Abbreviated Title: VVIP in R/R NHL
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Title: Phase 1/2 Study of VIP152, Venetoclax, and Prednisone (VVIP) in Relapsed/Refractory Lymphoid Malignancies

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Drug/Device Name:	VIP152	venetoclax	prednisone	Vysis LSI MYC Break Apart Rearrangement Probe Kit
IND/IDE Number:	160533			NSR Device
Sponsor:	Center for Cancer Research, NCI			
Manufacturer:	Vincerx, Inc.	AbbVie Inc	generic	Abbott Molecular Inc.
Supplier:	Vincerx, Inc.	CC Pharmacy	CC Pharmacy	Laboratory of Pathology, NCI

PRÉCIS

Background:

- High unmet medical need for relapsed/refractory non-Hodgkin lymphoma (NHL) after exhausting chemotherapy and/or chemo-immunotherapy regimens
- Targeted therapies aimed at disrupting cell death pathway in hematologic malignancies are emerging and showing significant activity in both the relapsed and first-line settings
- VIP152 is a selective inhibitor of PTEFb/CDK9 and is expected to show efficacy in tumor indications that overexpress MYC and MCL-1. VIP152 monotherapy has demonstrated a mild toxicity profile and preliminary efficacy in Phase 1 studies in advanced cancer
- The combination of VIP152 with venetoclax and prednisone (VVIP) targets major cell-death pathways in lymphoid malignancies (BCL-2 and MCL-1) and may overcome chemo-resistance and/or single drug resistance to venetoclax

Objectives:

- Phase 1: To determine the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), and the safety and toxicity profile of the combination of VIP152 with venetoclax and prednisone (VVIP) in relapsed/refractory lymphoid malignancies
- Phase 2: To determine the complete response (CR) rate of the combination of VIP152 with venetoclax and prednisone (VVIP) in R/R lymphoid malignancies

Eligibility:

- Individuals $\geq$ 18 years of age
- ECOG performance status of ≤ 2
- Histologically or cytologically confirmed relapsed and/or refractory NHL
- Adequate organ function unless dysfunction secondary to disease effect

Design:

- Open-label, single-center, non-randomized Phase 1/2 study
- Phase 1: Standard "3 + 3" design will be used to determine the MTD and RP2D of dose-escalated VIP152 and venetoclax with fixed dose prednisone in relapsed/refractory lymphoid malignancies
- Phase 2: Expansion cohorts of defined aggressive NHL subtypes will be treated at the RP2D to determine the ORR and CR rate in these disease groups
- Up to 24 cycles of combination targeted therapy given in 21-day cycles with the option to stop therapy after 12 cycles if in CR following cycles 6 and/or 12 of therapy.
- To explore all dose levels of VIP152 and venetoclax in combination prednisone (VVIP) in R/R NHL in the Phase 1 study (24 participants max) and to assess the CR rate in 3 defined cohorts of aggressive NHL in a Phase 2 dose expansion (3 cohorts x 29 participants = 87 participants max) at RP2D, the accrual ceiling will be set at 130 participants.

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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

- Phase 1: To determine the MTD, RP2D, and the safety and toxicity profile of the combination of VIP152 with venetoclax and prednisone (VVIP) in relapsed/refractory lymphoid malignancies
- Phase 2: To determine the complete response (CR) rate of the combination of VIP152 with venetoclax and prednisone (VVIP) in R/R lymphoid malignancies

1.1.2 Secondary Objective

- To assess the activity (overall response rate (ORR), time to response [TTR], duration of response [DOR], event-free survival [EFS], progression-free survival [PFS] and overall survival [OS]) of VIP152 in combination with venetoclax and prednisone (VVIP) in relapsed/refractory lymphoid malignancies

1.1.3 Exploratory Objectives

- To assess the ORR and CR rate to VVIP rechallenge in participants who achieve CR, discontinue therapy after 12 cycles and subsequently relapse more than 6 months after initial study drug discontinuation
- To assess circulating tumor DNA (ctDNA) response and correlate with molecular tumor analysis
- To evaluate biomarkers of sensitivity or resistance to VIP152, venetoclax and prednisone
- To assess the pharmacokinetics and pharmacogenomics of VIP152, venetoclax, and prednisone when given in combination

1.2 BACKGROUND AND RATIONALE

1.2.1 Disease background

Relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) remain incurable and represent a high unmet medical need.

1.2.1.1 Diffuse large B-cell lymphoma (DLBCL)

DLBCL is the most common aggressive B-cell non-Hodgkin lymphoma (NHL), accounting for 30–40% of B-cell lymphoma in the United States. Although much progress has been made since the advent of chemoimmunotherapy, patients with relapsed or refractory DLBCL have limited treatment options and an overall poor prognosis.

Based on gene expression profiling (GEP) studies, DLBCL can be classified based on the cell of origin (COO) into two major groups: germinal center B-cell (GCB) subtype, and the activated B-cell (ABC) subtype. Approximately 15%–20% do not fit into these two categories, and therefore, are molecularly unclassifiable. Different immunohistochemistry (IHC) methods are also used to classify DLBCL based on the COO. The most widely used algorithm is based on publication by Hans et al. (1), which evaluates the expression of 3 cellular proteins: CD10, BCL6, and MUM1/IRF4. Using this algorithm, DLBCL is classified as GCB or non-GCB. In general, DLBCL of the non-GCB subtype is associated with an unfavorable outcome when treated with standard R-CHOP chemotherapy regardless of how they are defined.

In addition to the COO, recent genetic and proteomics studies identified a prognostic role for MYC and BCL2 genetic translocations and/or protein co-expression. Approximately 10% of diffuse large B-cell lymphomas (DLBCLs) harbor an MYC oncogene rearrangement (MYC+). MYC rearrangement was associated with significantly worse overall survival, especially for the cases with GCB phenotype (2-4). Earlier studies using fluorescent in situ hybridization (FISH) reported that 7% to 10% of DLBCL harbored MYC, BLC2 and/or BCL6 translocations, and were called "double hit" lymphoma (DHL), or triple hit lymphoma. In the most recent World Health Organization (WHO) revision of lymphoma classification, this category is now recognized as "high grade B-cell lymphoma (HGBCL) with rearrangements of MYC and BCL2 and/or BCL6". The vast majority of the cases of DLBCL with DH genetics are observed in the GCB subtype. The aggressive clinical course and poor response to therapy seen with DHL is in direct contrast to the favorable prognosis typically associated with GCB subtype.

Front-line combination chemo-immunotherapy regimens such as R-CHOP or dose-adjusted EPOCH-R can cure approximately 65-70% of patients with DLBCL (5). Additionally, in a prospective study of dose-adjusted EPOCH-R in patients with *MYC*-rearranged DLBCL or DHL, approximately 71% of patients were cured with front-line DA-EPOCH-R chemo-immunotherapy (6). Standard therapy for relapsed/refractory disease often includes salvage chemotherapy followed by autologous stem cell transplant (ASCT), but less than 20% of patients achieve durable remission with this treatment approach, especially those who have received prior rituximab therapy and those who relapse within 12 months of diagnosis (7). Chemotherapy refractory patients and those with early relapse following ASCT have a dismal prognosis with an ORR and CR rate of 26% and 7%, respectively, to next line of therapy and a median survival of only 6.3 months (8). Anti-CD19 CAR-T therapy has been shown to result in durable remission in approximately 30-40% of these chemotherapy-refractory patients but can be associated with significant cost and

toxicity and is not readily available or accessible for all patients (9, 10). Novel treatment options are desperately needed to improve outcome in these poor-risk patients.

1.2.1.2 Peripheral T-cell lymphoma (PTCL)

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of rare neoplasms counted among the mature T-cell malignancies (TCM), and accounts for 5-10% of all lymphomas. Currently, the World Health Organization (WHO) classification combines mature T- and NK-cell neoplasms under the umbrella term PTCL and the category is composed of 24 different entities, based on the different morphologic, phenotypic, molecular, and clinical features, including disease site (11). Compared with B-cell lymphomas, many types of PTCL develop not in lymph nodes, but in specific extranodal sites such as extranodal NK/T cell lymphoma, nasal type (ENKL) in the nasal cavity, enteropathy-associated T-cell lymphoma (EATL) in the small intestine and hepatosplenic T-cell lymphoma (HSTL) in the liver and spleen. The most common histologic subtype is peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), followed by angioimmunoblastic T-cell lymphoma (AITL) or anaplastic large cell lymphoma (ALCL), either ALK positive (ALK+) or ALK negative (ALK-) and these three types account for about 60% of all cases of PTCLs (12); however, it is still rare and the age-adjusted incidence in the U.S. for PTCL-NOS, AITL and ALCL is 0.30, 0.05 and 0.25 per 100,000 person-years, respectively (13-15).

The presentation of patients with PTCL largely depends on the subtype. PTCL-NOS, AITL, and ALCL often present with generalized lymphadenopathy, and there is also frequent involvement of the skin, gastrointestinal tract, liver, spleen, and bone marrow. In contrast, a number of rare specific subtypes, such as ENKL, HSTL, and EATL, present primarily with extranodal disease, and other subtypes, such as adult T-cell leukemia (ATL) and T prolymphocytic leukemia (T-PLL), may have a leukemic presentation. Advanced stage disease (stages III and IV) is common: PTCL-NOS 69%, AITL 89%, ALK+ALCL 65%, ALK-ALCL 58%, EATL 69%, HSTL 90%.

Although front-line anthracycline-containing chemotherapy can cure approximately 36-60% of patients with ALCL, durable remission with such therapy is achieved in less than 1/3 of patients diagnosed with other subtypes of PTCL (12). In previously untreated CD30+ PTCL, the addition of brentuximab to CHP chemotherapy improved median progression-free survival over CHOP (48.2m vs 20.8m, p=0.0110) and has become a standard up-front treatment approach for CD30+ tumors (16). Although chemotherapy remains the standard front-line treatment for PTCL, a majority of patients will relapse following or are refractory to treatment and require additional therapy.

Since 2009, the U.S. Food and Drug Administration approved several drugs with novel mechanisms of action for the treatment of patients with recurrent PTCL); these included pralatrexate in 2009, brentuximab vedotin (BV) for ALCL in 2011, romidepsin in 2011, and belinostat in 2014. With the exception of BV, all of the approvals were based on response rates without demonstration of survival benefit, even though the response rates were less than 30% and any survival benefit is yet to be demonstrated. MD Anderson Cancer Center retrospectively analyzed 321 patients with PTCL-NOS and AITL and found that the median PFS after pralatrexate and romidepsin as single agents were 3.0 and 2.5 months respectively, which was not significantly different from chemotherapy approach (14). A meta-analysis of available treatments for relapsed/refractory PTCL showed that even though approved, belinostat and pralatrexate have

lower safety than several other regimens (17). New therapeutic approaches with higher efficacy and better safety profile are therefore needed.

1.2.1.3 Disease background summary

In summary, while significant advances in the cure of aggressive B-cell malignancies have occurred in the past decades, R/R DLBCL of above-mentioned COO or molecular subtype and R/R PTCL represent patient populations with highly unmet medical need. Identification of key survival pathways in lymphoid malignancies and development of drugs that target those pathways have resulted in recent therapeutic advances. Whereas chemo-immunotherapy combinations are empirically driven- as cytotoxic drugs do not target specific pathogenetic pathways- mechanistically based combinations of targeted agents will likely further leverage their benefits. Insights into the molecular pathogenesis of these tumor types 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, BCL-XL and MCL-1 expression and gene hypomethylation.

