlined in **Appendix C** to prevent pregnancy of their partner and should also agree to not donate sperm while taking the study treatment and for the durations as listed below.

Contraception Requirements		
Time frame/Study Drug	**Individuals of childbearing potential**	**Individuals who can father children**
Pre-Treatment/During Treatment	*Time frame prior to/during dosing:*	
All drugs	Begins 28 days prior to treatment	Begins on day 1
Post-Treatment	*Time frame after the last dose:*	
Venetoclax	90 days	90 days
Ibrutinib	3 months	3 months
Obinutuzumab	18 months	6 months
Revlimid®	28 days	28 days

2.1.1.11 All study participants must be registered into the mandatory Revlimid REMS™ program and be willing and able to comply with the requirements of Revlimid REMS™.

2.1.1.12 Nursing participants must be willing to discontinue nursing from study treatment initiation through designated time points after study drugs discontinuation (as required in the table above)

2.1.2 Exclusion Criteria

2.1.2.1 Participants with plasmablastic lymphoma and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma are not eligible.

2.1.2.2 Chemotherapy (excluding corticosteroids), radiation therapy, and/or monoclonal antibody ≤ 7 days prior to first administration of study treatment. Rationale for a short 7-day window is that participants with relapsed CNS lymphomas often have existing neurologic conditions that mandate urgent therapy.

2.1.2.3 Previous treatment with more than one of the following classes of medications: (1) BTK inhibitors, (2) BCL2 inhibitors, (3) immunomodulatory imide drugs (IMIDs) (including lenalidomide and pomalidomide).

2.1.2.4 Participants who require continuous treatment with a strong CYP3A inhibitor/inducer (i.e., with the exception of any medication to be specifically studied in this protocol).

- **NOTE:** A comprehensive list of inhibitors, inducers, and substrates may be found at: https://drug-interactions.medicine.iu.edu/MainTable.aspx

2.1.2.5 HIV-positive participants

2.1.2.6 Pregnant participants- a pregnancy test (urine or serum) with a sensitivity of 25 mIU/mL must be done at screening.

2.1.2.7 Participants with second malignancies requiring active systemic therapy are excluded.

2.1.2.8 Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification

2.1.2.9 History of any ventricular arrhythmia

2.1.2.10 Unable to swallow capsules, or disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, or symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.

2.1.2.11 Uncontrolled ongoing or active infection

2.1.2.12 Concomitant use of warfarin or other vitamin K antagonists

2.1.2.13 Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.

2.1.2.14 Currently active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the NCI/Child Pugh classification (**Appendix B**))

2.1.2.15 Uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.3 Recruitment strategies

Study participants will be recruited from the population of participants screened in the lymphoid malignancies clinic of the National Institutes of Health. These will include both referrals from outside physicians as well as participant self-referrals. This protocol may be abstracted into a plain language announcement posted on NIH websites, including clinicaltrials.gov and the CCR website, and on NIH social media platforms.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the participant has signed a consent include the following:

- Email, written, in person or telephone communications with prospective participants
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the participant has signed this study consent . Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

Assessments and procedures to confirm study eligibility should be completed within 28 days prior to treatment initiation (unless otherwise noted).

2.2.2.1 Clinical Assessments

- Medical history, including diagnosis, treatment (e.g., systemic treatments, radiation, and surgeries), status, and significant prior/ongoing side effects and symptoms

- Physical examination, including weight, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); and, assessment of performance status using the ECOG scale
- Review of concomitant medications

2.2.2.2 Laboratory Evaluations

- CBC with differential
- Chemistry panels including: Acute Care Panel (Sodium (NA), Potassium (K), Chloride (CL) Total CO_2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR); Mineral Panel (Albumin, Calcium, Magnesium, Phosphorus); Hepatic Panel (Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin); and, 24-hour urine creatinine clearance (if needed to measure CrCl in cases where serum creatinine >1.5 mg/dl)
- Coagulation panel, including PT and aPTT
- HIV 1 /2 antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), and Hepatitis C antibody (HCV Ab)
    - Participants who are HBsAg negative and HBcAb positive or HBsAg positive will have viral load testing by HBV PCR.
    - Participants who are HCV Ab positive will have viral load testing by HCV PCR.
- Urine and/or serum HCG in IOCBP (within 14 days prior to initiation of study treatment)
    - A pregnancy test (urine or serum) with a sensitivity of 25 mIU/mL must be done in accordance with Celgene Revlimid REMS™ guidelines for individuals of childbearing potential (IOCBP) only.

2.2.2.3 Imaging Studies

- CT chest, abdomen, and pelvis (C/A/P) (with IV and PO contrast unless contraindicated)
- MRI brain
- ^{18F} FDG-PET brain and body (must be performed at NIH)

2.2.2.4 Other Assessments and Procedures (within 14 days prior to treatment unless otherwise stated)

- Pathologic review of archival sample for confirmation of B-cell lymphoma by Laboratory of Pathology, NCI (no time limit). If the sample is not available, and there is an accessible tumor, a biopsy will be done to confirm the diagnosis.
- Lumbar puncture/Ommaya tap for CSF studies including protein, glucose, cell count/differential, cytology, and flow cytometry for confirmation of CNS involvement
- Electrocardiogram (EKG)
- Confirmation of registration to Revlimid REMS™ program

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at:
https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a laboratory abnormalities may be rescreened. Only SAEs occurring after the administration of an investigational agent will be reported to the Sponsor. SAEs will be reported to IRB as required.

2.3.2 Treatment Assignment Procedures

2.3.2.1 Cohorts

Number	Name	Description
1	CNS lymphomas	Participants with primary diffuse large B-cell lymphoma of the CNS (PCNSL) or secondary CNS lymphoma (SCNSL)

2.3.2.2 Arms

Number	Name	Description
1	Experimental-lenalidomide + nivolumab window; followed by VIPOR-Nivo (Closed on 06/06/2022)	Nivolumab on day 1 with lenalidomide (days 1-14) for a 21-day cycle. Following Window, VIPOR-Nivo (venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide, and nivolumab) in 21-day cycles for up to 6 cycles
2	Experimental-VIPOR	VIPOR (venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide) in 21-day cycles for up to 6 cycles

***NOTE:** participants with CrCl >60 mL/min will receive lenalidomide 15mg (dose level 1) while those with CrCl >40 mL/min and <60mL/min will receive lenalidomide 10mg (dose level -1) (Table 3).

2.3.2.3 Arm Assignment

In the original study design, participants in Cohort 1 were directly assigned to Arm 1. After 4 participants were enrolled, that arm was closed to further accrual on 06/06/22. All participants will now be assigned to Arm 2.

2.4 BASELINE EVALUATION

The baseline evaluations should be performed within 14 days prior to the first dose of the study treatment unless otherwise noted; tests performed as part of screening do not need to be repeated if they were performed within the specified window prior to initiation of study therapy. See the Study Calendar (**Appendix D**) for details.

3 STUDY IMPLEMENTATION

NOTE: The original study design included nivolumab, i.e., VIPOR-Nivo, for up to 6 cycles with an initial treatment window of lenalidomide with nivolumab alone. Due to safety concerns, study enrollment was suspended after enrollment of 4 participants, and re-designed as is reflected below.

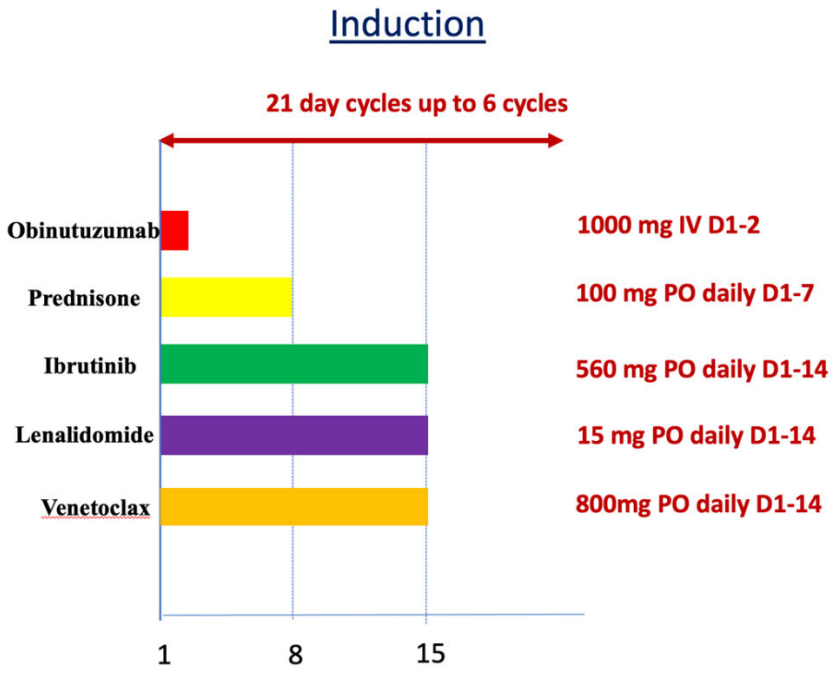
3.1 STUDY DESIGN

This is a non-randomized, open-label, single institution study evaluating the combination of VIPOR regimen in up to 16 participants with CNSL (PCNSL and SCNSL). Participants may undergo optional fresh tumor research biopsies prior to treatment and at the time of progression wherever feasible. In patients without an Ommaya catheter, this may be placed prior to the start of therapy but is not required for treatment. The study treatment will assess the safety, tolerability, and efficacy of VIPOR in CNSL which may continue for up to 6 cycles, or until one of the criteria in Section **3.8.1** applies.

Treatment should be delivered on an outpatient basis in most situations. Treatment can be delivered on an inpatient basis for other reasons clearly documented in the medical record (preplanned decision for increased monitoring, convenience, or collection of correlative samples).

Participants will be restaged regularly as explained in the Study Calendar (**Appendix D**) and followed for up to 10 years.

3.1.1 Study Schema



3.2 DRUG ADMINISTRATION

After enrollment participants will proceed to induction therapy. A maximum of 6 cycles of induction therapy will be given every 21 days with the following dosing schedule:

- Obinutuzumab 1000 mg IV rate escalated infusion[a] on days 1 and 2
- Prednisone 100 mg PO daily days 1-7 (approximately 30-60 minutes prior to obinutuzumab infusion on days 1 and 2)
- Ibrutinib 560 mg PO daily days 1-14
- Lenalidomide 15 mg PO daily days 1-14 (if CrCl > 60 mL/min) or 10 mg PO daily days 1-14 (if CrCl <60 mL/min but >40 mL/min)
- Venetoclax 800 mg PO daily on days 1-14
- Acetaminophen 650 mg PO daily on days 1 and 2 (approximately 30-60 minutes prior to Obinutuzumab infusion)
- Diphenhydramine 50 mg PO daily on days 1 and 2 (approximately 30-60 minutes prior to Obinutuzumab infusion)
- Peg-filgrastim 6 mg subcutaneous once on day 8 only

[a] Obinutuzumab infusion starting at 50 mg/hr with rate increase by 50 mg/hr every 30 minutes as tolerated to a maximum rate of 400 mg/hr. If tolerated, subsequent infusions may start at 100 mg/hr with rate increase by 100 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. Monitor participants closely for signs/symptoms of the infusion reaction and interrupt/discontinue infusion for any signs of a reaction and contact the investigator.

For more details see Section **14**

3.3 DOSE MODIFICATIONS AND DOSE DELAYS

The following sections detail dose modifications guidelines for each individual drug of the VIPOR regimen based on documented toxicity. Dose reductions for multiple study agents based on the same toxicity is not necessary and dosing should be modified only for the most likely offending agent identified.

3.3.1 Criteria for Starting a New Cycle of Study Therapy

A new course of study treatment may begin on Day 1 of a new cycle if:

- ANC ≥ 1000/μL and
- Platelet count ≥ 50,000/μL and
- CrCl > 40 ml/min
- No drug-related ≥ Grade 3 toxicity

If the criteria are not met, assessments may be repeated after 1 week. The initiation of a new cycle of study therapy should be delayed until participant meets criteria to receive study drug as planned.

A dose delay of up to 6 weeks from the planned start of an induction cycle is permitted to allow recovery of toxicities. Actions for recurrent hematologic adverse events are described in the tables for each drug in the sections below (lymphopenia is not considered a hematologic toxicity, as it is an expected outcome of therapy). If treatment is delayed for more than 6 weeks, the participant should be withdrawn from the study treatment.

If one of the study drugs is discontinued because of toxicity as addressed below, participant will continue treatment with other drugs. If two or more drugs are discontinued, participants will be taken off study treatment.

3.3.2 Dose Modifications for Venetoclax and Obinutuzumab

Sample guidelines for dose delay and modification of venetoclax when paired with obinutuzumab are shown in **Table 1** . These guidelines pertain to dose delays and modifications based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment administration.

No dose modifications of obinutuzumab are allowed. Venetoclax dose may be re-escalated (even to the full dose) at the discretion of the investigator. See **Table 2** for the dose levels for venetoclax dose reduction.

For non-hematologic toxicities, dosing of study therapy may be resumed upon resolution to Grade ≤ 1 or baseline status.

Table 1: Sample Guidelines for Dose Delay or Modification of Venetoclax when given with Obinutuzumab and Combination Targeted Therapy

Event(s)	Dose Delay or Modification
Neutropenia: • Grade 3 (ANC <1,000/μL) for ≥ 7 days, OR • Grade 4 (ANC <500/μL) for any duration	• Hold venetoclax. • Administer growth factors (e.g., G-CSF for neutropenia as indicated). -If ANC < 1000/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If ANC < 1000/μL for > 7 days, reduce the dose of venetoclax by 1 dose level. • For subsequent episodes, dose reduction 2 of venetoclax and drug discontinuation will be considered. • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the Principal investigator may elect not to reduce the dose of venetoclax .
Febrile neutropenia or neutropenia with infection	• Hold venetoclax and obinutuzumab until resolution.
Thrombocytopenia: • Grade 3 (decrease to <50,000/ μL) associated with > Grade 2 bleeding, OR • Grade 4 (decrease to <25,000/ μL) with or without bleeding	• Hold venetoclax. -If platelet count < 50,000/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If platelet count < 50,000/μL for > 7 days, reduce the dose of venetoclax by 1 dose level. • For subsequent episodes, dose reduction 2 of venetoclax and drug discontinuation will be considered.
Severe thrombocytopenia (platelets < 10,000/μL) and/or symptomatic bleeding in participants who are not receiving concomitant anticoagulants or platelet inhibitors	• Hold obinutuzumab in case of severe thrombocytopenia (platelets < 10,000/μL) or symptomatic bleeding (irrespective of platelet count) until it resolves.
Thrombocytopenia with platelets < 20,000/μL and/or symptomatic bleeding in participants who are receiving concomitant anticoagulants or platelet inhibitors[a,b]	• Hold obinutuzumab in case of platelets < 20,000/μL or symptomatic bleeding (irrespective of platelet count) until it resolves. -For participants who are receiving concomitant anticoagulant when thrombocytopenia with platelets < 20,000/μL develops, adjust the dose or hold the drug per investigator discretion.[a] -For participants who are on platelet inhibitors when thrombocytopenia with platelets < 20,000/μL develops, consider temporarily holding their use.[b]
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay.

Event(s)	Dose Delay or Modification
Any other Grade 4 toxicity or unmanageable Grade 3 toxicity attributed to venetoclax	• Hold venetoclax. -If improves to ≤ Grade 2 in ≤ 7 days, administer full dose of study treatment for the next cycle. -If improves to ≤ Grade 2 in > 7 days, reduce the dose of venetoclax by 1 dose level. • For subsequent episodes, dose reduction 2 of venetoclax and drug discontinuation will be considered.
ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor. [a] If the participant's clinical condition requires the use of concomitant anticoagulants, the participant is at increased risk of bleeding when thrombocytopenia with platelets < 20, 000/μL develops. [b] Clinical decision-making may be adjusted depending on the participant-specific assessment of benefit and risk	

.

Table 2: Venetoclax Dose Reduction

Dose Reduction	Venetoclax Dose
1	600 mg
2	400 mg

3.3.3 Dose Modifications for Ibrutinib

Sample guidelines for dose delay and modification of ibrutinib are shown in **Table 3**. At the discretion of investigator, dose-modification guidelines should be evaluated and revised, as appropriate, based on the risk associated with the regimen employed. See **Table 4** for the dose levels for ibrutinib dose reduction.

Table 3: Guidelines for Dose Delay or Modification of Ibrutinib

Event(s)	Dose Delay or Modification
Neutropenia: • Grade 3 (ANC <1,000/μL) for ≥ 7 days, OR • Grade 4 (ANC <500/μL) for any duration	• Hold ibrutinib. • Administer growth factors (e.g., G-CSF for neutropenia as indicated). -If ANC < 500/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If ANC < 500/μL for > 7 days, reduce the dose of ibrutinib by 1 dose level. • For subsequent episodes, dose reduction 2 of ibrutinib and drug discontinuation will be considered. • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the Principal investigator may elect not to reduce the dose of ibrutinib .

Event(s)	Dose Delay or Modification
Febrile neutropenia or neutropenia with infection	• Hold ibrutinib until resolution.
Thrombocytopenia: • Grade 3 (decrease to <50,000/ µL) associated with > Grade 2 bleeding, OR • Grade 4 (decrease to <25,000/ µL) with or without bleeding	• Hold ibrutinib. -If platelet count < 50,000/µL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If platelet count < 50,000/µL for > 7 days, reduce the dose of ibrutinib by 1 dose level. • For subsequent episodes, dose reduction 2 of ibrutinib and drug discontinuation will be considered.
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay.
Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy	• Hold ibrutinib. -If improves to ≤ Grade 2 in ≤ 7 days, administer full dose of study treatment for the next cycle. -If improves to ≤ Grade 2 in > 7 days, reduce the dose of ibrutinib by 1 dose level. • For subsequent episodes, dose reduction 2 of ibrutinib and drug discontinuation will be considered.
Grade 3 or 4 atrial fibrillation/flutter or persistent atrial fibrillation/flutter of any grade	• Hold ibrutinib. • Initiate medical management of atrial fibrillation/flutter. • Consider the risks and benefits of restarting ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation.
Any other Grade 4 toxicity or unmanageable Grade 3 toxicity attributed to ibrutinib	• Hold ibrutinib. -If improves to < Grade 2 in < 7 days, administer full dose of study treatment for the next cycle. -If improves to < Grade 2 in > 7 days, reduce the dose of ibrutinib by 1 dose level. • For subsequent episodes, dose reduction 2 of ibrutinib and drug discontinuation will be considered.

Table 4: Ibrutinib Dose Reduction

Dose Reduction	Ibrutinib Dose
1	420 mg
2	280 mg

Please see Section **4.2.1** for guidelines for management of ibrutinib in participants who require treatment with a strong CYP3A inhibitor.

3.3.4 Dose Modifications for Lenalidomide

Sample guidelines for dose delay and modification of lenalidomide are shown in **Table 5**.**Table 6** for the dose levels for lenalidomide dose reduction.

Table 5: Guidelines for Dose Delay or Modification of Lenalidomide

Event(s)	Dose Delay or Modification during a cycle
Neutropenia: • Grade 3 (ANC <1,000/μL) for ≥ 7 days, OR • Grade 4 (ANC <500/μL) for any duration	• Hold lenalidomide. • Administer growth factors (e.g., G-CSF for neutropenia as indicated). -If ANC < 1000/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If ANC < 1000/μL for > 7 days, reduce the dose of lenalidomide by 1 dose level. • For subsequent episodes, dose reduction 2 of lenalidomide and drug discontinuation will be considered. • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the Principal investigator may elect not to reduce the dose of lenalidomide .
Febrile neutropenia or neutropenia with infection	• Hold lenalidomide until resolution.
Thrombocytopenia: • Grade 3 (decrease to <50,000/ μL) associated with > Grade 2 bleeding, OR • Grade 4 (decrease to <25,000/ μL) with or without bleeding	• Hold lenalidomide. -If platelet count < 50,000/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If platelet count < 50,000/μL for > 7 days, reduce the dose of lenalidomide by 1 dose level. • For subsequent episodes, dose reduction 2 of lenalidomide and drug discontinuation will be considered.
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay.
Rash: • Any Grade desquamating (blistering), OR • Grade 4 non-blistering	• Discontinue lenalidomide.
Thromboembolic event ≥ Grade 3	• Hold lenalidomide. • Initiate therapeutic anticoagulation as clinically indicated, please evaluate interactions with other study drugs. • Resume lenalidomide without dose modifications at Day 1 of next cycle if benefit of therapy outweighs bleeding risk.
Hyperthyroidism or hypothyroidism ≥ Grade 2	• Hold lenalidomide. • Evaluate etiology & initiate appropriate therapy. • Reduce lenalidomide by 1 dose level at Day 1 next cycle. Start new cycle when participant meets cycle initiation criteria.

Event(s)	Dose Delay or Modification during a cycle
Creatinine Clearance <60 mL/min (CrCl, Cockcroft-Gault)	-CrCl 30–60 mL/min: 10 mg every 24 hours -CrCl <30 mL/min: hold lenalidomide • If CrCl becomes >60mL/min for a minimum of 2 cycles, may re-escalate to the prior dose at investigator's discretion.
Any other Grade 4 toxicity or unmanageable Grade 3 toxicity attributed to lenalidomide	• Hold lenalidomide. -If improves to ≤ Grade 2 in ≤ 7 days, administer full dose of study treatment for the next cycle. -If improves to ≤ Grade 2 in > 7 days, reduce the dose of lenalidomide by 1 dose level. • For subsequent episodes, dose reduction 2 of lenalidomide and drug discontinuation will be considered.

Table 6: Lenalidomide Dose Levels Reduction

Dose Levels	Lenalidomide Dose
Dose level 1	15 mg
Dose level -1	10 mg
Dose level -2	5 mg

3.4 On Study Assessments/Evaluations

The following describes all tests and procedures to be conducted on the study and during treatment. Assessments will be performed according to the Study Calendar, **Appendix D**.

3.4.1 Timing of Visits

For each time period, consider the following order of assessments:

- **Screening:** Refer to section **2.2**
- **Baseline:** Baseline assessments should be performed within 14 days of initiating study treatment unless otherwise specified on the Study Calendar. Tests performed as part of screening do not need to be repeated if they were performed within the specified window prior to initiating treatment.
- **Study Drug Administration:** See Section **3.2**. Treatment will be given for a maximum of 6 cycles of induction therapy, until unacceptable toxicity or until any other criteria is met per Section **3.8.1**. Dose delay of up to 6 weeks from the planned start of an induction cycle is permitted to allow for recovery from toxicities. A delay of more than 6 weeks will require the participant to be taken off treatment.
- **Pre-Cycle 1 (C1D1) of Induction Therapy:** Laboratory tests are required to be collected pre-dose of Day 1 of Cycle 1 (within 24 hours).

- **Pre-Subsequent Cycles (D1 C2-C6) of Induction Therapy:** After Cycle 1, pre-dose assessments may be performed up to 3 days prior to Day 1 of a cycle except where otherwise noted.