1.2.2 Drug background

1.2.2.1 Venetoclax

Venetoclax (GDC-0199, ABT-199, A-1195425.0, or RO5537382) is a selective, orally bioavailable, small-molecule Bcl-2 family protein inhibitor being developed by AbbVie and Roche/Genentech for oncology and immunology indications. In vitro, venetoclax demonstrated cell-killing activity against patient-derived CLL and acute myeloid leukemia (AML) cells and a variety of lymphoma and leukemia cell lines, including B-cell FL, mantle cell lymphoma (MCL), DLBCL, and multiple myeloma (MM). Venetoclax was especially potent against NHL cell lines expressing high levels of Bcl-2. Leukemia and lymphoma cell lines bearing the t(14;18) translocation were significantly more sensitive to venetoclax than non-mutated lines.

Venetoclax is currently undergoing evaluation in NHL and MM and is approved as monotherapy or in combination with rituximab or obinutuzumab for the treatment of CLL/small lymphocytic lymphoma (SLL) and is approved in combination with azacytidine, decitabine or low-dose cytarabine in older individuals with AML. Rapid reductions of peripheral lymphocytes and lymphoid masses observed after initial dosing with venetoclax has provided support for evaluation of a non-chemotherapy combination treatment regimen as well as for future combinations with myelosuppressive chemotherapy as part of the overall clinical development plan. Venetoclax is also undergoing evaluation in systemic lupus erythematosus.

For detailed information of Venetoclax clinical data please refer to venetoclax prescribing information.

1.2.2.1.1 Safety of Venetoclax

A total of 106 patients with relapsed or refractory NHL were treated with venetoclax 200 to 1200 mg daily in dose-escalation and safety expansion cohorts of a phase 1 study (18). Venetoclax monotherapy was overall well tolerated with no clinical TLS observed and 3 patients with laboratory evidence of TLS only. Treatment-emergent adverse events (AEs) were reported in 103 (97%) patients, most being grade 1-2 in severity. Grade 3-4 AEs occurred in 59 (56%) patients,

most commonly hematologic, including anemia (15%), neutropenia (11%), and thrombocytopenia (9%). Less common grade 3-4 AEs included fatigue (7%), diarrhea (3%), constipation (2%), decreased appetite (1%), cough (1%), back pain (1%), and URI (1%).

1.2.2.1.2 Efficacy of Venetoclax monotherapy

A phase 1 trial of venetoclax monotherapy was performed in 106 patients with relapsed and or refractory NHL. In 34 patients with DLBCL, ORR was 18% with CR rate of 12% and a median PFS of only 1 month (18). Venetoclax 1200 mg daily was determined to be the recommended single-agent dose for future studies in FL and DLBCL, with 800 mg being sufficient to consistently achieve durable response in patients with MCL.

1.2.2.2 VIP152

VIP152, previously known as BAY 1251152, is a potent and selective inhibitor of positive transcription elongation factor b (PTEFb) / cyclin-dependent kinase 9 (CDK9). CDK9 is the key factor regulating eukaryotic messenger ribonucleic acid (mRNA) transcription at the level of elongation. Cyclin-dependent kinases (CDKs) belong to a family of serine / threonine kinases, which associate with an activating cyclin regulatory sub-unit. Cell cycle CDKs (CDK1, CDK2, CDK4, and CDK6) are required for the correct timing and order of the events of the cell division cycle, whereas several non-cell cycle CDKs, including CDK9, have been shown to be involved in gene transcription. De-regulated CDK activity results in loss of cell cycle checkpoint function and increased expression of anti-apoptotic proteins, which has been directly linked to the molecular pathology of cancer. CDK9 has been shown to have several binding partners including cyclin T1, cyclin T2, and cyclin K. CDK9 and cyclin T1 form the PTEFb complex that is essential to mRNA elongation.

Selective PTEFb inhibition is expected to show efficacy in tumor indications, which exhibit increased activity of PTEFb due to upstream alterations or those that are addicted to transcription of short-lived RNAs encoding for anti-apoptotic survival proteins downstream of PTEFb, like MYC, MCL1 (myeloid cell leukemia 1 protein), and CCND1 (cyclin D1). VIP152 has exhibited convincing single agent *in vivo* antitumor efficacy and good tolerability in c-myc amplified models of TNBC and gastric cancer in mice and partial or complete remissions in various models of AML, DLBCL and multiple myeloma (MM) in mice and rats (19). Other inhibitors of CDK9 have shown similar *in vitro* and *in vivo* activity across various ABC and GCB DLBCL cell lines and xenografts as well as in DLBCL cell lines with elevated *MYC* expression (20). Also, non-GCB DLBCL is more commonly associated with high MCL1 expression and frequent co-expression of MCL1 and BCL2 is seen in DLBCL cell lines suggesting that therapeutic strategies that target only one will lead to treatment failure due to compensatory upregulation of the other (21). Based on these data, VIP152 is planned to be developed as an innovative, novel treatment of select solid cancers and hematologic malignancy, which may be dependent on MYC, MCL1, and CCND1. For more information in the preclinical results of VIP152 refer to the IB.

1.2.2.2.1 Safety of VIP152

Safety for VIP152 is based on clinical experience in completed and ongoing studies (22, 23). In Study VNC-152-101, a total of 37 subjects were evaluated at five VIP152 dose levels (5, 10, 15, 22.5, and 30 mg). The MTD for this study was declared as 30 mg; neutropenia was the dose-limiting toxicity. Data for 21 subjects are available at 4 dose levels (5, 10, 20 and 30 mg) in the clinically complete Study 18117. VIP152 was well tolerated, and AEs were relatively mild. No

MTD was determined for Study 18117.

The most commonly reported toxicities were neutropenia and gastrointestinal toxicity. The observed toxicity seen so far has been manageable with anti-emetics and G-CSF. Administration of G-CSF has led to a fast recovery of neutropenia in all treated patients.

Based on the pooled analysis of both studies (VNC-152-101 and 18117), the most commonly reported drug-related treatment-emergent adverse events (>20% of subjects) were nausea (58.6%), vomiting (39.7%) and neutropenia (20.7%). In >10% of subjects, anemia, diarrhea, and fatigue were observed.

In Study VNC-152-101, the most commonly (occurring in >10% of subjects) reported drug-related treatment-emergent adverse event (TEAEs) were nausea (70.3%), vomiting (48.6%) neutropenia (35.1%), fatigue (21.6%), anemia (18.9%), and diarrhea (16.2%). In Study 18117, the most commonly reported drug-related TEAEs (occurring in >10% of subjects) were nausea (38.1%), vomiting (23.8%), and fatigue (14.3%).

To date, no tumor lysis syndrome or cytokine release syndrome has been reported in patients with AML, NHL or solid tumors who have received VIP152. No drug-related deaths have been reported for VIP152 to date.

1.2.3 Preclinical synergy with VIP152 and venetoclax

Preclinical synergy has been demonstrated with another CDK9 inhibitor (BAY 114-3572) which possesses similar selectivity to VIP152 in combination with venetoclax (ABT-199). In this SU-DH-10 cell line xenograft in vivo mouse model, the tumor cells are resistant to venetoclax (ABT-199) alone, while combination with the CDK9 inhibitor (BAY 114-3572), shows complete tumor regression (**Figure 1**).

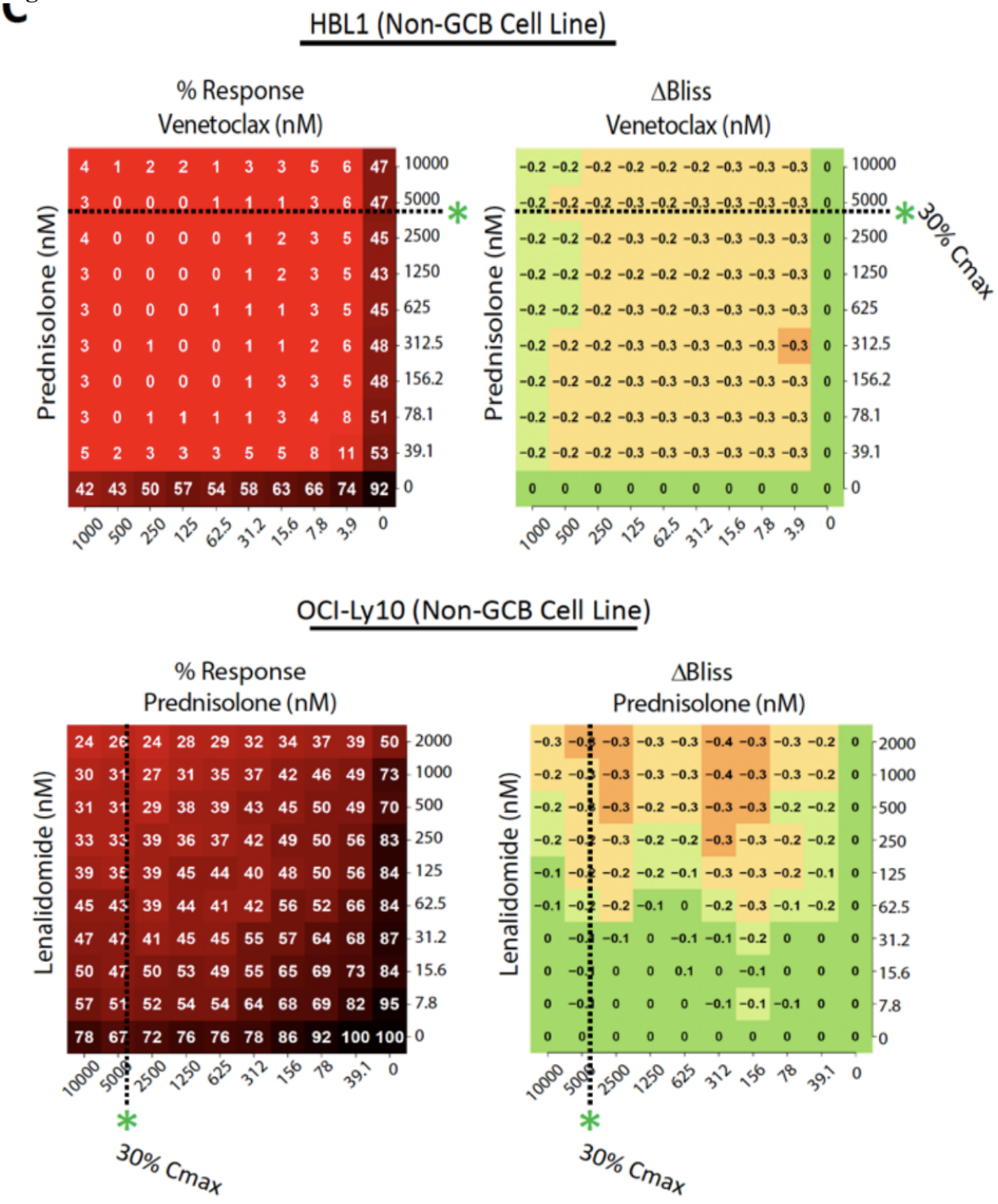
Figure 1

Other inhibitors of CDK9, such as AZD4573, have shown similar *in vitro* and *in vivo* activity with the combination of CDK9 inhibitors with the BCL2 inhibitor ventoclax in DLBCL cell lines and xenograft models (24). Furthermore, inhibition of MCL1 with agents such as AZD5991 in addition to treatment with BH3 mimetics such as venetoclax and navitoclax have also demonstrated *in vitro* and *in vivo* activity across a number of PTCL cell lines and xenografts, suggesting a potential therapeutic benefit for combination therapy simultaneously targeting both pathways (25).