Response Assessments: Response assessments will be done per Section **3.4.3.1** below. Once treatment is complete, participants will be restaged per Section **3.5.**

- **Unscheduled Visits:** In the event of an unscheduled/unplanned visit (e.g., additional clinical assessment(s) due to toxicity), the investigator should use best clinical judgement as to the necessary assessments. In the event that the decision is made to continue treatment, all tests/assessments as required by the next visit on the Study Calendar (**Appendix D**) should still be conducted (or repeated) within the applicable windows. If a decision is made to discontinue treatment, the participant should have an End of Treatment Visit followed by post-therapy follow-up with tests/assessments completed (or repeated) within the applicable windows.
- **Post Treatment Evaluations:** See Section **3.5**

3.4.2 Description of Procedures

- Medical history: a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
- Physical exam: review of organ systems, weight, and vital signs (i.e., temperature, pulse, respirations, blood pressure).
- Performance status (ECOG): an assessment of activities of daily living; see **Appendix A**
- Ophthalmologic evaluation and VTE risk assessment at baseline and during treatment as clinically indicated
- Laboratory assessments: the following comprises the required tests/analytes per panel. These may be performed at CLIA (or equivalent) certified laboratories outside NIH and results forwarded to the study team for review and management. Given that the methodologies utilized are similar across all laboratories, no significant variability is expected and there is no anticipation that study data will be affected.
    - CBC with differential: includes Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, and Platelets.
    - Panels:
        - Acute care panel: includes Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, and eGFR.
        - Hepatic panel: includes Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, and Direct Bilirubin.
        - Mineral panel: includes Albumin, Calcium, Magnesium, and Phosphorus.
    - Other: LDH, Uric Acid
    - TSH and T3 and/or T4 if needed
    - PT/ PTT
    - Lymphocyte phenotyping TBNK

  - HIV 1/2 antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), and Hepatitis C antibody (HCV Ab) to determine eligibility
  - HBV and HCV viral load in positive participants to determine eligibility and to monitor for reactivation (see Section **4.1.2**)
  - CMV and EBV PCR
  - Pregnancy test: Urine or serum HCG with a minimum sensitivity of 25 mIU/mL for individuals of child-bearing potential:
    - Individuals of childbearing potential (IOCBP) with regular or no menstruation must have a pregnancy test weekly for the first 21 days and then every 21 days while on lenalidomide therapy (including breaks in therapy); at discontinuation of lenalidomide and at 30 Day safety visit.
    - A FCBP with irregular menstruation must have a pregnancy test weekly for the first 21 days and then every 14 days while on lenalidomide therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 (+/-1 day) and at 30 Day safety visit.
  - 24-hour urine creatinine clearance (if needed to measure CrCl in cases where serum creatinine >1.5 mg/dl)
  - Urinalysis
  - Quantitative Immunoglobulin Panel
- EKG to determine eligibility
- Imaging evaluations:
  - CT scans (chest, abdomen, and pelvis); may be adjusted to assess additional known sites of disease
  - Brain MRI
  - ^{18}F-FDG-PET Scan brain and body (must be performed at NIH only). Additional PET/MRI may be performed as clinically indicated.

  These scans (with the exception of ^{18}F-FDG-PET) may be performed outside of the NIH and the result forwarded to the study team for review at screening or any time during the study. Given that the methodologies utilized are similar across all facilities, no significant variability is expected and there is no anticipation that study data will be affected.
- Lumbar puncture/Ommaya tap for CSF studies including protein, glucose, cell count/differential, cytology, and flow cytometry to determine eligibility and during the study if clinically indicated.
- Bone marrow aspiration/biopsy should be performed within 3 months prior to starting protocol treatment. May be repeated after Cycle 6 if the previous test result was positive or if otherwise clinically indicated.
- Study drug administration schedule- see Section **3.2**
- Adverse events and concomitant medication review: Adverse events and concomitant medication will be continuously monitored throughout the study until disease progression

or end of treatment visit. Adverse events that occur beyond 30 days after the last administration will be recorded per **6.1.**

- Correlative studies: Refer to section **5**

3.4.3 Additional Information

3.4.3.1 Response Assessments

Participants will be restaged at the following time points. Response assessments will be done by investigators. For additional details on response criteria, see Section **6.3** .

- After cycle 1 (within 7 days prior to treatment on day 1 of cycle 2)
- After cycle 3 (within 7 days prior to treatment on day 1 of cycle 4)
- After cycle 6 (cycle 6 day 21 +/- 7 days)

NOTE: If a participant stops treatment for any reason other than disease progression before completion of 6 cycles, response assessments should continue as listed in Study Calendar (**Appendix D**).

NOTE: Restaging scans should only be performed based on involved sites of disease at baseline (e.g., patients with CNS disease only should undergo restaging MRI brain and PET brain while those with systemic disease should also undergo CT C/A/P and PET torso).

3.4.3.2 Disease Progression

At the time of suspected or confirmed disease progression, the following are required:

- Imaging by MRI brain, CT scan, and FDG-PET (only if can be performed at NIH)
- Lumbar puncture/Ommaya tap for CSF studies including protein, glucose, cell count/differential, cytology, and flow cytometry
- Ophthalmologic evaluation (only if ocular involvement was noted at baseline evaluation)
- Symptom-guided clinical assessment with physical exam
- Lymphocyte phenotyping TBNK

NOTE: In the event that disease progression is not confirmed, yet a decision is made to initiate a new anti-cancer treatment for any reason, all of these assessments should be done prior to start of the new therapy.

3.5 POST-TREATMENT EVALUATIONS

All post-treatment visit(s) may be completed by remote visit with a member of the study team (e.g., if the participant is not able to return to the NIH CC). Remote visits will be conducted in by phone, email or other NIH approved remote platform used in compliance with local policy, including M20-1. Required labs/scans can be obtained by a local provider, with results sent for review and any suggested management by the study team. A participant may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the investigator; otherwise, physical exams are not required at these time points. In the case of any visits with participants' local providers, records will be obtained for the research records. Remote contact not necessary if participant seen at study site.

3.5.1 End of Treatment/Disease Progression Visit

When a participant completes all 6 cycles of treatment or discontinues early, all applicable activities scheduled for the End of Treatment Visit/PD should be performed at the time of discontinuation (**Appendix D**).
Some procedures indicated in Study Calendar should be done only in case of PD. This visit should take place as soon as possible after the last administration of study drug (no more than 30 [+/-7] days). If a new anti-neoplastic therapy is to be initiated, this visit should occur before starting the new therapy. In cases where treatment was on hold, the visit should occur no more than 30 (+/-7) days after the date participant is taken off treatment, and if needed may coincide with the 30-day safety follow up visit (as needed).

3.5.2 30-Day Safety Follow-Up Visit

The safety follow-up visit should occur approximately 30 days after the end of the last cycle; or before the initiation of a new anti-cancer treatment, whichever comes first. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

3.5.3 Follow-Up Visits – Prior to Disease Progression

Participants who complete trial therapy or discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed as below by clinical evaluation and radiologic imaging to monitor status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or withdrawal/end of the study.

In follow-up post-treatment prior to disease progression, participants will be seen at the following time points:

- Every 3 months during post treatment year 1 (+/- 14 days)
- Every 4 months during post treatment year 2 (+/- 14 days)
- Every 6 months during post treatment year 3 (+/- 21 days)
- Every 1 year during post treatment years 4-10 (+/- 28 days)

All required testing is as noted in the Study Calendar (**Appendix D**).
NOTE: Restaging scans should only be performed based on involved sites of disease at baseline (e.g., patients with CNS disease only should undergo restaging MRI brain while those with systemic disease should also undergo CT C/A/P. Patients who achieve CR by post-treatment PET only need repeat PET imaging as clinically indicated).

3.5.4 Follow-Up Visits – Survival/Post-Disease Progression

Once participants progress or start use of alternative antineoplastic therapy, they will be contacted, approximately every 3 months (+/- 14 days), for a maximum of 10 years to assess survival and the use of alternative antineoplastic therapy and stem cell transplant until withdrawal/end of the study (Section **3.8.2**).

3.6 STUDY CALENDAR

See **Appendix D**. Appendix D: Study Calendar

3.7 COST AND COMPENSATION

3.7.1 Cost

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA

Prior to removal from study, every effort must be made to have all participants complete a safety visit approximately 30 (+7) days following the last dose of study therapy. Additional safety visits and follow-up will continue as per Section **3.5**.

3.8.1 Criteria for removal from protocol therapy

- Disease progression
- Unacceptable adverse event(s) as explained in Section **3.3**
- Delay of treatment for more than 6 weeks, unless it is felt by the Principal Investigator to be in the participant's best interests to remain on study in exceptional circumstances.
- Participant requests to be withdrawn from the treatment
- Participant requires a prohibited concomitant medication as explained in Section **4.3**
- Participant HBV DNA level exceeds 100 IU/mL while on antiviral medication as explained in Section **4.1.2**
- Pregnancy
- Investigator's discretion
- Study is cancelled for any reason

3.8.2 Off-Study Criteria

- Screen failure and/or failure to maintain eligibility (i.e., between enrollment and day 1 of study treatment)
- Completion of 10 years follow-up period
- Participant requests to be withdrawn from the study
- Lost to follow-up
- Death
- Study is cancelled for any reason

3.8.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to report for two (2) scheduled visits and is unable to be contacted by the study site staff.

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

- The team will attempt to contact the participant and reschedule the missed visit within 5 business days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB-approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 PERMITTED CONCOMITANT MEDICATIONS

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) is permitted per institutional policy and in accordance with the ASCO guidelines. Transfusions may be given in accordance with institutional policy.

4.1.1 For Participants on pre-treatment corticosteroids

Pretreatment dexamethasone (or other corticosteroid) is part of the standard treatment for participants with CNS mass lesions. Dexamethasone or other steroid doses will be reduced and/or terminated as early as possible according to safe medical practice.

4.1.2 Prophylaxis of Hepatitis B reactivation

Participants who are positive for either Hepatitis B core antibody (HBcAb) or Hepatitis B surface antigen (HBsAg) and not acutely infected are at varying risk for reactivation of Hepatitis B especially when combined with novel agents like ibrutinib and rituximab. Participants may be included in the study provided that they have HBV DNA levels below the World Health Organization's cutoff of 100 IU/mL prior to starting therapy. These participants will be treated with entecavir (or equivalent) to prevent hepatitis B reactivation and should have HBV DNA levels obtained monthly during treatment, and at: End of Treatment, 30 Day Post-Treatment Safety Visit; and every 3 months for 12 months after the last cycle of therapy by means of real-time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL.

If the HBV DNA assay becomes positive during combination therapy, study treatment should be held, and the participant should be immediately referred to a gastroenterologist or hepatologist for management recommendations.

If a participant's HBV DNA level exceeds 100 IU/mL while the participant is receiving antiviral medication, study treatment must be permanently discontinued

4.1.3 Prophylaxis of Pneumocystis jiroveci (previously Pneumocystis carinii)

All participants will receive prophylaxis for Pneumocystis Jiroveci during VIPOR therapy. Trimethoprim/sulfamethoxazole 1 double strength (DS) tablet by mouth for three days each week. Monday, Wednesday, Friday is the preferred schedule. Participants allergic to either component may receive inhaled pentamidine 300 mg once a month or other standard treatments.

4.1.4 Nausea

Medications to prevent nausea and vomiting are permitted as clinically indicated.

4.1.5 Febrile Neutropenia

This is a life-threatening complication requiring urgent broad-spectrum antibiotics. Management may be as an inpatient or outpatient depending on the clinical situation.

4.1.6 Symptomatic anemia

This should be treated with appropriate red blood cell support. Only irradiated leukodepleted blood products should be used.

4.1.7 Thrombocytopenia

In the absence of bleeding or planned invasive procedures, platelet transfusions should be given for platelets < 10,000/mm^3. If invasive procedures are planned or the participant develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count > 50,000/mm^3.

4.1.8 Central Venous Access

Central Venous Access may be used for administration of intravenous medications and for drawing blood samples. Possible lines include:

- Temporary internal jugular line;
- PICC lines via the brachial vein;
- semi-permanent HICKMAN,
- GROSHONG catheters; or
- medi-port implanted devices.

All devices will have nursing supervision to include participant self-care and cleaning/flushing of the devices.

4.1.9 Venous Thromboembolism Prophylaxis

The use of lenalidomide has been associated with the development of venous thromboembolism, including deep venous thrombosis and pulmonary embolism. Ibrutinib has been associated with increased risk of bleeding, including serious intracranial hemorrhage. VTE risk assessment will be performed in all participants at baseline and the risks and benefits of anticoagulation with aspirin or low molecular weight heparin will be assessed by the investigators and discussed with the participant. General risk factors for participants with cancer include, but are not limited to underlying disease, family history, age, obesity, immobilization, hormonal therapy, central venous

catheter, recent DVT, sex, renal dysfunction, and certain chemotherapy-based regimens. It is not known whether prophylactic anticoagulation or anti-platelet therapy prescribed in conjunction with Revlimid® may lessen the potential for venous thromboembolism. It is up to the discretion of the Investigator after consideration of the participant's individual risk/benefit profile whether to institute VTE prophylaxis.

4.2 MEDICATIONS TO BE USED WITH CAUTION

Concomitant medications that fall into the categories below could potentially lead to adverse reactions and should be considered cautionary (except where noted). If a potential study participant is taking any of the medications in the categories described below, the investigator must assess and document the use of medications known or suspected to fall in the following medication categories:

- Moderate/weak CYP3A inducers such as efavirenz and oxcarbazepine
- CYP2C8 substrates such as thiazolidinediones (glitazones) and select statins (because of expected inhibition of the metabolism of CYP2C8 substrates by venetoclax)
- CYP2C9 substrates such as tolbutamide (because of expected inhibition of the metabolism of CYP2C9 substrates by venetoclax). It is recommended to exclude CYP2C9 substrates with a narrow therapeutic index such as phenytoin.

For participants taking digoxin, periodic monitoring of digoxin plasma levels is recommended due to increased Cmax and AUC with concomitant lenalidomide therapy (please see lenalidomide product insert).

Participants taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies, may have an increased risk of venous thromboembolism with lenalidomide (please see lenalidomide product insert).

4.2.1 CYP3A Inhibitors/Inducers

Venetoclax and ibrutinib are metabolized primarily by CYP3A4. Avoid co-administration with strong CYP3A4 inhibitors or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 280 mg or withhold treatment temporarily. Participants should be monitored for signs of ibrutinib toxicity. No dose adjustment is required in combination with mild or moderate inhibitors. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of inhibitors, inducers, and substrates may be found at: https://drug-interactions.medicine.iu.edu/MainTable.aspx

Although the ibrutinib Package Insert (dated May 2022) indicates to dose reduce ibrutinib to 280 mg daily in participants with B-Cell malignancies if it is co-administered with a moderate CYP3A inhibitor and results in toxicity, in this protocol dose modifications are different because ibrutinib is being used indefinitely where dose interruptions are more clinically feasible. In our study of combination therapy, we use time-limited therapy and holding doses even for just a few days can have a detrimental effect on efficacy. Furthermore, this study is testing the agent in patients where lymphoma is involving the central nervous system (CNS). Our data with ibrutinib

suggests that higher doses to achieve CNS penetration are critical to efficacy. In other scenarios (such as CLL and MCL), one gets full BTK occupancy at lower doses, so it is less of an issue. We do not think that we should make any changes to our dose modification tables for these scientific reasons and do not anticipate additional toxicity based on this decision.

4.2.2 QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms and electrolytes should be considered.

4.2.3 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp) or other transporters, except OCT2. Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There is no clinical data available; therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib. Inhibition of the BCRP pathway may increase exposure to drugs that undergo BCRP mediated hepatic efflux, such as rosuvastatin.

4.2.4 Antifungal Agents

Given the overlapping toxicity of these targeted agents as well as other immunosuppressive therapies, such as steroids, there is an increased risk of infectious complications, including potential invasive fungal infections. Participants on this study will be undergoing frequent imaging for response evaluation and the investigators will also evaluate these imaging studies for potential infectious complications, including possible invasive fungal infection. Further clinical work-up may include, but is not limited to, peripheral blood analysis for fungal blood markers and/or bronchoscopy with bronchoalveolar lavage (BAL) testing for fungal markers/cultures and other infectious pathogens.

Antifungal therapy with echinocandins, such as micafungin or caspofungin, as well as treatment with ambisome are permitted on study if deemed clinically appropriate. Due to the strong inhibition of CYP3A with certain azoles (e.g., voriconazole, posaconazole, itraconazole or ketoconazole), treatment with any of these agents will require dose reduction of ibrutinib as per Section **4.2.1**. Prophylactic antifungals will not be routinely used given the low estimated risk of fungal infections with cyclic, non-continuous dosing of targeted agents

4.2.5 Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in participants requiring other anticoagulants or medications that inhibit platelet function. Participants with congenital bleeding diathesis have not been studied.

For participants requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the participant is clinically stable and has no signs of bleeding. Participants should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study

drug is restarted.

4.2.6 Surgery

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib during the perioperative period for participants 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 **3 days prior** to the intervention when feasible and should be held at least **3 days after** the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguinous 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 **1 days prior** to the procedure when feasible and should not be restarted for at least **1 day after** the procedure. For bone marrow biopsies that are performed while the participant is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

4.3 PROHIBITED CONCOMITANT MEDICATIONS

4.3.1 Prohibited Therapy

Participants who require the use of any of the excluded therapies listed below will be discontinued from study treatment.

Use of the following therapies is prohibited during the study:

- Immunotherapy
- Hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate)
- Any therapies intended for the treatment of lymphoma whether FDA approved or experimental (outside of this study)
- Warfarin or warfarin derivatives

The following concomitant medications are not allowed from 7 days prior to the first dose of study drugs and during study drug administration:

- Strong CYP3A4 inhibitors such as voriconazole, ketoconazole, and clarithromycin
- Strong CYP3A4 inducers such as rifampin and carbamazepine

A comprehensive list of inhibitors, inducers, and substrates may be found at: https://drug-interactions.medicine.iu.edu/MainTable.aspx. Pretreatment corticosteroids for CNS disease is permitted before entering this study as explained in Section **2.1.2.4**.

4.3.2 Vaccines

Live-virus vaccines should not be given at any time during study therapy and are not recommended until B-cell recovery post completion of study therapy.

4.3.2.1 Clarification regarding vaccination against COVID-19:

Vaccines currently authorized or approved for use against COVID-19 in the United States include mRNA vaccines (Pfizer and Moderna vaccines) and a viral vector vaccine (JNJ-78436735 manufactured by Janssen Pharmaceuticals).

In general, it is preferred that participants considering vaccination or booster against COVID-19 complete the vaccination procedures prior to enrollment. Discussion with the Sponsor Medical Monitor to agree upon a safe and appropriate strategy for vaccination of these participants is advised, but not mandatory.

For participants in the study, vaccination against COVID-19 with a vaccine authorized or approved in the United States is permitted. Relevant details regarding vaccination will be documented as a concomitant medication and will include the name of the manufacturer of the COVID-19 vaccine. Any adverse events thought to be related to the vaccine will be recorded in the Adverse Event case report form.

5 CORRELATIVE STUDIES FOR RESEACH

5.1 BIOSPECIMEN COLLECTION

Sample	Collection Details*	Time Points	Supervising Laboratory/ Investigator^
Blood Samples			
ctDNA	• 2 x 10 mL Streck/BCT tube	• Baseline • At the end of every cycle • At follow-up visit (not at 30 Day Safety visit) • At disease progression	BPC
PBMCs for mutational analysis	• 1 x 8 ml CPTs (sodium heparin)	• Baseline • At the end of every cycle • At disease progression	BPC
Cytokines	• 1 x 8-10 mL RTT	• Baseline • End of treatment visit	BPC
Ibrutinib and Venetoclax PK	• 2 x 2ml GTT (sodium heparin)	• C1D1: ➢ Prior to dose of ibrutinib and venetoclax ➢ 1 hour post ibrutinib and venetoclax (+/-20 min) ➢ 10-18 hours post ibrutinib and venetoclax	BPC
*CSF**			
ctDNA	• 3 ml in a sterile syringe	• Baseline • At the end of every cycle • At follow-up visit (not at 30 Day Safety visit) • At disease progression	BPC

Sample	Collection Details*	Time Points	Supervising Laboratory/ Investigator^
Ibrutinib and Venetoclax PK	• 0.5 mL in a cryovial supplied by Lymphoma Team Research Nurse	• C1D1: ➢ Prior to dose of ibrutinib and venetoclax ➢ 1 hour post ibrutinib and venetoclax (+/-20 min) ➢ 10-18 hours post ibrutinib and venetoclax	BPC
Other samples			
Archival and/or Fresh Tissue Biopsy for gene expression profiling, mutational analysis, and DNA/RNA sequencing.	• FFPE (block or slides); • Excision (single or multiple nodes) or core (4-6 passes); placed in formalin/FFPE and media, as appropriate	• Baseline (optional) • At disease progression (optional)	NCI LP/ Staudt
Germline DNA for whole exome sequencing	• Blood, Buccal swab, or Saliva 1 x 8 ml CPTs (sodium heparin) for blood	• Baseline	BPC
*CSF studies will only be performed in participants with Ommaya Reservoirs. **Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the best samples are collected for planned analyses. ^The location of specimen processing or analysis may be adjusted with the permission of the PI or laboratory investigator.			

5.2 SAMPLE COLLECTION AND PROCESSING

Any specimens collected on the protocol for specific research analysis that is left over after the analysis is done will be stored for future research.

Note: Platforms and procedures for analysis may be adjusted based upon current technology and/or collaborations in place at the time of actual analysis.

5.2.1 Tissue Samples

Tissue samples, both archival and fresh lymph node excision or core needle biopsy samples may be collected as outlined in the table above for research studies, including gene expressing profiling, and mutational analysis.

Archival block(s) or slides (e.g., 15 unstained slides, 5-microns) may be collected, when available from prior or future routine procedures.

Tissue samples will be sent to the Hematopathology Section of Laboratory of Pathology until they are retrieved by staff in the lab of Lou Staudt, MD, PhD, Lymphoid Malignancies Branch, CCR, NCI.

5.2.2 Lymph node excision or core needle biopsy procedure

Participants with accessible tumor tissue who agree to have an optional biopsy performed will be biopsied as outlined in the table in Section **5.1**. These samples will be processed as per the standard operating procedures of the Hematopathology Section of the Laboratory of Pathology, NCI, including fresh, frozen and/or formalin-fixed, paraffin-embedded (FFPE) tissue.

If participant has a biopsy during screening to confirm eligibility, baseline biopsy will not be repeated.

Optional tumor biopsies will be obtained by core needle biopsy or surgery. If core biopsies are collected, it is preferable that the interventional radiologist will collect 4-6 core needle biopsies. Biopsies for research will be performed only if there is minimal risk of morbidity. Deep-seated organs such as lung will be excluded from biopsy for research purposes. General anesthesia will not be performed to obtain biopsies for research purposes but when necessary, conscious sedation may be used. If a biopsy is being performed for medical or diagnostic purposes, with or without general anesthesia, a sample may be obtained for research purposes, if adequate tissue is available to meet medical or diagnostic purposes, upon participant consent.

5.2.3 Gene expression profiling

Gene expression profiling using Affymetrix U133plus 2.0 arrays will be performed for all cases. For those cases with available fresh frozen pre-treatment biopsy samples, gene expression profiling will be performed as described by the Staudt laboratory, with assignment to ABC or GCB subgroups based on a Bayesian predictor. For participants with only an FFPE biopsy sample, we will use a newly described method that can use RNA from FFPE biopsies to accurately predict ABC vs. GCB DLBCL subtypes. Briefly, RNA is extracted from FFPE samples with a Qiagen FFPE extraction kit followed by amplification using uniform and state of the art assay kits, prior to standard Affymetrix U133Plus2.0 array analysis.