1.2.4 Preclinical synergy with venetoclax and prednisone

Prednisone has been included in this study as well as other combination targeted therapy studies (i.e., ViPOR) as an inducer of genotoxic stress to the lymphoma cells. *In vitro* data in DLBCL cell lines supports this concept showing significant synergy (as measured by %Response or ΔBliss) with the combination of corticosteroids and targeted agents such as venetoclax (**Figure 2**).

Figure 2



1.2.5 Justification of dosing

A major limiting factor for targeted therapy is the need for long-term continuous dosing schedules, which precludes the ability to give multiple agents at once due to overlapping toxicities. Recent

combination targeted therapy studies have utilized an intermittent dosing strategy and/or fixed duration schedule in order to maximize efficacy as well as reduce potential toxicity.

An ongoing phase 1b/2 study of ViPOR (venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide) is being conducted at the NCI with preliminary safety and efficacy demonstrated in patients with relapsed and/or refractory B-cell non-Hodgkin lymphomas (26). A phase I "3+3" design was used to determine the maximum tolerated dose (MTD) of 4 dose-levels (DLs) of dose-escalated venetoclax (200mg, 400mg, 600mg, and 800mg) PO D2-14 (starts cycle 2 for DL1) in combination with fixed-dose ibrutinib 560mg PO D1-14, prednisone 100mg PO D1-7, obinutuzumab 1000mg IV D1-2, and lenalidomide 15mg PO D1-14. A phase II expansion in R/R DLBCL and FL was included at the MTD. Up to 6 cycles of ViPOR every 21-days was given without maintenance or consolidation. A single dose-limiting toxicity (DLT) of G3 intracranial hemorrhage occurred at DL1 with concomitant enoxaparin and ASA. No other DLTs occurred and venetoclax 800mg was used in expansion. Hematologic AEs (% cycles) were most common and included thrombocytopenia (23%), neutropenia (23%) and anemia (7%). G-CSF was used in 92% of pts and 89% of cycles with only 3 (6%) cases of febrile neutropenia. Non-hematologic AEs (% pts) were mainly G1-2 and included diarrhea (67%), hypokalemia (56%), nausea (52%), and rash (42%). Most common G3-4 non-hematologic AEs included hypokalemia (19%), diarrhea (8%), and a.fib/flutter (6%). G4 TLS occurred in 1 patient with HGBCL after the first venetoclax dose and was successfully treated without further TLS upon continued treatment. Dose reductions and delays occurred in only 8% and 9% of cycles, respectively. Tumor reduction occurred in 90% of patients overall with responses observed across all DLs and NHL subtypes. In all evaluable patients, ORR was 70% with 49% CR; including an ORR of 56% with 37% CR in aggressive NHL and an ORR of 94% with 69% CR in indolent NHL. Despite the intermittent, fixed-duration dosing of all study agents, 25 (69%) of 36 responses remained ongoing at the time of presentation.

Venetoclax as monotherapy or in combination with anti-CD20 antibody therapy is FDA-approved for use in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) using a 5-week ramp-up schedule from an initial dose of 20 mg daily to a maximum dose of 400 mg daily. This 5-week ramp-up schedule; however, has been shown to be unnecessary in other lymphoid malignancies with a lower risk of TLS development. The phase Ib/II CAVALLI study assessed the combination of venetoclax with R-CHOP or G-CHOP in patients with B-cell NHL and DLBCL(27). In the dose finding phase I portion of the study, venetoclax at doses ranging from 200 to 800 mg (without initial ramp-up) in 4 cohorts were tested in combination with R-CHOP and G-CHOP and the MTD was not reached and thus 800 mg was taken forward to the phase II portion of the study. Due to greater than expected hematologic toxicity, the continuous daily dosing regimen starting at day 3 was modified after cohort 1 (200 mg of venetoclax) to a non-continuous 10-day dosing schedule using venetoclax (400 mg, 600 mg, and 800 mg) on days 4-10 of cycle 1 and days 1-10 of cycles 2-8.

Given the safety and efficacy shown with time-limited, cyclic dosing of targeted agents as well as fixed venetoclax dosing without ramp-up in several lymphoid malignancies including DLBCL, 2 dose levels of venetoclax (600mg and 800mg) daily given days 1 through 10 in 21-day cycles will be utilized in this phase 1/2 study in combination with VIP152. Weekly dosing of VIP152 in 3 dose levels (15mg, 22.5mg, and 30mg) will be given IV on days 2 and 9 of each 21-day cycle as weekly IV dosing was shown to be safe in the phase 1 monotherapy study (22).

1.2.6 Rationale for combination

Given the pathogenesis and preclinical/clinical data available, we hypothesize that inhibiting multiple pathogenic survival pathways will leverage the efficacy of targeted agents in lymphoid malignancies and may overcome single agent resistance of BH3 mimetics. Combining venetoclax and VIP152 may provide a chemotherapy-sparing option to patients with certain lymphoid malignancies. Strong scientific rationale supports combined treatment with venetoclax and VIP152, as the two agents may have complementary activity that target different cellular proteins expressed on malignant lymphoid cells. Both agents have demonstrated potent reductions of malignant B cells after single- agent administration in early phase clinical studies in R/R DLBCL.

Venetoclax has been associated with laboratory and clinical TLS, as well as neutropenia and thrombocytopenia. VIP152, in early phase 1 studies, has been associated with neutropenia. Such cell-killing effects are familiar to oncologists, and intensive management measures have been incorporated into the combination studies, including prophylactic treatment to prevent or reduce the severity of effects, adjustment of initial dose and schedule, and careful monitoring. In this combination study, prednisone will be given as another mechanism of genotoxic stress and granulocyte-colony-stimulating factor (G-CSF) will be included to mitigate the overlapping risk of neutropenia. Also, a major limiting factor for targeted therapy is the need for long-term continuous dosing schedules, which will likely preclude the ability to give multiple agents at once. Thus, intermittent dosing will almost certainly be necessary. Indeed, if these targeted agents undermine multiple essential survival mechanisms in the tumor cells and retard the emergence of resistance, combination targeted treatment may significantly improve the outcome of lymphoid malignancies.

The overlapping toxicities of the regimen include hematologic toxicity, mainly neutropenia, and GI toxicity (i.e., nausea, vomiting, and diarrhea). These toxicities in monotherapy studies have generally been mild and manageable with G-CSF as well as anti-emetics and anti-diarrheals. As this is a phase 1/2 study, the safety of the combination is not yet known and is being determined in the current protocol. The safety and toxicities of each individual agent when given as monotherapy is listed above.

Given the rationale and considerations above, we propose a Phase 1/2 study of VIP152 in combination with venetoclax and prednisone (VVIP) in relapsed/refractory lymphoid malignancies. The phase 1 portion of the study includes inter-patient dose escalation of VIP152 at 3 dose levels (15 mg, 22.5 mg and 30 mg) and venetoclax at 2 dose levels (600mg and 800mg) in combination with fixed doses of prednisone in 21-day cycles.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Participants must have a histologically or cytologically confirmed lymphoid malignancy as listed below, confirmed by the Laboratory of Pathology, NCI, as follows:

- R/R MYC-rearranged DLBCL/HGBCL (MYC aberration must be confirmed by NCI Laboratory of Pathology to enroll)
- R/R non-GCB DLBCL without MYC-rearrangement (COO and non-MYC aberration must be confirmed by NCI Laboratory of Pathology to

enroll. COO determination at enrollment will utilize immunohistochemistry and Han's algorithm (28))

- R/R PTCL (PTCL-NOS, PTCL-TFH, follicular TCL, AITL, ATLL, ALK+ ALCL and ALK- ALCL per 2016 WHO classification)

2.1.1.2 Relapsed and/or refractory disease, as defined below:

- Aggressive B-cell lymphoma: relapsed after and/or refractory to at least 2 prior systemic therapies, 1 or more which includes an anthracycline and anti-CD20 targeting agent
- PTCL: relapsed after and/or refractory to at least 2 prior systemic therapies, 1 or more which includes an anthracycline (and a brentuximab vedotin-containing regimen for participants with ALK+ or ALK- ALCL)

2.1.1.3 Must have evaluable disease by clinical exam (i.e., palpable lymphadenopathy, measurable skin lesions, etc.), laboratory assessment (i.e., disease involvement of bone marrow or peripheral blood by morphology, cytology or flow cytometry), and/or imaging (measurable lymph nodes, masses, or bony lesions on CT or MRI and/or evaluable FDG-avid lesions on PET).

NOTE: Lesions that have been irradiated cannot be included in the tumor assessment unless unequivocal tumor progression has been documented in these lesions after radiation therapy.

2.1.1.4 Age ≥18 years

2.1.1.5 ECOG performance status ≤2 (see **Appendix A**).

2.1.1.6 Adequate organ and marrow function as defined below unless dysfunction is secondary to disease:

Absolute neutrophil count*	≥1,000/mcL
Hemoglobin*	≥8 g/dL
Platelets	≥75,000/mcL
INR	≤1.5 X institutional upper limit of normal (ULN) for participants not receiving therapeutic anticoagulation
PTT/aPTT	≤1.5 X institutional ULN normal except if the aPTT is elevated because of a positive Lupus Anticoagulant
Total bilirubin**	≤1.5 X institutional ULN (or ≤3 X institutional ULN for participants with documented Gilberts syndrome)
AST(SGOT)/ALT(SGPT)***	≤2.5 X institutional ULN
Serum creatinine	≤ 2.0 mg/dL
OR	
Creatinine clearance****	≥40 mL/min/1.73 m^2 for participants with creatinine levels above 2 mg/dL
Cr Cl will be calculated with the use of the 24-hour creatinine clearance or modified Cockcroft-Gault equation (eCCR; with the use of ideal body mass [IBM] instead of mass): $\frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine (mg/dL)}}$	
*RBC transfusions and use of G-CSF will be allowed in order to meet eligibility parameters.	

**Total bilirubin must be ≤3 X institutional ULN for eligibility even if secondary to disease. ***AST(SGOT)/ALT(SGPT) must be ≤5 X institutional ULN for eligibility even if secondary to disease. ****Creatinine clearance must be ≥30 mL/min for eligibility even if secondary to disease.

2.1.1.7 Negative serum or urine pregnancy test must be obtained within 7 days before the first dose of study drug in individuals of childbearing potential. Postmenopausal individuals as defined below, are allowed to enroll without a pregnancy test:

- Age >50 years with amenorrhea for at least 12 months or
- Age ≤50 years with 6 months of spontaneous amenorrhea and follicle stimulating hormone (FSH) level within postmenopausal range (>40 mIU/mL) OR
- Permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, uterine ablation)

2.1.1.8 Individuals of reproductive potential must agree to use highly effective contraception when sexually active. This applies for the period between signing of the informed consent and 90 days after the last administration of study drug.

Highly effective contraception includes:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of certain intrauterine devices (IUD) or intrauterine systems (IUS)
- Hysterectomy, oophorectomy, salpingectomy or vasectomy of the partner (provided that partner is the sole sexual partner of the individual of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success)

In addition, participants must agree to use condoms.

2.1.1.9 Participants that are positive for hepatitis B core antibody (HBcAb), hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCVAb) must have a negative hepatitis B and/or C viral load by polymerase chain reaction (PCR), and agree to additional monitoring as listed in Section **4.1.7**.

2.1.1.10 Ability of participant to understand and the willingness to sign a written informed consent document.

2.1.1.11 Nursing participants must be willing to discontinue nursing from study treatment initiation through 90 days after the last administration of study drug.