5.2.4 Mutational analysis

Most primary CNS lymphomas appear to be of non-GCB origin and studies that have looked at mutational analysis of tumors have found a high rate of mutations of the B-cell receptor as well as MYD88 mutations and CARD11 mutations. Therefore, mutational analysis will include but is not restricted to CD79B, CD79A, CARD11 and MYD88, ITAM and A20. This is an evolving field so there may be other mutations and signaling pathways related to NF-kappa B that may also be evaluated. For collection timepoints see table above.

5.2.5 Blood and Cerebrospinal Fluid (CSF) Samples

5.2.5.1 Cytokine analysis and circulating tumor DNA (ctDNA)

Cytokine analysis may include but is not limited to the following: IL-6, IL-10, interferon beta, and TNF alpha. Analysis of ctDNA will be performed using blood and CSF samples as described above. CSF studies will only be performed in participants with Ommaya Reservoirs.

5.2.5.2 PBMCs for Mutational Analysis

Peripheral blood samples will be sent to Biospecimen Processing Core (BPC)where the samples will be processed to separate out mononuclear cells (PBMC) by Ficoll gradient. The PBMC will be viably frozen and stored in the BPC. Mutational analysis will include but is not restricted to CD79B, CD79A, CARD11 and MYD88, ITAM and A20.

5.2.5.3 Pharmacokinetic Analyses of Oral Targeted Therapy (OTT- ibrutinib and venetoclax)

This study provides the opportunity to study the peripheral blood and CSF PK of several anticancer agents. The goal is to have samples of plasma/serum, peripheral blood and CSF PK; CSF PK studies will only be performed in participants with Ommaya Reservoirs.

NOTE: Timing of PK sample collection: Every effort will be made to collect samples for PK analysis as prescribed in the table above.

5.2.6 Future use of blood, serum, CSF, and tissue specimens

Specimens (blood, serum, CSF, and tissue) collected in the course of this research project will be banked and used in the future to investigate new scientific questions. Future investigations will be conducted on blood, serum, CSF, and tissue specimens and may include analysis of cellular, molecular, genetic and genomic biology and RNA analysis. These studies may involve sequencing of tumor DNA. Samples derived from biopsies may be utilized for procedures such as electron microscopy, immunofluorescence, immunohistochemistry, other histopathologic special stains, establishment of cell cultures, and as a source of material for laboratory studies of nucleic acids and proteins.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.3.1 General

All specimens obtained in the protocol are used as defined in the protocol. Samples from consenting participants will be stored until they are no longer of scientific value or if a participant withdraws consent for their continued use, at which time they will be destroyed.

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.3.2 Hematopathology Section of Laboratory of Pathology (Tissue samples)

Archival and/or freshly collected and processed tumor tissue may be stored in the Hematopathology Section of Laboratory of Pathology until ready for planned and/or future research assays if the participant has agreed to allowing specimens to be used in future research studies. IRB approval will be obtained before using any samples to conduct studies that are not described within this protocol. Samples will be stored under conditions appropriate to the type of sample and processing (e.g., ambient or frozen).

Tissue that is given to the technician will be assigned an accession number (HP#) in the HP Case Logbook; sample tracking also takes place with a FileMaker Pro data base called HP Patient Information and Specimen Inventory. A participant background sheet may be filled out and filed with any accompanying paperwork, with final reports and any supplemental reports that follow added as completed.

Archival and/or freshly collected and processed tumor tissue as well as germline DNA samples will be transferred upon request to the Staudt lab for sequencing and molecular analysis. These analyses may include, but are not limited to, whole-genome sequencing (WGS), whole-exome sequencing (WES), copy-number alterations (CNA), RNA-sequencing as well as single-cell RNA-sequencing.

5.3.3 Biospecimen Processing Core /Clinical Pharmacology Program

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main biospecimen processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov

In addition to performing analyses, samples will be processed, barcoded, and stored in the BPC until requested by the investigator.

5.3.3.1 Sample Data Collection

All samples sent to the Biospecimen Processing Core (BPC) will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined BPC personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by the BPC. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to participants without Labmatrix access. The data recorded for each sample includes the ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the clinical center participant number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.3.3.2 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.3.4 Staudt Lab

5.3.4.1 Sample Data Collection

Participant samples, collected for research under this IRB approved protocol, may be archived in the Staudt laboratory. All data associated with archived clinical research samples is entered into the web-based NCI Labmatrix database, a centralized system with access controlled via centralized login. Access to this database for samples collected from this study is limited to Dr. Staudt and his research staff, each requiring individual login and password. All staff in the laboratory receive annually updated NIH/CITI or other training, as appropriate, and maintain standards of computer security.

The data recorded for each sample may include the participant ID, trial name/protocol number, date drawn/collected, treatment cycle/time point, sample source (e.g., peripheral blood, marrow, tissue, etc.) as well as box and freezer location. All received samples will be given a unique bar code number, which will be added to the sample NCI Labmatrix database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to Participants without authorized access to the NCI Labmatrix database.

5.3.4.2 Sample Storage

Samples are stored in freezers at -80°C (e.g., sera, plasma, tissue samples) or under liquid nitrogen (e.g., cells), according to established stability requirements. These freezers are located onsite under the direction of Dr. Staudt. Access to samples from this protocol for research purposes will be as outlined in this protocol or by permission of the Principal Investigator only.

5.3.5 Study Completion, Future Use and Sample Destruction

The study will remain open so long as sample or data analysis continues. Following completion of the planned analyses, samples will remain in storage as detailed above. Tissue specimens and derived tissue lysates, RNA and DNA collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study that are not expressly stated in the present protocol. However, this research may only be done if the proposed research has undergone prospective IRB review and approval, including consent/reconsent if required.

If the participant withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.4.1 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors and circulating-tumor DNA (ctDNA). In addition, whole exome sequencing of blood, buccal swab, or saliva may include evaluation for known lymphoma mutations.

5.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

As stated in section **5.4**, unique identifiers are attached to samples and are linked through the secure database to medical record information, with the key provided only to researchers on the study. Therefore, potential identification would only occur in the event of a data breach – an unlikely event given the security standards of the databases utilized. A certificate of confidentiality has been obtained (section 13.4). Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy (**6.2.2**). The pedigree analysis will not be performed.

5.4.3 Management of Results

Participants will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis

5.4.4 Genetic Counseling

Participants will be contacted with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the participant will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the participant does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

6.1.1 Summary

The PI will be responsible for overseeing entry of data into a data capture system provided by the NCI CCR and ensuring data accuracy, consistency, and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human participant.

All adverse events (AEs), including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the date of first dose of any study drug, through 30 days after the last dose of any study drug. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded

All grade 3, grade 4 and grade 5 abnormal laboratory values will be recorded in the database.

Grade 1 and grade 2 abnormal laboratory values will be recorded in the database as an AE only if

the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

The PI (or designee) evaluation of each AE not captured in the clinical database determining that it meets the criteria above will be documented in the source documents.

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

Adverse Events of grade 1 will not be collected.

Information on all concomitant medications, administered blood products, as well as interventions occurring during the study must be recorded on the participant's eCRF in C3D

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_X_ Coded, linked or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

_X_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov, dbGaP.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Publications and/or public presentations.

When will the data be shared?

_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

This study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

Therefore, unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated as outlined in **Appendix D: Study Calendar**
. In addition to a baseline scan, restaging scans will be performed after cycles 1, 3, and 6. Cases with complete resection of tumor mass will not be evaluable for response assessment; however, will be included in the PFS and OS statistics. When appropriate, for participants with disease involvement of the bone marrow at baseline, repeat assessment will be done to confirm response.

6.3.1 Response Criteria for PCNSL

The following response criteria as per the CNS lymphoma working group ([35]) will be used for participants on study with PCNSL:

Response	Brain Imaging	Corticosteroid dose	Eye examination	CSF cytology
CR	No contrast enhancement	None	Normal	Negative
CRu	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
PD	25% increase in lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: CNS or systemic			
Abbreviations: CR, complete response; CRu, unconfirmed complete response; RPE, retinal pigment epithelium; PR, partial response; PD, progressive disease				

6.3.2 Response Criteria for SCNSL

The response categories being used to assess overall efficacy of combination therapy are based on the Revised Response Criteria for Malignant Lymphoma [36].

6.3.2 Complete Response (CR)

For CR determination, all the following criteria must be met:

1. Complete disappearance of all detectable evidence of disease and disease-related symptoms, if present before therapy
2. All lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in the greatest transverse diameter [GTD] for nodes >1.5 cm before therapy, regardless of the short axis). Previously involved nodes that were between 1.1 cm and 1.5 cm in the long axis and more than 1.0 cm in the short axis before treatment must have decreased to ≤1.0 cm in the short axis after treatment. All splenic and hepatic nodules and other extranodal disease must have disappeared.
3. FDG-PET scan must be negative (for the combined CT+PET assessment of CR). A posttreatment residual mass of any size is permitted as long as it is PET-negative. The Five-Point Scale (5-PS) Deauville criteria will be used to interpret PET scans with a score of 1-3 being considered PET negative and 4-5 considered PET positive [37] (Section **6.3.6**).
4. The spleen and/or liver, if enlarged before therapy on the basis of physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies.
5. If the bone marrow was involved before treatment, the infiltrate must have cleared on repeated bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If a sample is indeterminate by morphology, it should be negative by IHC (if bone marrow was involved before therapy and a radiological CR was achieved, but with no bone marrow assessment after treatment, the response should be classified as a PR).
6. No new sites of disease are detected during assessment.

6.3.3 Partial Response (PR)

For PR determination in participants with measurable disease, all the following criteria must be met:

1. A ≥50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses.
2. No increase should be observed in the size of other nodes, liver, or spleen, meeting the criteria for PD.
3. Splenic and hepatic nodules must regress by ≥50% in the SPD or, for single nodules, in the GTD.
4. With the exception of splenic and hepatic nodules, other organs should not have any measurable disease.
5. Bone marrow assessment is not required for PR determination.
6. No new sites of disease should be observed.
7. At least 1 PET-positive site of disease (required for the CT+PET assessment of PR).

For PR determination in participants with evaluable disease that is not measurable, all the following criteria must be met:

1. A ≥50% decrease in the SUVmax from baseline PET scan.
2. Bone marrow assessment is not required for PR determination.
3. No new sites of disease should be observed.
4. At least 1 PET-positive site of disease (required for the CT+PET assessment of PR).

6.3.4 Stable Disease (SD)

Stable disease (SD) is defined as:

1. A participant is considered to have stable disease when he or she fails to attain the criteria needed for a CR, PR, or MR but does not fulfill those for PD.
2. The PET should be positive at, at least 1 previously involved site of disease, with no new areas of lymphoma involvement on the posttreatment CT or PET (for the combined CT+PET assessment of stable disease).

6.3.5 Progressive Disease (PD) or Relapsed Disease

Progressive disease or relapsed disease (after CR) is defined as:

1. Appearance of any new nodal lesion ≥1.6 cm in greatest tumor dimension or ≥1.1 cm in short axis during or after the end of therapy, even if other lesions are decreasing in size.
2. Appearance of any new unequivocal extra-nodal lesion measuring >1.0 cm, not thought to be benign by the reviewer, even if other lesions are decreasing in size
3. At least a 50% increase from the nadir in the sum of the product of diameters of any previously involved nodes, or in a single involved node, or in the size of other lesions (e.g., splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of <1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
4. At least a 50% increase from the nadir in the longest diameter of any single previously identified node more than 1 cm in its short axis.
5. Cytology confirmation of DLBCL is required when there is an appearance on CT of a new lesion ≥1.5 cm in its long axis and is PET-negative.

6.3.6 The Five-Point Deauville Scale (5-PS) for SCNSL

In addition to the CNS lymphoma working group criteria, the five-point Deauville scale (5-PS) has been validated for use at interim staging and at the end of treatment for systemic lymphomas

and was adopted as the preferred reporting method at the First International Workshop on PET in Lymphoma in Deauville, France (i.e., Deauville criteria), and in several international trials.

The 5-PS scores the most intense uptake in a site of initial disease:

1. if present, as follows:no uptake or no residual uptake (when used at interim)
2. slight uptake, but below blood pool (mediastinum)
3. uptake above mediastinal, but below or equal to uptake in the liver
4. uptake slightly to moderately higher than liver
5. markedly increased uptake or any new lesion (on response evaluation)

6.3.7 Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

6.3.8 Duration of Response

The duration of response (DOR) is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started), death, or, in the absence of PD, date of last assessment.

6.3.9 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, death, or 10 years post-treatment, whichever occurs first.

6.3.10 Overall Survival

Overall survival (OS) is defined as the duration of time from the date of study enrollment until time of death from any cause, or 10 years post-treatment whichever occurs first.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/hrpp-policy-guidelines/

7.2 OHSRP Office of Compliance and Training / IRB Reporting

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at:

https://irbo.nih.gov/hrpp-policy-guidelines/.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem or present new information that might affect the willingness of participants to enroll or remain on the study will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/hrpp-policy-guidelines/.

7.3 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (approximately weekly) when participants are being actively treated on the trial to discuss each participant.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a

medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

AESIs for this study include the following:

- 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:
    - Treatment-emergent ALT or AST > 3x ULN in combination with total bilirubin > 2x ULN
    - Treatment-emergent ALT or AST > 3x ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), 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 the study drug is suspected.

These AESI will be reported to the sponsor through expedited reporting on the SAE report form (see Section **8.3**).

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution (return to baseline or stabilization) of the event, seriousness, and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution (return to baseline or stabilization).

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

8.3 Reporting of Serious Adverse Events

Reported to sponsor from the first study intervention, Study Day 1 through the safety follow up visit. Beyond the safety follow-up visit, only adverse events which are serious and related to the study intervention will be reported. Exceptions are listed in section **8.4**.

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) via an electronic SAE reporting system (e.g. HiLIT). In the event of system downtime or issues, SAE reports will be submitted using the CCR SAE Report form to the sponsor at: OSROSafety@mail.nih.gov . CCR SAE report form and instructions can be found at:

https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of expedited reporting to CCR

As death due to disease progression are part of the study objectives, and captured as an endpoint in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.4**.

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

N/A.

8.6 Reporting Pregnancy

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

8.6.1 Maternal exposure

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Participants should refrain from fathering a child or donating sperm during the study and for 6 months after the last dose of obinutuzumab.

Pregnancy of the participant's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 6 months after the last dose of obinutuzumab should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the safety and feasibility of VIPOR in primary DLBCL of the CNS (PCNSL) and secondary CNS lymphoma (SCNSL)	The fraction of participants who completed at least 2 cycles of VIPOR therapy without stopping due to toxicity.	Standard endpoint for cancer clinical trials.
Secondary		
To determine the overall response rate (ORR) of up to 6 cycles of VIPOR in CNSL	ORR = CR+PR- assessed after cycles 3 and 6	Standard endpoints for cancer clinical trials

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To determine the complete response (CR) rate of up to 6 cycles of VIPOR in CNSL	CR- The rate of complete response by Lugano, assessed after cycles 3 and 6	Standard endpoints for cancer clinical trials, CR is the endpoint chosen because with these diseases, PR is not relevant as all participants will relapse.
To determine the duration of response (DOR) after VIPOR in CNSL	Duration of response (DOR)- measured from the time of first response until the first date that recurrent or progressive disease is objectively documented, death, or, in the absence of PD, date of last assessment (10 years post-treatment)	Standard endpoints for cancer clinical trials, success of regimens will be determined by these endpoints.
To estimate the progression-free survival (PFS) after VIPOR in CNSL	Progression free survival (PFS) – calculated up to 10 years post-treatment	Standard endpoints for cancer clinical trials, success of regimens will be determined by these endpoints.
To assess overall survival (OS) after VIPOR in CNSL	Overall survival (OS)- calculated up to 10 years post-treatment	Standard endpoints for cancer clinical trials, success of regimens will be determined by these endpoints.
Tertiary/Exploratory		
To perform comprehensive molecular profiling of CNSL tumors and explore correlations with clinical response	Each of these will be evaluated using descriptive methods and reported as exploratory results. If any statistical tests are performed in these analyses, the results will be presented without adjustment for multiple comparisons but reported in the context of the number of tests performed. See Section **5.1** for collection timepoints.	Exploratory analysis
To genotype circulating-tumor DNA (ctDNA) from plasma and CSF and correlate to tissue genotyping		
To study cytokine changes across VIPOR therapy		
To assess the pharmacokinetics (PK) of venetoclax and ibrutinib, in the plasma and CSF		

10.2 SAMPLE SIZE DETERMINATION

In participants with CNS lymphoma, it would be desirable if the success rate were consistent with 80% or better as opposed to 50%. To do so, the following design will be used. In this small pilot trial, 10 evaluable participants who receive VIPOR will be evaluated for the feasibility of achieving success. If there are 7 or more who exhibited a success, the probability of this occurring is no more than 17.2% if the true probability of success is 50% or less and is at least 87.9% if the true probability of success is 80% or more. Thus, attaining success in 7 or more treated participants would be considered enough to demonstrate an adequate level of safety and feasibility for the treatment based on the specified criterion.

As of 6/6/2022, four total participants were enrolled and treated on Cohort 1, Arm 1 (i.e., VIPOR-Nivo). These participants will not be included in the analysis of the primary endpoint but will be evaluated for toxicity and survival outcomes.

10.2.1 Accrual Ceiling

It is expected that 10 evaluable participants can be accrued within 1 year.

The accrual ceiling will be set at 16 participants to account for the 4 participants treated in Cohort 1, Arm 1 (VIPOR-Nivo; closed) in addition to the 10 participants required to assess success in Cohort 1, Arm 2 (VIPOR), and to also allow for 2 inevaluable participants.

10.3 POPULATIONS FOR ANALYSES

Any participants who received at least one dose of any study drugs will be evaluated for success.

10.3.1 Evaluable for toxicity:

All participants will be evaluable for toxicity from the time of their first treatment with any of the VIPOR study drugs.

10.3.2 Evaluable for objective response:

Only those participants who have measurable or evaluable disease present at baseline, have received at least one cycle of VIPOR, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions in Section **6.3**. (**NOTE:** Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.3.3 Evaluable Non-Target Disease Response:

Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

Participants will be evaluated to see if they are successful with respect to feasibility and safety.

10.4.2 Analysis of the Primary Endpoints

Success is defined as completing at least 2 cycles of VIPOR therapy without the need to discontinue treatment due to toxicity. The fraction of participants who achieve a success will be determined and reported along with a 95% confidence interval.

10.4.3 Analysis of the Secondary Endpoints

The following secondary endpoints will be analyzed as described:

- The overall response rate (ORR) of up to 6 cycles of VIPOR in PCNSL and SCNSL will be reported along with a 95% confidence interval.
- The complete response (CR) rate of up to 6 cycles of VIPOR in PCNSL and SCNSL will be reported along with a 95% confidence interval.
- The duration of response (DOR) after VIPOR in PCNSL and SCNSL will be determined starting at the date a response is identified and will be estimated using a Kaplan-Meier curve along with a median DOR, and its associated 95% confidence interval.
- The progression-free survival (PFS) after VIPOR in PCNSL and SCNSL will be estimated using progression or death without progression as events, using a Kaplan-Meier curve. The median will be determined and presented with its associated 95% confidence interval.
- Overall survival (OS) after VIPOR in PCNSL and SCNSL will be determined using a Kaplan-Meier curve. The median will be determined and presented with its associated 95% confidence interval.

10.4.4 Safety Analyses

The safety of the agents will be reported by tabulating the number of participants who experience toxicity, by grade and type of toxicity.

10.4.5 Baseline Descriptive Statistics

The on-study demographic and clinical characteristics of participants will be summarized in a table.

10.4.6 Planned Interim Analyses

None

10.4.7 Sub-Group Analyses

None

10.4.8 Tabulation of Individual Participant Data

None

10.4.9 Exploratory Analyses

The exploratory objectives are:

- To molecularly profile tumors with whole exome sequencing, gene expression profiling, transcriptome profiling, and copy number alterations

- To genotype circulating-tumor DNA (ctDNA) from plasma and CSF and correlate to tissue genotyping.
- To assess the pharmacokinetics (PK) of venetoclax and ibrutinib in the plasma and CSF
- To study cytokine changes across VIPOR therapy

These will be evaluated using descriptive methods. If any statistical tests are performed, they will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

N/A

12 HUMAN PARTICIPANTS PROTECTIONS

12.1 RATIONALE FOR PARTICIPANT SELECTION

Participants from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in the protocol.

Participants with HIV infection will be excluded because the unknown effects of the combination targeted therapy on the underlying HIV infection are unknown and could be adverse. In addition there is potential for pharmacokinetic interactions with venetoclax, ibrutinib and lenalidomide and combination antiretroviral therapy.

Pregnant participants and those not willing to stop nursing are excluded because of the potential teratogenic effects of therapy.

12.2 PARTICIPATION OF CHILDREN

Participants under the age of 18 are excluded because recurrent B-cell lymphomas are rare in young participants, and the inclusion of an occasional younger participant will not provide generalizable information that would justify their inclusion on this study. Additionally, no dosing or adverse event data are currently available on the use of VIPOR in participants <18 years of age.

12.3 PARTICIPATION OF PARTICIPANTS UNABLE TO GIVE CONSENT

Adults unable to consent may enroll in or be retained on this protocol because there is prospect of direct benefit from research participation (Section **12.4**) and these participants, due to their disease, will likely be unable to consent. All participants ≥ age 18 who have capacity will be offered the opportunity to fill in their wishes for research and care and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

NOTE: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the participants and to identify an LAR, as needed.

Please see section **12.5.1** for consent procedure.

12.4 RISK/BENEFIT ASSESSMENT

12.4.1 Known Potential Risks

12.4.1.1 Study Drug Risks

The main risks associated with the study agents include hematologic side effects (neutropenia including febrile neutropenia, thrombocytopenia, anemia, and leukopenia), infusion-related reactions, gastrointestinal (diarrhea, nausea, vomiting, constipation), constitutional (fatigue), peripheral neuropathy and infection. Serious side effects requiring hospitalization are possible including tumor lysis syndrome, neutropenic fever, and severe infusion reactions. Additional toxicity may be seen with the combination of these study agents that was not seen with monotherapy or prior combination trials. The risks associated with research procedures (i.e., research blood and tissue collection, including planned analyses and risks associated with genetic research) are described in detail in the informed consent document. See Section **14** also.

12.4.1.2 Risks of Tissue Biopsy

The risks associated with biopsies are pain and bleeding at the biopsy site. In order to minimize pain, conscious sedation will be used. Biopsies for research purposes are optional on this study. Rarely, there is a risk of infection at the sampling site.

12.4.1.3 Risks of Urine, Saliva, Cheek/Buccal Collection

There are no physical risks associated with urine or saliva collection and cheek/buccal swabs.

12.4.1.4 Risks of EKG

Side effects of EKG are skin irritation where EKG electrodes are placed.