2.1.2 Exclusion Criteria

2.1.2.1 The following restrictions apply to current or prior anti-cancer treatment, prior to the first dose of study drug:

- Participants who are actively receiving any other anti-cancer investigational agents.
- Any chemotherapy, targeted therapy, or anti-cancer antibodies within 2 weeks prior to the first dose of study drug
- Radio- or toxin-immunoconjugates within 10 weeks prior to the first dose of study drug

- Prior allogeneic stem cell (or other organ) transplant within 6 months or any evidence of active graft-versus-host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug
- Not recovered (i.e., ≤ Grade 1 or baseline) from adverse events due to previously administered anti-cancer treatment, surgery, or procedure. **NOTE:** Exceptions to this include events not considered to place the participant at unacceptable risk of participation in the opinion of the PI (e.g., alopecia).

2.1.2.2 Participants requiring the following agents within 14 days or 5 half-lives of the drug (whichever is shorter) prior to the first dose of venetoclax and VIP152 are excluded:

- Strong CYP3A inhibitors (see **Appendix B**)
- Strong CYP3A inducers (see **Appendix B**)
- Moderate CYP3A inhibitors (dose-escalation cohort only)
- Moderate CYP3A inducers (dose-escalation cohort only)

NOTE: Moderate CYP3A inhibitors and inducers should be used with caution (see Section **4.2**) for participants in the dose-expansion cohorts and an alternative medication used, whenever possible.

2.1.2.3 Known allergy to both xanthine oxidase inhibitors and rasburicase; or, known hypersensitivity to any of the study drugs

2.1.2.4 Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 2 weeks prior to first dose of study drug

2.1.2.5 HIV-positive participants

2.1.2.6 Active CMV infection as determined by a positive CMV PCR

2.1.2.7 Active SARs-CoV-2 infection based on PCR assay; prior SARs-CoV-2 infection allowed if completely recovered from infection and negative PCR testing

2.1.2.8 Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis; as well as active infection with HBV or HCV except as noted above in inclusion criteria **2.1.1.9**

- Participants with occult or prior HBV infection (defined as positive hepatitis B surface antigen (HBsAg) or positive hepatitis B core antibody (HBcAb)) may be included if HBV DNA is undetectable (i.e., "none detected" in copies/mL or IU/mL). These individuals must be willing to undergo HBV DNA testing during treatment and in surveillance for at least 12 months after completion of study therapy.
- Participants who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation

2.1.2.9 Malabsorption syndrome or other condition that precludes enteral route of administration

2.1.2.10 History of other active malignancy requiring therapy that could affect compliance with the protocol or interpretation of results

2.1.2.11 Symptomatic congestive heart failure,unstable angina pectoris, or cardiac arrhythmia

2.1.2.12 Left ventricular ejection fraction (LVEF) < 45%

2.1.2.13 Clinically relevant findings on electrocardiogram (ECG) such as a second- or third-degree AV block or prolongation of the QTc interval (Fridericia) over 470 msec (participants with AV block and pacemaker in place for >1 year and checked by a cardiologist within <6 months before the first dose of study drug, will not be excluded).

2.1.2.14 Uncontrolled intercurrent illness (including psychiatric) or social situations that may limit interpretation of results or that could increase risk to the participant

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms. 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.

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, x-ray, 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 the study consent or the consent for study 01-C-0129 (provided the procedure is permitted on that study) on which screening activities may also be performed. 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 unless otherwise specified below.

Assessments and procedures to confirm study eligibility should be completed within 28 days prior to the start of treatment unless otherwise indicated. See also the Section **3.5**, Study Calendar.

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: height (screening only), 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- to assess bone marrow function.
- Chemistry panels including: Acute Care Panel (Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (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 >2.0 mg/dl)- to assess organ function and rule-out active TLS.
- Others: Lactic dehydrogenase (LDH) and Uric acid- to assess tumor burden and rule-out active TLS.
- Coagulation panel, including: PT/INR and aPTT- to assess liver synthetic function and rule out DIC.
- Urinalysis- to rule out active infection and assess for underlying renal dysfunction.
- CMV serology and PCR- to rule out active infection
- SARs-CoV-2 PCR (All COVID testing will be done under an EUA)- to rule out active infection
- HIV 1/2 antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), and Hepatitis C antibody (HCVAb) (within 3 months)- to rule out active infection
    - Participants who are HBsAg positive or HBcAb positive are required to have viral load testing by HBV DNA PCR. If HBV DNA > 100 they are ineligible and should be referred to hepatology for HBV treatment prior to study enrollment. If HBV DNA ≤ 100 they should have repeat testing approximately 1-2 weeks later and if continued positivity should be referred to hepatology for HBV treatment prior to retesting for eligibility (See Section **4.1.7**).
    - Participants who are HCV Ab positive should have viral load check by HCV PCR. If HCV PCR positive they are ineligible and should be referred to hepatology for HCV treatment prior to retesting for eligibility.
- Urine and/or serum HCG in individuals of childbearing potential. **Note:** Individuals of reproductive potential must agree to use highly effective contraception when sexually active. These methods should be documented in source documents. The investigator or a designated associate is requested to advise the participant on how to achieve highly effective birth control- to rule out active pregnancy
- PTCL cohort only: T-cell receptor gene rearrangement (peripheral blood),

HTLV-I serology- to diagnosis PTCL

2.2.2.3 Imaging Studies

NOTE: Results from NIH only.

- CT neck, chest, abdomen and pelvis (with IV and PO contrast unless contraindicated)
  - Lesions in other anatomic locations or locations that are not well visualized by the above listed CT may be measured at baseline by an alternative CT and/or MRI instead and should continue to be measured by CT and/or MRI until disease progression.
  - In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis and CT of the chest and neck without contrast. In this case, neck nodes cannot be used as target lesions.
- PET Imaging (i.e., whole body ^{18}F-FDG PET/CT)

2.2.2.4 Other Assessments and Procedures

- Pathologic review of archival sample for confirmation of diagnosis by Laboratory of Pathology, NCI (any time prior to enrollment). If the sample is not available, and there is an accessible tumor, a biopsy will be done to confirm the diagnosis.
- Electrocardiogram (EKG)
- ECHO for LVEF determination

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://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions.

2.3.1 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently treated on the protocol. 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, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a transient underlying condition not related to the condition under study may be rescreened once after the underlying condition has resolved.

2.3.2 Treatment Assignment and Randomization/Stratification Procedures

2.3.2.1 Cohorts

Number	Name	Description
1	Phase 1-Dose Escalation	Participants with either R/R MYC-rearranged DLBCL/HGBCL, R/R non-GCB DLBCL (no MYC rearrangement) and/or R/R PTCL

Number	Name	Description
2	Phase 2- R/R MYC-rearranged DLBCL/HGBCL	Participants with R/R MYC-rearranged DLBCL/HGBCL for Phase 2 dose expansion
3	Phase 2-R/R non-GCB DLBCL	Participants with R/R non-GCB DLBCL (no MYC-rearrangement) for Phase 2 dose expansion
4	Phase 2-R/R PTCL	Participants with R/R PTCL for Phase 2 dose expansion

2.3.2.2 Arms

Number	Name	Description
1	Phase 1: Arm 1 – Dose Escalation	VVIP-VIP152 and venetoclax at escalating doses with prednisone at fixed doses to determine the MTD and RP2D of VIP152 and venetoclax
2	Phase 2: Arm 2 – Dose Expansion	VVIP- VIP152 and venetoclax at the RP2D with prednisone at fixed doses

2.3.2.3 Treatment Assignment

Participants in cohort 1 will be directly assigned to Arm 1. Participants in cohorts 2, 3, and 4 will be directly assigned to arm 2.

2.4 BASELINE EVALUATION

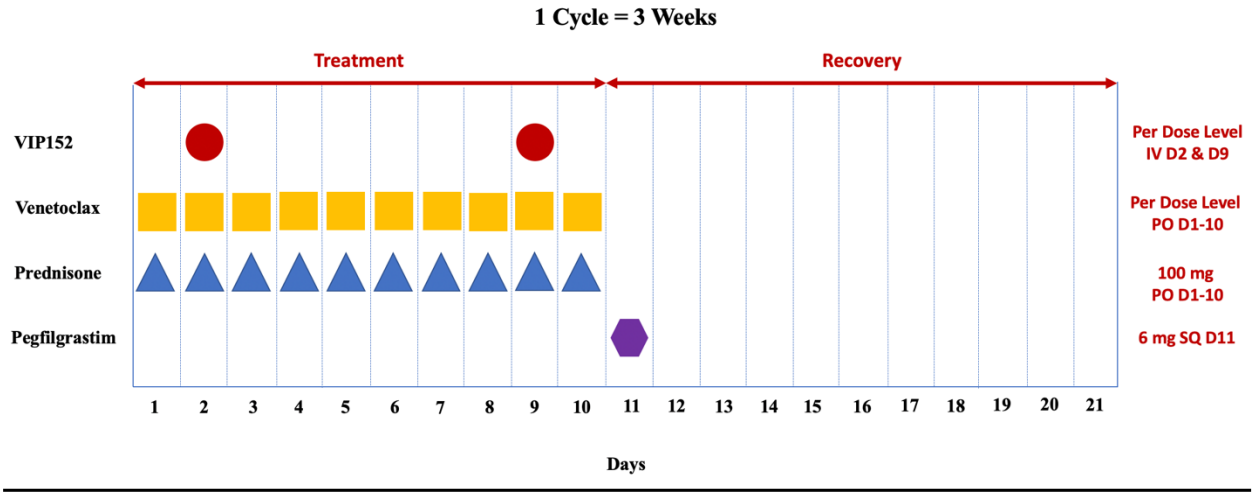
The baseline evaluations should be performed within 28 days prior to the first dose of study drug unless otherwise noted; tests performed as part of screening do not need to be repeated if they were performed within the specified window. **NOTE:** See Study Calendar, Section **3.5** for details and tests required within 7 days of first dose of study drug.

It should be noted that some participants are admitted prior to the initiation of the first dose of venetoclax for prophylaxis for TLS (Section **4.1.3**). In the event that labs are repeated after initiation of TLS prophylaxis and prior to drug, and any value(s) falls outside of the eligibility criteria (e.g., dilutional changes from hydration for TLS prophylaxis, etc.), the participant may still initiate treatment if it is determined that the change in value(s) is related to this intervention and documented in the records by the investigator.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

To determine the MTD, RP2D, and the safety and toxicity profile of VIP152 and venetoclax in combination with prednisone (VVIP) in relapsed/refractory NHL, a standard "3 + 3" design will be used to determine the MTD and RP2D of dose-escalated VIP152 and venetoclax with fixed dose prednisone in the phase 1 portion of the study. Phase 2 expansion cohorts of participants with relapsed/refractory aggressive NHL (3 different subgroups) will be treated at the RP2D for a further assessment of safety and efficacy. Transition from phase 1 to phase 2 will occur after interim analysis as described in section **10.4.6.1**.