12.4.1.5 Risks of Bone Marrow Biopsy

Bone marrow biopsy is minimally invasive and is typically a very safe procedure. Usually, the hipbone is numbed with anesthesia. Using a needle, the solid and liquid portion of bone marrow is taken out. This procedure causes some pain. Very rarely, infection or bleeding may occur at the needle site.

12.4.1.6 Ophthalmic Evaluation

There are no long-term effect. Short term side effect include light sensitivity, blurry vision and trouble focusing on close objects (if using dilation)

12.4.1.7 Lumbar Puncture

Risks associated with lumbar puncture include headache, back pain, bleeding, and brainstem herniation.

12.4.1.8 Fluid Collection by Ommaya Reservoir

Withdrawing spinal fluid from an Ommaya Reservoir conveys a small risk of infection and a minor amount of discomfort from the needle puncture.

12.4.1.9 Risks of Blood Sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting. Up to 92 mL of blood may be collected at any day, up to 235 mL may be collected within 8 weeks.

12.4.1.10 Risks of Imaging

CT, PET, and/ or MRI scans may be used to monitor a participant's disease on this study. MRI scans can be claustrophobic. CT and PET scans expose a participant to radiation; the amount depends on the number of body areas scanned. In addition, CT, PET, and MRI scans involve use of contrast (oral and/or IV). An IV line may need to be inserted for administration of the contrast agent and can cause pain at the site where the IV is placed. There is also a small risk of bruising or infection. If a contrast agent is given with the scan, there is a small risk of having a reaction to the contrast. In the small group of participants who have a reaction, the most common symptoms are nausea, pain in the vein where the contrast was given, headache, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely, these symptoms may require treatment. In very rare cases, people have had more severe allergic reactions that result in skin rashes, shortness of breath, wheezing, or lowering of the blood pressure.

12.4.1.11 Risks of Radiation Exposure

This study will involve radiation from the following sources:

- Up to 8 CT scans of chest, abdomen pelvis in 1 year
- Up to 8 whole body 18F-FDG PET scans in 1 year
- Up to 2 CT scans for CT-guided biopsies in 1 year

The maximum exposure in one year is 20 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 2.0 out of 100 (2.0%) and of getting a fatal cancer is 1.0 out of 100 (1.0%).

12.4.1.12 Non-Physical Risks of Genetic Research

Risk of receiving unwanted information:

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Participants will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with participant's, family members or health care providers.

Risk related to possibility that information may be released:

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the participants, family members or health care providers, this risk will be included in the informed consent document.

Risk to family or relatives:

Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems. As previously noted, participants will be notified of any medically significant and actionable incidental findings. Study results will not be shared with participants.

12.4.2 Known Potential Benefits

The potential benefits could include shrinking of the tumor or lessening of symptoms, such as pain, that are caused by the cancer. See also Section **1.2.6**. The results may help the investigators learn more about the disease and develop new treatments for participants with this disease.

12.4.3 Assessment of Potential Risks and Benefits

It is possible that treatment on this protocol may reduce cancer burden or lessen symptoms caused by cancer. While treatment on this protocol may not individually benefit participants, the knowledge gained from this study may help others in the future who have this cancer. Potential risks include the possible occurrence of any of a range of side effects listed above.

12.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts, and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the participant will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

NOTE: When required, witness signature will be obtained similarly as described for the investigator and participant as described below.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus, or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at:

https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit

12.5.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.5**

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation

Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil,

criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 VENETOCLAX

14.1.1 Source, Acquisition and Accountability

Venetoclax is a commercially available agent and will be purchased by the CCR and supplied to the Participants enrolled on the study by the NIH Clinical Center Pharmacy Department.

14.1.2 Toxicities

Please refer to the package insert.

14.1.3 Administration Procedures

Venetoclax should be taken with a meal and may be administered with ibrutinib, prednisone, and lenalidomide. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the participant should take the dose as soon as possible and ensure that the minimal interval between the current dose and the next dose is at least 16 hours in order to avoid excessive drug accumulation after the next dose.

Venetoclax will be dispensed to participants in bottles. All doses of venetoclax taken in the clinic or day hospital should be taken from the bottle dispensed to the participant. Unused venetoclax tablets dispensed during previous visits must be returned to the site and drug accountability records must be updated. Returned tablets must not be re-dispensed to anyone. Participants should return all used bottles to the site when they receive new study drug. See also Section **3.2**

14.1.4 Incompatibilities

Venetoclax is a small molecule administered orally and is primarily metabolized by cytochrome P450 3A4 (CYP3A4). Concomitant use of venetoclax and strong inducers or inhibitors of CYP3A is contraindicated (see Sections **4.2** and **4.3**). Please refer to the package insert and PDR for full drug interactions and toxicities.

14.2 IBRUTINIB

14.2.1 Source, Acquisition and Accountability

Ibrutinib is a commercially available agent and will be purchased by the CCR and supplied to the Participants enrolled on the study by the NIH Clinical Center Pharmacy Department.

14.2.2 Toxicities

Please refer to the package insert.

14.2.3 Administration Procedures

Ibrutinib is administered orally with approximately 8 ounces (240 mL) of water. Ibrutinib may be

taken with or without food and may be administered with venetoclax, prednisone, and lenalidomide. Grapefruit or Seville orange juice should be avoided due to CYP3A inhibition. The capsules should be swallowed intact and participants should not attempt to open capsules or dissolve them in water.

If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. No extra capsules to make up missed doses of ibrutinib should be taken. See also Section **3.2**

14.2.4 Incompatibilities

Ibrutinib is a small molecule administered orally and is primarily metabolized by cytochrome P450 3A4 (CYP3A4). Concomitant use of ibrutinib and strong inducers or inhibitors of CYP3A is contraindicated (see Sections **4.2** and **4.3**). Please refer to the package insert and PDR for full drug interactions and toxicities.

14.3 PREDNISONE

14.3.1 Source, Acquisition and Accountability

Prednisone is a commercially available agent and will be purchased by the CCR and supplied to the participants enrolled on the study by the NIH Clinical Center Pharmacy Department. Please refer to the package insert for additional guidance on drug preparation, handling and storage.

14.3.2 Toxicity

The most commonly reported toxicities have included insomnia; mood, appetite, and skin changes; gastrointestinal problems/pain; and headache, dizziness, and redistribution of body fat. Please refer to the package insert for a complete listing of all toxicities.

14.3.3 Administration Procedures

Prednisone will be administered orally per the drug administration schedule in Section **3.2**

14.3.4 Incompatibilities

Please refer to the package insert and PDR for full drug interactions and toxicities.

14.4 OBINUTUZUMAB

14.4.1 Source, Acquisition and Accountability

Obinutuzumab is a commercially available agent and will be purchased by the CCR and supplied to the participants enrolled on the study by the NIH Clinical Center Pharmacy Department.

14.4.2 Administration Procedures

Obinutuzumab will be administered by IV on Days 1 and 2 of each 21-day treatment cycle (Cycles 1–6). Premedication will be used to reduce the risk of infusion related reactions (IRRs) as outlined in Section **3.2**, prior to the obinutuzumab infusion.

Hypotension may occur during obinutuzumab IV infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each obinutuzumab infusion, and for the first hour after administration.

14.4.3 Incompatibilities

No formal drug interaction studies have been performed with obinutuzumab. Please refer to the package insert and PDR for full drug interactions and toxicities.

14.5 LENALIDOMIDE

14.5.1 Source, Acquisition and Accountability

Lenalidomide is a commercially available agent and will be purchased by the CCR and supplied to the Participants enrolled on the study by the NIH Clinical Center Pharmacy Department.

Lenalidomide will be provided in accordance with the Revlimid REMS™ program of Celgene Corporation. Per standard Revlimid REMS™ requirements, all physicians who prescribe lenalidomide for research participants enrolled into this study, and all research participants enrolled into this study, must be registered in, and must comply with all requirements of the Revlimid REMS™ program.

Further information about the Revlimid REMS™ program is available at www.celgeneriskmanagement.com.

Drug will be shipped on a per participant basis by the contract pharmacy to the clinic site for IND studies.

NOTE: Prescriptions must be filled within 7 days for individuals of childbearing potential and within 14 days for all other risk categories. Only enough lenalidomide for one cycle of therapy will be supplied to the participant each cycle, unless otherwise agreed to by the investigator/Celgene in advance.

14.5.2 Toxicities

Please refer to the package insert.

14.5.3 Administration procedures

Lenalidomide should be taken orally at about the same time each day. The capsules should not be opened, broken, or chewed. Lenalidomide capsules should be swallowed whole, preferably with water, either with or without food, and may be administered with venetoclax, ibrutinib and prednisone.

Individuals of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

If less than 12 hours has elapsed since missing a dose, the participant can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the participant should not take the dose, but take the next dose at the normal time on the following day. Do not take 2 doses at the same time.

If a Day 1 (of any cycle) is delayed due to scheduling, instruct the participant that lenalidomide dosing should not be initiated until Day 1 assessments can occur.

14.5.4 Incompatibilities

For participants taking digoxin, periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant lenalidomide therapy (please see prescribing

information).

Participants taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies, may have an increased risk of venous thromboembolism (please see prescribing information).

Results from human in vitro studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be participant to P450-based metabolic drug interactions (please see lenalidomide prescribing information).

Please refer to the package insert and PDR for full drug interactions and toxicities.

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16 LIST OF ABBREVIATIONS

Abbreviation	Term
ABC	Activated B-cell
ACAT	Ability to Consent Assessment Team
AE	Adverse Event/Adverse Experience
AESI	Adverse Event/Experience of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AST	Aspartate Aminotransferase
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BTK	Bruton's tyrosine kinase
BTRIS	Biomedical Translational Research Information System
CAP	CT chest, abdomen, and pelvis
CCR	Center for Cancer Research
CDA	Confidential Disclosure Agreement
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central nervous system
CNSL	CNS lymphomas
CONSORT	Consolidated Standards of Reporting Trials
COV	Close-out Visit
CR	Complete Response
CrCl	Creatinine Clearance
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CRADA	Cooperative Research and Development Agreement
CT	Computed Tomography
CTA	Clinical Trials Agreement
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating DNA
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DS	Double strength
DSMB	Data Safety Monitoring Board (DSMB)
DTA	Data Transfer Agreement
EBV	Epstein Barr Virus
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival

Abbreviation	**Term**
EKG	Electrocardiogram
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HCV	Hepatitis C virus
HCVAb	Hepatitis C antibody
HD-MTX	High dose methotrexate
HHS	Health and Human Services
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICD/ICF	Informed Consent Document/Form
ICH	International Council for Harmonisation
IMIDs	Immunomodulatory imide drugs
IMV	Interim Monitoring Visit
IND	Investigational New Drug
IOCBP	Individuals of childbearing potential
IPI	International Prognostic Index
IRB	Institutional Review Board
IRBO	Institutional Review Board Office
IRR	Infusion related reactions
IV	Intravenous
LAR	Legally Authorized Representative
LD	Lactate dehydrogenase
LDH	Lactic dehydrogenase
MBL	Monoclonal B-cell lymphocytosis
MGUS	Monoclonal gammopathy of undetermined significance
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trial (number)
NHL	Non-Hodgkin lymphoma
NIH	National Institutes of Health
OHSRP	Office for Human Subjects Research Protections
OHRP	Office for Human Research Protections
OS	Overall survival

Abbreviation	**Term**
OSRO	Office of Sponsor and Regulatory Oversight
OTT	Oral Targeted Therapy
PCR	Polymerase chain rEACTION
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic
PCNSL	Primary diffuse large B-cell lymphoma of the CNS
PR	Partial Response
PS	Performance Status
PT	Prothrombin time
PTT	Partial thromboplastin time
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAV	Site Assessment Visit
SCNSL	Aggressive B-cell lymphomas with secondary CNS involvement
SIV	Site Initiation Visit
SD	Stable Disease
SOP	Standard Operating Procedure
TEDDI-R	Ibrutinib with temozolomide, etoposide, liposomal doxorubicin, dexamethasone, and rituximab
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
WBRT	Whole brain radiation
WHO	World Health Organization
VIPOR	Venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide
VTE	Venous thromboembolism

17 APPENDICES

17.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

17.2 APPENDIX B: 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:
[38], [39]

17.3 APPENDIX C: RISK OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS FOR LENALIDOMIDE

Risks Associated with Pregnancy

The use of lenalidomide in pregnant and nursing individuals has not been studied nor has the effect of lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory Revlimid REMS™ program and be willing and able to comply with the requirements of Revlimid REMS™.