Combination targeted therapy will be given in cycles every 21 days:

- VIP152 dose escalation in 3 dose levels (DL) IV on day 2 and day 9 (see dose levels below)
- Venetoclax dose escalation in 2 dose levels (DL) by mouth daily days 1-10 (see dose levels below)
- Prednisone 100 mg by mouth daily days 1-10
- Pegfilgrastim 6 mg SQ one time dose on day 11

Study treatment will continue as long as:

- Participant is deriving clinical benefit (complete remission [CR], partial remission [PR], or stable disease [SD]) and
- Participant is not experiencing any unacceptable toxicity

It is anticipated that treatment will be given primarily on an outpatient basis; however, treatment may be initiated as inpatient in participants at high-risk of tumor lysis syndrome (TLS). See section **4.1.3** for details. Treatment may also be given on an inpatient basis for other reasons as clearly documented in the medical record (e.g., pre-planned decision for increased participant monitoring/follow-up, participant/scheduling convenience, etc.); see also Section **8.1.2.**

Restaging CT scans will be performed after cycles 1 and 2 of therapy and then every other cycle as an early assessment of disease response to combination therapy. Full disease restaging with CT, FDG-PET and bone marrow (as clinically indicated) will be performed following cycles 6 and 12 of study therapy. Participants who achieve CR will stop study therapy after completion of cycle 12 and will enter follow-up. These participants may be rechallenged with study therapy if relapse occurs ≥ 6 months after stopping study therapy (see Section **3.2.3**). Participants who do not achieve such responses will continue therapy until disease progression (PD), unacceptable toxicity, or a maximum of 24 total cycles of therapy.

3.1.1 Dose Limiting Toxicity

A DLT (dose-limiting toxicity) is defined as a grade 3 or higher adverse event (AE) that occurs in the dose-escalation cohort within the first 22 days after initiation of VVIP (i.e., Cycle 1, Day 1

to Cycle 2, Day 1 pre-dose) and is considered related to study drug (i.e., VIP152, venetoclax, and/or prednisone) or a treatment delay of cycle 2 of > 7 days for hematologic or non-hematologic toxicities with the following exceptions:

3.1.1.1 Non-Hematologic DLT exceptions to above definition

- Grade 3 nausea with maximum medical supportive care and persisting ≤ 7 days
- Grade 3 vomiting or diarrhea if the participant does not require total parenteral nutrition (TPN) or tube feeding, and the toxicity improves to < grade 3 within 72 hours
- Grade 3 fatigue persisting ≤ 7 days
- Grade 3 fever or infection
- Grade 3 rash or dry skin with maximum medical supportive care and persisting ≤ 7 days
- Grade 3 hypo- or hypernatremia, hypo- or hyperkalemia, hypo- or hypercalcemia, hypo- or hypermagnesemia, and/or hypo- or hyperphosphatemia that improves to < grade 3 within ≤ 7 days
- Grade 3 atrial fibrillation that is adequately controlled with medical management

3.1.1.2 Hematologic DLT exceptions to above definition:

- Grade 3 febrile neutropenia (ANC <1000/mm^3 with a temperature of >38.3°C [single] or ≥38°C [sustained ≥1 hour]) that is uncomplicated and not associated with infection
- Grade 3 neutropenia (ANC <1000/mm^3) with maximal G-CSF use persisting for ≤ 7 days
- Grade 4 neutropenia (ANC <500/mm^3) with maximal G-CSF use persisting for ≤ 7 days
- Grade 4 thrombocytopenia (<25,000/mm^3) persisting for ≤ 7 days and not associated with grade 2 or greater bleeding
- Grade 3 thrombocytopenia not associated with grade 2 or greater bleeding
- Grade 3 anemia persisting for ≤ 7 days

3.1.2 Dose Escalation

Dose escalation of VIP152 and venetoclax with fixed doses of prednisone will proceed in cohorts of 3–6 participants at each dose level. The MTD is the dose level at which no more than 1 of up to 6 participants experience DLT during the DLT evaluation window(s), or the dose below that at which at least 2 (of ≤6) participants have DLT. If a participant did not experience a DLT and did not finish treatment during the DLT window, he or she will not be evaluable for toxicity and will be replaced in that dose level.

No new participants will initiate study treatment at the next higher (or lower) dose level until the required number of participants have completed DLT evaluation.

Each dose-escalation or de-escalation decision will be documented in the study file.

The report including the supporting safety data and delineation of each criteria met, with the dose-escalation/de-escalation decisions will be provided to the Sponsor by email

(OSROSafety@nih.gov) before additional participants will be enrolled onto the study. Sponsor approval will be required prior to continued enrolllment of participants on study. The Dose Escalation Determination form on the sponsor website: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions may be used for this purpose. The reports will be shared with the DSMB.

Dose level 4 (VIP152 given at 30 mg IV weekly and Venetoclax 800 mg by mouth daily days 1-10) is the RP2D based on a Phase 1 monotherapy studies in advanced cancers (lymphoma and solid tumors) and is the maximum administered dose (MAD) in this study. If in dose level 4, DLTs occur in <33% of the participants, then the MTD will not be identified. In that case, the MAD of VIP152 at 30 mg IV and Venetoclax 800mg PO from dose level 4 will be used for further study as RP2D for this combination therapy.

NOTE: The dose of VIP152 and venetoclax selected for further evaluation may not be the MTD identified in the dose-escalation portion of the trial. The RP2D evaluated in the dose-expansion phase will be the dose or doses showing a maximal efficacy potential and minimal toxicity potential.

Table 1: VIP152 dose escalation

Dose Level	Dose of VIP152	Dose of Venetoclax
1	15 mg IV on day 2 and day 9	600 mg PO daily days 1-10
2	22.5 mg IV on day 2 and day 9	600 mg PO daily days 1-10
3	30 mg IV on day 2 and day 9	600 mg PO daily days 1-10
4	30 mg IV on day 2 and day 9	800 mg PO daily days 1-10

Table 2: **Dose escalation rules**

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter up to 3 participants at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter up to 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group experience DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.

≤1 out of 6	This is the MTD and is generally the recommended Phase 2 dose. At least 6 participants must be entered at the recommended Phase 2 dose. **NOTE:** If ≤1 out of 6 participants with DLT occurs at DL4, the MTD will not have been identified and DL4 will be declared the MAD for further study.

Participants will be monitored through all cycles of treatment for related toxicities. Dose-limiting toxicities are defined in Section **3.1.1**

3.2 DRUG ADMINISTRATION

3.2.1 All Cycles

- Venetoclax per specified dose level by mouth daily days 1-10[a]
- VIP152 per specified dose level IV days 2 and 9
- Prednisone 100mg by mouth daily days 1-10
- Pegfilgrastim 6mg SQ on time dose on day 11[b] as supportive care

[a]Venetoclax tablets should be taken orally once daily with a meal and water. Do not chew, crush, or break tablets.
[b]Pegfilgrastim may be self-administered by the participant.

Participants will be asked to complete and return a drug diary as a memory aid to help document the date and time of all self-administered study drugs. This drug diary as well as study drug containers and any unused study drug should be returned to the research team at the end of each cycle of therapy. Study drug accountability will be assessed per CCR SOP #PM-8 f.

3.2.2 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 ≥ 1,000/μL and
- Platelet count ≥ 50,000/μL and
- No study drug-related ≥ Grade 3 toxicity

If the criteria are not met, per investigator's discretion, assessments may be repeated. The initiation of a new cycle of study therapy should be delayed until participant meets criteria to receive study drug as planned.

3.2.3 Discontinuation of Treatment after CR

Participants who attain a CR following cycles 6 and/or 12 of study therapy will discontinue VVIP after completing 12 cycles of treatment. Participants who later experience disease relapse/progression ≥6 months following discontinuation of study therapy will be eligible for retreatment with VVIP if no additional cancer treatment was administered since the last dose of study therapy, the participant meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Participants will resume therapy at the same dose level and schedule that they were receiving at the time of initial treatment discontinuation and may receive up to a maximum of 12 additional cycles of study therapy (i.e., 24 cycles total). Participants who fail to achieve CR following cycles 6 and/or 12 of study therapy will continue VVIP therapy without interruption for up to a maximum of 24 total cycles of therapy.

3.3 DOSE MODIFICATIONS

The following sections detail dose modifications guidelines for VIP152 and venetoclax based on documented toxicity. Dose modifications of prednisone will not be permitted. In general if overlapping toxicities occur with unclear attribution to study agent, dose reductions of venetoclax will be performed first with dose reductions of VIP152 performed second for recurrent toxicity. Recurrent toxicities or toxicities that are prolonged or severe may require dose modification of both study agents as applicable.

3.3.1 Exceptions During DLT Evaluation Windows

In general, dose modifications should follow the schedule and guidelines below with the exception of the DLT evaluation window. Dose modifications of VIP152 and venetoclax should be avoided during the DLT evaluation window (i.e., Cycle 1) in order to allow identification of toxicities during the dose escalation phase (phase 1). A participant who experiences a DLT should be removed from protocol therapy (see Section **3.7.1**) but will remain on study for all follow-up visits (safety, progression and survival).

In the case of an event otherwise meeting the DLT definition but occurring outside of the DLT window or any non-DLT that would require a dose modification, the offending drug(s) should be held for the remainder of the DLT evaluation window and consideration given to restarting it with dose modification in the next cycle.

3.3.2 Dose Modifications for VIP152

Every effort should be made to administer study intervention on the planned dose and schedule in the dose escalation cohort (phase 1). When clinically significant study intervention related toxicities are observed, appropriate and optimal treatment of the toxicity is assumed prior to considering dose modification as per Tables 4-7 below. For all treatment-emergent adverse events (TEAEs) the NCI CTCAE v5.0 will be used to assess the severity of TEAEs.

The principles of the assessment of causal relationship between the adverse events and study drug are listed in Section **12.3** and **8.1.5**. If a participant experiences a TEAE that requires dose delay or modification, the next dose of VIP152 may be delayed for up to 21 days. If treatment is delayed for more than 21 days (except for hepatitis B reactivation), the participant should be withdrawn from study treatment. Dose will not be re-escalated to the original dose level after reduction for toxicity. **Table 3** assumes 30 mg weekly IV is identified as the MTD/RP2D. If MTD/RP2D is identified as 22.5 mg, then the next lower dose (when "decrease 1 dose level" is called for) would be 15 mg.

Table 3: Scheme for dose reduction of VIP152

Dose Reduction	Action
0	30 mg as a 30-minute IV infusion on day 2 and 9 of each cycle[a]
1	22.5 mg as a 30-minute IV infusion on day 2 and 9 of each cycle[a]
2	15.0 mg as a 30-minute IV infusion on day 2 and 9 of each cycle[a]
3	Discontinue study drug permanently

[a]The dose will not be re-escalated after reduction for toxicity. If more than 2 dose reductions are required, study drug will be discontinued permanently

Table 4: Platelet Criteria for dose delay and dose modification

Grade	Platelets ($x10^9$/L)	Dose Delay	Dose Modification
0 - 2	≥50	Treat on time	No change
3 ≥7 days or with ≥G3 bleeding	<50 – 25	Delay[a] until ≤ Grade 2 or baseline before treatment	Decrease 1 dose level[b]
4	<25	Delay[a] until ≤ Grade 2 or baseline before treatment	Decrease 1 dose level[b]

[a]If no recovery to Grade ≤2 after 21 days delay, VIP152 treatment will be discontinued

[b]Dose will not be re-escalated to original dose level after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

Table 5: ANC criteria for dose delay and dose modification

Grade	ANC ($x10^9$/L)	G-CSF/ Dose delay	Dose modification
0 - 2	>1.0	No additional G-CSF required; Treat on time	No change
3 ≥7 days	<1.0 - 0.5	Consider additional G-CSF if neutropenia persists ≥3 days; Delay VIP152[a] until Grade ≤2 or baseline before treatment	No change[b] If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of VIP152. Decisions must be made in consultation with and with approval of the Principal Investigator.
3 with fever ≥38.5ºC and / or infection	<1.0 -0.5	Consider additional G-CSF if neutropenia persists ≥3 days; Delay VIP152[a] until Grade ≤2 or baseline before treatment	First occurrence: No change[b] Second occurrence: Decrease 1 dose level Third occurrence: Decrease 2 dose levels[c] If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of VIP152. Decisions must be made in consultation with and with approval of the Principal Investigator.
4 ≥7 days	<0.5	Consider additional G-CSF if neutropenia persists ≥3 days;	First occurrence: Decrease 1 dose level Second occurrence:

Grade	ANC ($x10^9$/L)	G-CSF/ Dose delay	Dose modification
		Delay VIP152[a] until Grade ≤2 or baseline before treatment If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of VIP152. Decisions must be made in consultation with and with approval of the Principal Investigator.	Decrease 2 dose levels[c]

ANC = absolute neutrophil count
[a]If no ANC recovery to Grade ≤2 or baseline before treatment after 21 days dose delay: discontinue study treatment.
[b]The option to reduce 1 dose level may be discussed between the investigator and sponsor at any time.
[c]Dose will not be re-escalated to original dose level after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

Table 6: Hematological criteria (except for ANC and platelets) for dose delay and dose modification

Grade	Dose Delay	Dose Modification
0 - 2	Treat on time	No change
3 ≥7 days	Delay[a] until ≤ Grade 2 or baseline before treatment	Decrease 1 dose level[b]
4	Delay[a] until ≤ Grade 2 or baseline before treatment	Decrease 1 dose level[b]

[a]If no recovery to Grade ≤2 after 21 days delay, VIP152 treatment will be discontinued

[b]Dose will not be re-escalated to original dose level after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

Table 7: Non-hematological criteria for dose delay and dose modification

Grade[a]	Dose delay	Dose modification
0 – 2	Treat on time	No change
3	Delay[b] until ≤ Grade 2	Decrease 1 dose level[c]
4	Discontinue study drug permanently	Discontinue study drug permanently

[a]Excludes alopecia, non-refractory nausea / vomiting, and non-refractory diarrhea.
[b]If no recovery to Grade ≤2 after 21 days delay, VIP152 treatment will be discontinued
[c]Dose will not be re-escalated after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

3.3.3 Dose modification for venetoclax

Every effort should be made to administer study intervention on the planned dose and schedule in the dose escalation cohort (phase 1). Sample guidelines for dose delay and/or modification of venetoclax are shown in **Table 8.** Venetoclax dose may be re-escalated (even to the full dose) if resolution of TEAEs occur following initial dose modification. See **Table 9** for the dose levels for venetoclax dose reduction. **Table 9** assumes 800 mg PO daily days 1-10 is identified as the MTD/RP2D. If MTD/RP2D is identified as 600 mg, then the next lower dose (when "decrease 1 dose level" is called for) would be 400 mg.

A dose delay of 21 days is generally permitted for study therapy to allow recovery of hematologic toxicities to Grade ≤ 2 or non-hematologic toxicities to Grade ≤ 1. Actions for recurrent hematologic adverse events are described in **Table 8.** If treatment is delayed for more than 21 days (except for hepatitis B reactivation), the participant should be withdrawn from study treatment. Participants who discontinue all study treatment for adverse events should remain in the study and continue to have disease assessments through progression and standard follow-up.

Dose-modification guidelines should be evaluated and revised, as appropriate, based on the risk associated with the regimen employed.

Table 8: Guidelines for Dose Delay or Modification of Venetoclax

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 further doses of venetoclax. • Consider additional G-CSF if neutropenia persists ≥3 days. -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, further dose reduction of venetoclax and consideration of drug discontinuation will be considered. • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of venetoclax. Decisions must be made in consultation with and with approval of the Principal Investigator.
Febrile neutropenia or neutropenia with infection	• Hold further doses of venetoclax until resolution.

Event(s)	Dose Delay or Modification
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 further doses of 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, further dose reduction of venetoclax and consideration of drug discontinuation will be considered. • If the participant had baseline thrombocytopenia and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of venetoclax. Decisions must be made in consultation with and with approval of the Principal Investigator.
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay.
Any other Grade 4 toxicity or unmanageable Grade 3 toxicity attributed to venetoclax	• Hold further doses of 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, further dose reduction of venetoclax and consideration of drug discontinuation will be considered.

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.

Table 9: Venetoclax Dose Reduction

Dose Reduction	Venetoclax Dose
0	800 mg
1	600 mg
2	400 mg
3	200 mg
4	Discontinue venetoclax

3.4 On Study Assessments/Evaluations

The following describes all tests and procedures to be conducted on study and during treatment. Assessments will be performed according to the Study Calendar (Section 3.5). **NOTE:** Laboratory results from outside NIH are accepted unless otherwise requested or specified by the investigator due to safety concerns.

3.4.1 Timing of Procedures

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

- **Screening:** Refer to section **2.2**
- **Baseline:** Baseline assessments should be performed within 28 days of initiating 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 until confirmed progression, unacceptable toxicity (those TEAEs that require drug discontinuation as listed in the Dose Modification Section, Section **3.3** and in the DLT criteria, Section **3.1.1**), or any criterion in Section **3.7.1** are met. Aggressive NHL participants who achieve CR following cycles 6 and/or 12 may discontinue therapy after completing 12 cycles (see Section **3.2.3**). Dose administration may be delayed up to 21 days. If treatment is delayed for more than 21 days (except for hepatitis B reactivation), the participant should be withdrawn from study treatment.
- **Treatment Cycles**
  - **Pre-Cycle Assessments:** Assessments are to be performed on Day 1 of each cycle (-7 days for Cycle 1 and for all other cycles -3 days). If any baseline procedures are conducted within the timeframe necessary for Day 1 of Cycle 1 of trial treatment then the assessments scheduled on Cycle 1, Day 1 does not need to be repeated.
  - **All Other On-Cycle Assessment Windows:** A time window of ±1 day (except for Cycle 1 Day 2 PK testing).
- **Disease Progression/ End of Treatment:** When a participant who achieves CR completes all 12 cycles of treatment or for all other participants when meeting any of the other criteria listed in Section **3.7.1**, all applicable activities of the Disease Progression/End of Treatment visit should be performed at the time of discontinuation ± 1 day. Any adverse events which are present at the time of discontinuation should be followed in accordance with the safety requirements outlined in Section **6.1**.
- **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 (Section **3.5**) should still be conducted (or repeated) within the applicable windows. If a decision is made to discontinue treatment, the participant should have a Disease Progression/End of Treatment Visit followed by post-therapy follow-up with tests/assessments completed (or repeated) within the applicable windows.
- **Safety Follow-up visit:** The safety follow-up visit should occur 30 days (-2/+7 days) after the last dose of study drug**.**
- **Long-term Follow-up:** All post-treatment visit(s) may be completed by remote visit (NIH approved remote platform used in compliance with local policy, including HRPP policy 303) with a member of the study team (e.g., if the participant is not able to return to the NIH CC). Required labs/scans can be obtained by a local provider, with results sent in. 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.

- **Prior to Disease Progression**: Participants who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed as per the Study Calendar 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. All required testing is as noted in the Study Calendar. Follow-up will be every 3 months ±14 days for years 1, every 4 months ±14 days for year 2, every 6 months ±21 days for year 3, and every 12 months ±28 days for years 4 and 5. After 5 years of monitoring without disease progression the decision to continue further follow-up imaging, including any assessments and procedures, will be left to the discretion of the investigator.
- **Survival/Post-Disease Progression**: Once participant progress or start use of alternative antineoplastic therapy, they will be contacted approximately every 6 months (± 28 days) from last dose by clinic visit or telephone to assess survival and the use of alternative antineoplastic therapy and stem cell transplant. Participants will be contacted until death, participant withdrawal, lost to follow-up, or study termination, whichever occurs first.

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 to determine eligibility as well as to assess safety.
- Physical exam: review of organ systems, height (at screening only), weight, and vital signs (i.e., temperature, pulse, respirations, blood pressure). After initiation of study drug, symptom-directed physical examinations will be performed. Exam conducted to determine eligibility, assess safety and assess efficacy of study regimen.
- Performance status (ECOG): an assessment of activities of daily living to determine eligibility and clinical benefit; see **Appendix A**
- Laboratory assessments: The following comprises the required tests/analytes per panel. These may be performed 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, Platelet. Performed to determine eligibility and to assess safety of regimen.
  - Acute care panel includes Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR. Performed to determine eligibility and to assess safety of regimen.
  - Hepatic panel includes Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin. Performed to determine eligibility and to assess safety of regimen.

- Mineral panel includes Albumin, Calcium, Magnesium, Phosphorus. Performed to assess safety of regimen.
- LDH, uric acid, total protein – to assess safety of the regimen.
- Urinalysis- to rule out infection and renal dysfunction at baseline.
- 24-hour urine creatinine – performed to determine eligibility if serum creatinine levels high. (Note: CrCl may also be calculated)
- CMV serology and PCR – to establish eligibility and safety (reactivation)
- EBV serology- for safety (reactivation)
- SARs CoV-2 PCR – to determine eligibility
- HIV, HBV and HCV testing – to determine eligibility and to monitor Hep B recurrence during the study in participants that screened positive
- T-cell receptor gene arrangement, HTLV-1 serology (PTLC cohort only) – to determine eligibility
- IL-2Rα (PTLC cohort only)- to determine efficacy
- PT/INR, PTT – to determine eligibility
- Lymphocyte phenotype TBNK- to assess safety
- Pregnancy test: Urine or serum HCG - for individuals of child-bearing potential to determine eligibility, to determine pregnancy status prior to study drug administration and potential fetal drug exposure at safety visit

- Optional tumor biopsy – correlative research studies (see section **5**)
- Bone marrow aspiration and biopsy with flow cytometry – to assess disease status
- EKG, ECHO – to determine eligibility
- CT scans- neck, chest, abdomen and pelvis; may be adjusted to assess additional known sites of disease, as needed, and/or MRI – to determine eligibility and assess disease status Scans during follow up may be performed at other sites. Given that the methodologies and machinery utilized are similar across all laboratories/providers, no significant variability is expected and there is no anticipation that study data will be affected.
- Whole body ^{18}F-FDG PET/CT or as clinically indicated – to determine eligibility and assess disease status
- 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 Section **6.1.**
- Correlative studies: Refer to section **5**

3.4.3 Additional Information

3.4.3.1 Pregnancy Testing

Individuals of childbearing potential (ICBP) must have a pregnancy test prior to day 1 of each cycle.

3.4.3.2 Response Assessments

Tumor response will be assessed by the investigator using the Lugano Classification Response Criteria for NHL (**Appendix D**).

NOTE: For participants who continue on active treatment, refer to the Study Calendar for the imaging to be done as well as for other assessments and testing required at the time of each response assessment, including applicable pre-cycle windows. If a participant stops treatment for any reason other than disease progression, response assessments should still be performed at the similar time frames noted. If restaging imaging is performed per the above schedule and a participant's treatment is then delayed for toxicity, repeat imaging does not need to be performed again prior to the new day 1 of the delayed treatment cycle.

3.4.3.3 Suspected CR

If the investigator suspects CR based on clinical, radiographic and/or laboratory evaluation during treatment, the following procedures are also required to confirm CR:
In NHL participants:

- Imaging by CT or MRI; and PET if applicable (i.e., clinically indicated)
- Bone marrow aspirate and biopsy with flow cytometry (only if biopsy at screening was positive)

3.4.3.4 Disease Progression

At the time of suspected or confirmed disease progression either during or following treatment as part of post-treatment follow-up prior to first disease progression, the following are required:

- Imaging by CT or MRI; and PET if applicable (i.e., clinically indicated)
- Soluble IL-2Rα (PTCL cohort)
- Bone marrow aspirate and biopsy with flow cytometry if applicable (i.e., clinically indicated)

The following assessments should also be performed:

- Symptom-guided clinical assessment with physical exam
- T/B/NK cell count
- Research blood samples (see Section **5**)
- Optional tumor biopsy (if accessible)

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 STUDY CALENDAR

3.5.1 Screening, Baseline, and Treatment

Procedure	**Screening**[1]	**Baseline**[2]	**Treatment Cycle**												
			Cycle 1					Cycle 2				Cycles 3+			
Study Cycle/Day/Time point: *(1 cycle = 21 days)*			1	2	3	9	15	1	2	9	15	1	2	9	15
Scheduling Window (Days)	-28/+0		-7	0	0	±1	±1	-3	0	±1	±1	-3	0	±1	±1
Venetoclax			D1-10					D1-10				D1-10			
Prednisone			D1-10					D1-10				D1-10			
VIP152				X		X			X	X			X	X	
Tissue/Pathologic Review[3]	X														
Medical History	X														
Physical Exam and ECOG PS	X	X	X					X				X			
Vital Signs	X	X	X	X	X	X		X	X	X		X	X	X	
EKG	X														
ECHO	X														
Bone Marrow Aspiration/Biopsy[4]		X										X (post-C6 & C12)			
Symptoms/Adverse Events	X	X	X X												
Concomitant Medications	X	X	X X												
CBC/differential	X	X	X			X	X	X		X	X	X		X	X
Acute Care and Mineral Panels	X	X	X	X	X	X	X	X		X	X	X		X	X
Hepatic Panel	X	X	X			X	X	X		X	X	X		X	X
LDH and Uric acid	X	X	X	X	X	X	X	X		X	X	X		X	X
Total protein		X	X					X				X			
24-hour urine for CrCl if needed per **2.2.2.2**	X														
HIV, Hepatitis B, and Hepatitis C screening (Antibody / Antigen)	X														

Procedure	**Screening**[1]	**Baseline**[2]	**Treatment Cycle**												
			Cycle 1					Cycle 2				Cycles 3+			
Study Cycle/Day/Time point: *(1 cycle = 21 days)*			1	2	3	9	15	1	2	9	15	1	2	9	15
Scheduling Window (Days)	-28/+0		-7	0	0	±1	±1	-3	0	±1	±1	-3	0	±1	±1
Hepatitis B PCR testing (if initial screen positive)	X		prior to each treatment cycle in participants positive for Hepatitis B (See Section **4.1.7**)												
Coagulation Panel (PT/INR, PTT)	X														
T/B/NK Cell Subsets		X	X					X				X			
Soluble IL-2Rα (PTCL only)		X	X					X				X			
Urinalysis	X	X													
EBV PCR		X	X					X				X			
CMV PCR	X		X					X				X			
HTLV-I serology and TCR rearrangement (PTCL only)	X														
SARs-CoV-2	X														
Pregnancy Test	X	X	X					X				X			
Radiologic Imaging (CT/MRI)[5]	X							X				X (pre-odd cycles)			
PET Imaging[6]	X											X (pre-C7 & C13)			
Study Drug Diary[7]			X					X				X			
Biomarker Blood Samples		X	X			X (Day 11)		X				X			
Optional Tumor Tissue/Biopsy[8]		X													
PG Samples/Germline DNA		X													
PK Samples[9]				X	X				X				X (C4)		

NOTE: Additional assessments may be done as clinically indicated.

[1] Screening evaluations should be performed within 28 days, with the following exceptions: Confirmation of diagnosis (no time limit); HIV, Hepatitis B and Hepatitis C testing (within 3 months).
[2] Any Screening/Baseline tests performed within the specified time frame for Cycle 1 Day 1 treatment do not need to be repeated.
[3] Archival tumor tissue will be accessed/reviewed at Screening for confirmation of diagnosis and eligibility (no time limit applies to this review; i.e., may be >28 days).
[4] Repeat bone marrow aspiration and biopsy with flow cytometry in follow-up following C6 and C12 if required to confirm suspected CR (if positive at baseline); otherwise, repeat only if clinically indicated.
[5] CT neck, chest, abdomen and pelvis preferred (with IV and PO contrast unless contraindicated); MRI may be used if modality preferred to assess disease. The same imaging performed at Screening should be performed in follow-up to assess for response, or as clinically indicated; CT neck may be omitted after the baseline scan in participants without neck disease. See Section **2.2.2.3** for additional information. In addition, in case of suspected CR or PD at or between regular visits, see required testing in Sections **3.4.3.3** and **3.4.3.4** , respectively. **NOTE:** The window for pre-cycle imaging assessments is 28 days prior to cycle 1 and 7 days prior to the start of subsequent cycles.
[6] Repeat PET Imaging (i.e., whole body ^{18}F-FDG PET/CT or as clinically indicated) to confirm suspected CR (if positive at baseline) following C6 and C12 and at end-of-treatment; otherwise, repeat only if clinically indicated.
[7] Participants will be given a Study Drug Diary with each cycle to document administration of oral study drugs.
[8] Archival tissue will be accessed for research correlates, if available. Participants may also have an optional fresh tumor biopsy at baseline and at disease progression/recurrence if accessible tumor and acceptable risk. See Section **5.** If a fresh biopsy was taken at screening, then an additional biopsy will not be taken at baseline.
[9] Only select participants will undergo PK testing to ensure a large enough sample size for adequate analysis. Plasma samples collected on C1D2 will be drawn pre-dose and 30 min (+/-15 min), 45 min (+/-15 min), 1- (+/-15 min), 2- (+/-15 min), 4- (+/-15 min), 6- (+/-15 min), 8- (+/-15 min), and 24-hours (+/-15 min) post-study drug dosing. Plasma samples collected on C2D2 and C4D2 will be drawn 30 min (+/-15 min), 45 min (+/-15 min), 2- (+/-15 min), and 4- (+/-15 min) hours post-study drug dosing. See Section **5.1**

3.5.2 End of Treatment and Post-Treatment Follow-Up

Procedure	**Disease Progression/ End of Treatment**		**Post-Treatment Follow-Up**				
		Safety	Follow-Up (Pre-PD) 1st year post EOT	Follow-Up (Pre-PD) 2nd year post EOT	Follow-Up (Pre-PD) 3rd year post EOT	Follow-Up (Pre-PD) 4-5th year post EOT	Survival (Post-PD)
Study Cycle/Day/Time point: *(1 cycle = 21 days)*		30 days	Q 3 months	Q 4 months	Q 6 months	Q 12 months	Q6months
Scheduling Window (Days)	±1 day	-2/+7 days	±14 days	±14 days	±21 days	±21 days	±28 days
Medical History	X						
Physical Exam and ECOG PS	X	X	X	X	X	X	
Vital Signs		X	X	X	X	X	
Bone Marrow Aspiration/Biopsy[1]	X						
Symptoms/Adverse Events	X	X					
Concomitant Medications	X	X	X	X	X	X	
CBC/differential	X	X	X	X	X	X	
Acute Care and Mineral Panels	X	X	X	X	X	X	
Hepatic Panel	X	X	X	X	X	X	
LDH and Uric acid	X	X	X	X	X	X	
Total protein	X	X	X	X	X	X	
Hepatitis B PCR testing (if initial screen positive)	with each scheduled follow-up visit through 12 months after EoT in participants positive for Hepatitis B (See Section **4.1.7)**						
T/B/NK Cell Subsets	X	X	X	X	X	X	
Soluble IL-2Rα (PTCL only)	X	X	X	X	X	X	
Urinalysis		X					
EBV PCR	X	X	X	X	X	X	
CMV PCR	X	X	X	X	X	X	
Pregnancy Test		X					
Radiologic Imaging (CT/MRI)	X		X	X	X	X	
PET Imaging[2]	X						
Biomarker Blood Samples[3]	X		X	X	X	X	
Optional Tumor Tissue/Biopsy	X (at disease progression/recurrence)						
Survival Status[4]							X

[1] Repeat bone marrow aspiration and biopsy with flow cytometry in follow-up following C6 and C12 if required to confirm suspected CR (if positive at baseline); otherwise, repeat only if clinically indicated.

[2] Repeat PET Imaging (i.e., whole body ^{18}F-FDG PET/CT or as clinically indicated) to confirm suspected CR (if positive at baseline) following C6 and C12 and at end-of-treatment; otherwise, repeat only if clinically indicated.
[3] Correlative blood samples (e.g., Streck, red top, and CPT tubes) will be collected at each follow-up visit (pre-PD) and at disease progression/recurrence. See Section 5.
[4] After 5 years of follow-up without disease progression, or upon progression or initiation of alternative antineoplastic therapy, participants will be contacted approximately every 6 months (±28 days) from last dose of study drug(s) by clinic visit or telephone to assess survival, including collection of information regarding additional treatment(s)/interventions. Participants will be contacted until death, participant withdrawal, lost to follow-up, or study termination, whichever occurs first. **NOTE:** Investigators should continue to report serious adverse events that are attributed to the study treatment in follow-up.

3.6 COST AND COMPENSATION

3.6.1 Costs

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 if they are not covered by insurance company. Medicines that are not part of the study treatment will not generally be provided or paid for by the NIH Clinical Center

3.6.2 Compensation

Participants will not be compensated on this study

3.6.3 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.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Every effort must be made to have all participants complete a safety visit approximately 30 (-2/+7) days following the last dose of study therapy.

3.7.1 Criteria forremoval from protocol therapy

Participants who meet the following criteria should be discontinued from protocol therapy:

- Completion of 12 cycles of protocol therapy in those achieving CR (see Section **3.2.3**)
- Completion of 24 cycles of protocol therapy (see Section **3.2.3**)
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Delay of treatment for more than 21 days (except for hepatitis B reactivation), unless it is felt by the Principal Investigator to be in the participant's best interests to remain on study.
- Unacceptable adverse event(s) (see Sections **3.1.1** and **3.3**), unless it is felt by the Principal Investigator to be in the participant's best interests to remain on study (e.g., discontinue offending study agents while continuing others).
- Participant withdrawal of consent at any time
- Noncompliance with trial treatment or procedure requirements in the opinion of the investigator; such a decision/rationale will be clearly noted in the medical record
- Participant requires a prohibited concomitant medication

- Pregnancy
- Investigator's decision to withdraw the participant
- Study is cancelled for any reason

All participants, regardless of reason for discontinuation of study treatment (with the exception of withdrawal of consent; unless consent to follow-up activities is documented) will be followed for progression and survival.

3.7.2 Off-Study Criteria

Participants who meet the following criteria should be discontinued from the study:

- Completed study follow-up period
- Screen failure and/or failure to maintain eligibility (i.e., between enrollment and day 1 of drug) where changes in eligibility parameters are not felt to be study-intervention related (e.g., TLS prophylaxis) and initiation of treatment is not felt to be in the best interests of the participant in the opinion of the investigator (Section **2.4**)
- Participant requests to be withdrawn from study
- Participant is lost to follow-up
- Death
- Study is cancelled for any reason

3.7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return 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 site 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

All concomitant medications (including start / stop dates, total daily dose, and indication) taken 28 days before the first dose and while on study must be recorded in the participant's source documentation as well as in the appropriate pages of the case report form (CRF). This includes also antiemetic therapy and contrast media, which might be administered during assessment of tumor lesions. All concomitant medications should be reported to the investigator.