Criteria for individuals of childbearing potential (ICBP)

This protocol defines an individual of childbearing potential as a sexually mature individual who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Individuals of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Individuals NOT of childbearing potential acknowledge that they understand the hazards and necessary precautions associated with the use of lenalidomide
- Individuals who can father children taking lenalidomide acknowledge that they understand that traces of lenalidomide have been found in semen, that they understand the potential teratogenic risk if engaged in sexual activity with an individual of childbearing potential or pregnant individual, and that they understand the need for the use of a condom even if they have had a vasectomy, if engaged in sexual activity with an individual of childbearing potential or pregnant individual.

Contraception

Individuals of childbearing potential (ICBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. ICBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)

  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Condom for individuals who can father children
  - Diaphragm
  - Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in participants with neutropenia.

Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for individuals of childbearing potential, including individuals of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Individuals of Childbearing Potential:

ICBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10–14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The participant may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Individuals Who Can Father Children:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with individuals who are pregnant or of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Individuals of Childbearing Potential:

- ICBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 21 days of lenalidomide treatment, including dose interruptions and then every 21 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 30 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 21 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 30 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the ICBP that they are continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study participant, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a participant misses their period or if their pregnancy test or their menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.

- Individuals of childbearing potential must agree to abstain from nursing during study participation and for at least 28 days after lenalidomide discontinuation.

Individuals Who Can Father Children:

- Must practice complete abstinence or use a condom during sexual contact with individuals who are pregnant or of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of an individual who can father children during study participation, the investigator must be notified immediately.
- Individuals who can father children should not donate semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.

Additional Precautions:

- Participants should be instructed never to give lenalidomide to another person.
- Participants should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused lenalidomide must be returned as instructed through the Revlimid REMS™ program.

17.4 APPENDIX D: STUDY CALENDAR

17.4.1 Screening, Baseline and Treatment

Studies	**Screening**[1]		**Baseline**[2]	**Treatment**		
				D1 Cycles 1-6	**Weekly Each Cycle**	**Response Assessment** Post C1, C3 and C6
Scheduling Window:	≤28 days	≤14 days	≤14 days	≤1 day for C1 ≤3 days for C2-6	±1 day	≤7 days for C1 and C3 ±7 days for C6
Venetoclax				D1-14		
Lenalidomide				D1-14		
Obinutuzumab				D1, D2		
Ibrutinib				D1-14		
Prednisone				D1-7		
Medical History	X					
Interim History				X		
Confirmation of Diagnosis (any time before treatment initiation, may include biopsy)	X					
Physical and ECOG PS	X		X	X		
Vital Signs and Weight	X		X		X	
CBC/diff, platelets	X		X	X	X	
Acute Care Panel, **Mineral** Panel, **Hepatic** Panel	X		X	X	X	
LDH			X		X	
Uric acid			X		X	
Urinalysis			X			
VTE Risk Assessment			X			
PT/ aPTT	X		X			

Studies	**Screening**[1]		**Baseline**[2]	**Treatment**		
				D1 Cycles 1-6	**Weekly Each Cycle**	**Response Assessment** Post C1, C3 and C6
Scheduling Window:	≤28 days	≤14 days	≤14 days	≤1 day for C1 ≤3 days for C2-6	±1 day	≤7 days for C1 and C3 ±7 days for C6
TSH if abnormal T3 and/or T4			X			
Serum or urine HCG (for IOCBP)[3]		X		X		
Revlimid REMS® Registration	X					
HIV antibody, HBsAg, HBsAb, HBcAb, HCV Ab[4]	X			X		
CMV and EBV PCR			X			
TBNK and Quant. IG Panel			X			
MRI brain	X					X
CT scans (C/A/P)[5]	X					X
^{18}F-FDG-PET Scan brain and body[6]	X					X (C6 or suspected CR)
Electrocardiogram		X				
Lumbar puncture/Ommaya tap with CSF Testing to include glucose, protein, cell count/differential, cytology, and flow cytometry[7]		X	X			X (if + at baseline)
Bone marrow biopsy and aspirate [8]			X			X (C6 if + at baseline)
Ophthalmologic Evaluation[9]			X			X (C6 if + at baseline)
Symptoms/Adverse Events Assessment[10]	X		X		X	
Concomitant Medication Review	X		X		X	
Research bloods, saliva/buccal (baseline only), CSF samples (if Ommaya). See Section **5.1.**			X	X		

Studies	Screening[1]		Baseline[2]	Treatment		
				D1 Cycles 1-6	**Weekly Each Cycle**	**Response Assessment** Post C1, C3 and C6
Scheduling Window:	≤28 days	≤14 days	≤14 days	≤1 day for C1 ≤3 days for C2-6	±1 day	≤7 days for C1 and C3 ±7 days for C6
Research Tissues (archival/fresh biopsy)[11]			X			

[1] Screening evaluations should be performed within 28 days of initiation of protocol therapy, with the following exceptions: Confirmation of diagnosis (no time limit); Serum or urine HCG, Electrocardiogram, and Lumbar puncture/Ommaya tap with glucose, protein, cell count/differential, cytology, and flow cytometry (within 14 days). See additional screening requirements in Section **2.2.**

[2] Baseline evaluations should be performed within 14 days of initiation of protocol therapy, with the following exceptions: Urine and/or serum HCG (within 1 day); Bone marrow aspiration and biopsy (within 3 months), and Research samples (within 7 days). Ophthalmologic evaluation may be performed prior to or after initiation of study therapy (±28 days). Any Screening/Baseline tests performed within the specified time frame for start of treatment do not need to be repeated.

[3] Urine and/or serum HCG in participants of childbearing potential (within 14 days prior to initiation of Lenalidomide and again within 24 hours prior to initiation of Lenalidomide). See additional pregnancy testing requirements in Section **3.4.2.**

[4] Patients on HBV prophylaxis will have HBV DNA levels obtained monthly during treatment. See additional information in Section **4.1.2**.

[5] CT scans (C/A/P) are to be performed in restaging only if systemic disease present on baseline CT and/or PET imaging.

[6] PET will be performed at NIH after C6 to confirm CR or may be performed earlier in subjects with suspected CR based on interim imaging. PET body is to be performed in restaging only if systemic disease present on baseline CT and/or PET imaging.

[7] Performed to confirm disease status. Repeat after Cycles 1, 3 and 6 if CSF was positive for disease at baseline and the previous test result was positive. Once CSF cytology and flow cytometry are negative for disease, further CSF testing need not be repeated unless clinically indicated based on symptoms.

[8] To be performed within 3 months prior to starting protocol treatment. In follow-up: repeat after Cycle 6 if bone marrow was positive for disease at baseline.

[9] To be performed ±28 days from protocol treatment initiation. In follow-up: repeat after Cycles 3 and/or 6 if ophthalmologic evaluation was positive for disease at baseline.

[10] Adverse event evaluation begins immediately after the first dose of study drug and continues throughout the treatment/follow-up portion of the study.

[11] Archival and/or Fresh Tissue Biopsy for gene expression profiling, mutational analysis, and DNA/RNA sequencing are optional at both baseline and at disease progression.

17.4.2 End of Treatment and Post-Treatment Follow-Up

Studies	End of Treatment[1] Within 30 days after treatment discontinuation	Disease Progression (PD)[2]	Safety Post-Treatment Follow-Up		Prior to Disease Progression[3] Q 3 months for Year 1, Q 4 months for Year 2, Q 6 months for Year 3, Q 12 months for Years 4-10	Post-Disease Progression Survival Every 3 months for up to 10 years
			Day 14	Day 30		
Scheduling Window:	±7 days	ASAP	±1 days	+7 days	±14 days for Q 3, 4 months, ±21 days for Q 6 months, ±28 days for Q 12 months	±14 days
Interim History	X			X	X	
Physical and ECOG PS	X	X		X	X	
Vital Signs and Weight	X			X	X	
CBC/diff, platelets	X			X	X	
Acute Care Panel, **Mineral** Panel, **Hepatic** Panel	X			X	X	
LDH	X			X	X	
Uric Acid	X			X	X	
Serum or urine HCG (for IOCBP)[4]	X		X	X		
HBV DNA[5]	X			X	X	X
TBNK and Quant. IG Panel	X				X	
MRI brain		X			X	
CT scans (C/A/P)[6]		X			X	
^{18}F-FDG-PET Scan brain and body		X				
Lumbar puncture/Ommaya tap with CSF Testing to include glucose, protein, cell count/differential, cytology, and flow cytometry		X				
Bone marrow biopsy and aspirate		X				

Studies	End of Treatment[1] Within 30 days after treatment discontinuation	Disease Progression (PD)[2]	Safety Post-Treatment Follow-Up		Prior to Disease Progression[3]	Post-Disease Progression
			Day 14	Day 30	Q 3 months for Year 1, Q 4 months for Year 2, Q 6 months for Year 3, Q 12 months for Years 4-10	**Survival** Every 3 months for up to 10 years
Scheduling Window:	±7 days	ASAP	±1 days	+7 days	±14 days for Q 3, 4 months, ±21 days for Q 6 months, ±28 days for Q 12 months	±14 days
Ophthalmologic Evaluation		X				
Symptoms/Adverse Events Assessment[7]	X	X		X		
Concomitant Medication Review	X			X		
Research bloods, saliva/buccal (baseline only), CSF samples (if Ommaya) See Section 5.1.	X	X			X	
Research Tissues (archival/fresh biopsy)[8]		X				
Survival Status						X

[1] To be done within 30 days (±7 days) after treatment discontinuation (i.e., may coincide with the safety follow-up visit). If treatment is discontinued for a reason other than disease progression, assessments should be repeated at the time of progression. If a subject initiates new anti-cancer therapy, assessments should occur before the first dose of the new anti-cancer therapy.

[2] To be done as soon as possible after disease progression is identified. If a subject initiates new anti-cancer therapy, assessments should occur before the first dose of the new anti-cancer therapy.

[3] All post-treatment visit(s) may be completed by remote visit with a member of the study team (e.g., if the subject is not able to return to the NIH CC). Required labs/scans can be obtained by a local provider, with results sent in. A subject may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the investigator. Prior to disease progression, follow-up to occur every 3 months for year 1 (±14 days), every 4 months for year 2 (±14 days), every 6 months for year 3 (±21 days), and then yearly (±28 days) for years 4-10 or until disease progression. After disease progression or starting a new anti-cancer therapy, survival follow-up contact visits should occur every 3 months for a maximum of 10 years post-treatment.

[4] Urine and/or serum HCG in participants of childbearing potential. See additional pregnancy testing requirements in Section 3.4.2

[5] Participants on HBV prophylaxis will have HBV DNA levels obtained for 12 months after the last cycle of therapy per Section 4.1.2.

[6] CT scans (C/A/P) are to be performed in restaging only if systemic disease present on baseline CT and/or PET imaging.

[7] Adverse event evaluation begins immediately after the first dose of study drug and continues throughout the treatment/follow-up portion of the study.

[8] Archival and/or Fresh Tissue Biopsy for gene expression profiling, mutational analysis, and DNA/RNA sequencing are optional at both baseline and at disease progression.