In general, participants should be closely monitored for side effects of all concomitant medications regardless of elimination pathway, especially those with narrow therapeutic indices, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin.

4.1 PERMITTED THERAPY

4.1.1 Growth Factors

Participants will be monitored for the development of treatment-emergent neutropenia per protocol-specified laboratory testing. Growth factor support is allowed and should follow institutional guidelines and the protocol schedule for the administration of pegfilgrastim. Additional supplementation of long-acting G-CSF (e.g., pegfilgrastim) with short-acting G-CSF (e.g., filgrastim) is permitted for severe or prolonged neutropenia and should be considered for grade 3 of 4 neutropenia that persists for ≥3 days despite receipt of pegfilgrastim.

4.1.2 Prophylaxis of Pneumocystis Jiroveci (Previously Pneumocystis Carinii)

Adult participants should receive prophylaxis for Pneumocystis Jiroveci during study therapy administration. Trimethoprim/sulfamethoxazole 1 DS tablet by mouth on Monday, Wednesday, and Friday is the preferred schedule.

Participants allergic to either component may receive inhaled pentamidine 300 mg once a month or other standard treatments.

Treatment will begin with initiation of study therapy and will be stopped upon completion of study therapy unless continued administration beyond this point is deemed necessary based on inadequate immune reconstitution.

4.1.3 Tumor Lysis Syndrome

TLS is a risk for participants with lymphoid malignancies who are treated with high cell-killing agents, including venetoclax. Participant will be monitored closely for laboratory evidence of tumor lysis syndrome (TLS) prior to and during treatment with venetoclax. Perform tumor burden assessment with CT scan and CBC with WBC differential, assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all participant and correct pre-existing chemistry abnormalities prior to initiation of treatment with venetoclax. Elective admission for fluid hydration, correction of electrolyte abnormalities and closer monitoring is permitted and will not be considered an SAE.

Participant who show laboratory evidence of TLS as determined by elevated uric acid with hyperkalemia, hyperphosphatemia and/or elevated creatinine will be admitted to the hospital for appropriate management with intravenous fluids. Participant will receive prophylaxis as outlined in the guidelines below prior to the first cycle with venetoclax; this can be discontinued during subsequent cycles if there is no clinical or laboratory evidence of TLS as deemed by the investigator. Participant who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per **Appendix C**

Guidelines:

TLS is a risk for participant with lymphoid malignancies who are treated with high cell-killing agents, including venetoclax. Changes in blood chemistries consistent with TLS that require

prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Risk is highest for those with bulky disease, elevated leukocyte count, elevated pre-treatment LDH levels, compromised renal function, and dehydration. Perform tumor burden assessment with CT scan and CBC with WBC differential, assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all participant and correct pre-existing chemistry abnormalities prior to initiation of treatment with venetoclax.

All participants should receive prophylaxis for TLS before the initiation of the first dose of venetoclax. Prophylaxis will include the following:

- Appropriate hydration, consisting of a fluid intake of approximately 2 –3 L/day starting 24-48 hours before the start of treatment
- Administration of an agent to reduce uric acid (standard prophylaxis will involve Allopurinol 600 mg at least 24 hours prior to venetoclax with 300 mg daily for a minimum of the first 10 days of therapy) or rasburicase IV (given at least 24 hours prior to venetoclax for those high-risk participant with elevated uric acid levels before treatment, or when otherwise judged to be appropriate by the investigator) until normalization of serum uric acid and other laboratory evidence of TLS (e.g., elevated serum LDH levels).
- Laboratory results should be reviewed, and electrolyte values should not demonstrate any clinically significant abnormalities before the first dose of venetoclax, or the participant should receive additional prophylactic treatment and hydration before the initiation of dosing.

Guidelines for Hospitalization Due to TLS Risk:

Participant exhibiting specific characteristics at screening or initiation of venetoclax treatment are considered to be at high risk of developing TLS and **should be hospitalized** for more intensive prophylaxis and monitoring for the initial dose of venetoclax. These participants are identified by the presence of any of the following:

- Any lymph mass ≥ 10 cm on the screening CT scan
- Absolute lymphocyte count (ALC) ≥ 25 x 10^9/L AND any lymph mass ≥ 5cm

In addition to high-risk characteristics above, other participant characteristics may suggest an increased risk of TLS. These include, but are not limited to, the following:

- Overall disease burden (e.g., several enlarged lymph nodes, even if none reaching 10 cm)
- Elevated LDH levels
- Compromised renal function, as evidenced by low creatinine clearance < 80 mL/min
- Extensive bone marrow involvement
- Dehydration or concern about inability to meet oral hydration requirements (i.e., approximately 2-3 L/day 24-48 hours prior to and during study therapy)

Hospitalization is not mandatory for participant exhibiting these characteristics, but these and any other factors considered relevant to TLS should be considered in an overall assessment of the participant's state and their risk of TLS. Investigators should use their judgment in assessing TLS

risk for their participant and may optionally hospitalize any participant they consider to be at risk for TLS for closer monitoring; elective admission will not be considered an SAE.

Hospitalization Procedures:

For participants requiring hospitalization, hospitalization will begin 1 day prior to the first dose of venetoclax and continue for a minimum of 24 hours after receiving initial venetoclax dosing. Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of 150–200 cc/hr or as clinically appropriate. Laboratory results should be reviewed, and electrolyte values should not demonstrate clinically significant abnormalities before the first dose of venetoclax; otherwise, the participant should receive additional prophylactic treatment and hydration before the initiation of dosing. A nephrology (or acute dialysis) service should be consulted/contacted on hospital admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

High-risk participants who are hospitalized for TLS monitoring will have serial vital signs and TLS laboratory samples drawn (acute care panel, mineral panel, LDH, uric acid, and CBC with differential) prior to venetoclax dosing as well as 4 hours (+/- 60 min.), 8 hours (+/- 60 min.), 12 hours (+/- 60 min.), and 24 hours (+/- 60 min.) post-dose. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a participant developed a change related to TLS. Laboratory results of the 24-hour post-dose should be reviewed before receiving the dose of venetoclax for that day. Participant who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per **Appendix C.**

4.1.4 Standard Medical Care

Standard medical care for oncology will be provided for all other issues including treatment of neutropenic fever, transfusions of blood and platelets for cytopenias as well as pain, nausea, diarrhea management, etc. Furthermore, participants may receive palliative and supportive care for any underlying illness.

4.1.5 Hormone-Replacement Therapy

Participant who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.1.6 Corticosteroids

Short courses of corticosteroids (≤ 7 days) for non-cancer-related medical reasons (e.g., treatment for rash, arthritis, asthma) or for the prevention or treatment of study drug related side effects (e.g., tumor flare, rash, etc.) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

Participant may receive a brief (≤ 7 days) course of systemic steroids (≤ 100 mg/day prednisone or equivalent) prior to initiation of study therapy for control of lymphoma-related symptoms.

The use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) is also permitted.

4.1.7 Monitoring and Treatment for Hepatitis B Reactivation

Participants who test positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) and not acutely infected are at varying risk for reactivation of Hepatitis B. Participants may be included in the study provided that they have an undetectable HBV DNA level prior to starting therapy.

These participants should be treated with entecavir (or equivalent) during study treatment and for at least 12 months after completion of study treatment to prevent hepatitis B reactivation. These participants should also have HBV DNA levels obtained with each treatment cycle and at each scheduled follow-up visit in surveillance for at least 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 and is $\leq$ 100 IU/mL, the participant should be retested within 1-2 weeks. If the assay is still positive, study treatment must be held, and the participant should be immediately referred to a gastroenterologist or hepatologist for management.

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

4.1.8 Palliative Radiotherapy

Palliative radiotherapy during the study will be allowed for local pain control provided that:

- In the opinion of the investigator, the participant does not have progressive disease
- No more than 10% of the participant's bone marrow is irradiated and
- The radiation field does not encompass a target lesion; radiation to a target lesion is considered progressive disease and the participant should come off study

The safety of VIP152 administered concomitantly to radiation therapy has not been determined. Therefore, VIP152 treatment should be paused during palliative radiotherapy. Discussion with the sponsor is recommended before restarting treatment.

4.1.9 Non-conventional therapies

Treatment with "non-conventional therapies" (such as acupuncture), and vitamin / mineral supplements are permitted if they do not interfere with the study endpoints, in the opinion of the investigator. They must be recorded in the source notes and the CRF.

4.1.10 Other Anti-infective Prophylaxis

Antiviral, antifungal and antibacterial prophylaxis for participants at risk of infections per institutional guidelines are permitted as long as strong inducers or inhibitors of CYP3A are not used (See **Appendix B**).

4.2 CONCOMITANT 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.
- P-gp inhibitors such as ketoconazole, ritonavir, posaconazole, and rifampin and P-gp substrates such as digoxin

4.2.1 CYP3A Inhibitors/Inducers

Venetoclax is metabolized primarily by CYP3A. Avoid co-administration with moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor participant for toxicity and follow dose modification guidance as needed (Section **3.3**). If a moderate CYP3A inhibitor or P-gp inhibitor is used, the dose of venetoclax should be reduced by 50%. The venetoclax dose used prior to concomitant use of the moderate CYP3A inhibitor or P-gp inhibitor may be resumed 2-3 days after discontinuation of the inhibitor. Participants should avoid grapefruit and Seville oranges during treatment, as these contain moderate inhibitors of CYP3A.

Co-administration of venetoclax with strong CYP3A inducers, such as rifampin, is prohibited on study. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort) and consider alternative agents with less CYP3A induction.

Use of moderate CYP3A inducers or inhibitors is prohibited in the phase 1 dose-escalation portion of the study to allow for accurate assessment of DLTs and determination of MTD.

A list of common CYP3A inhibitors or inducers is provided in **Appendix B**; a comprehensive list of inhibitors, inducers, and substrates may be found at:

http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

This website is continually revised and should be checked frequently for updates.

4.2.2 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. Participant 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 work-up may include, but is not limited to, peripheral blood analysis for fungal blood markers and/or bronchoscopy with 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 is prohibited while receiving venetoclax therapy. Azole treatment during the days the participant is not receiving study therapy is permitted as long as enough time is permitted for the azole therapy to be out of the participant's system prior to initiation of the next cycle of study therapy that includes venetoclax. Furthermore, azoles with less

CYP3A inhibition such as isavuconazole may be considered with close monitoring for toxicity and consideration of dose reduction of study medications. Consultation with the infectious disease team as well as pharmacy is recommended to help guide antifungal use in participant being treated on study. Prophylactic antifungals will not be routinely used given the low estimated risk of fungal infections with cyclic, non-continuous dosing of targeted agents and prednisone and significant potential for drug-drug interactions with these antifungal agents.

4.2.3 QT Prolongation

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

4.3 PROHIBITED THERAPY

Participant 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:

- Other investigational treatment or other anticancer therapy (e.g., chemotherapy) while on this protocol
- Immunotherapy
- Hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate)

The following concomitant medications are not allowed from 14 days or 5 half-lives of the drug (whichever is shorter) prior to the first dose of study drugs and during study drug administration:

- Strong CYP3A4 inhibitors
- Strong CYP3A4 inducers
- Moderate CYP3A inhibitors (dose-escalation cohort only)
- Moderate CYP3A inducers (dose-escalation cohort only)

See **Appendix B** for a list of medications that fall into these categories.

4.3.1 Vaccines

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment or at any time during study treatment.

4.3.1.1 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. However, if the subject chooses to receive a COVID-19 vaccination or booster after enrollment, a discussion will be had with the Sponsor Medical Monitor to agree upon a safe and appropriate vaccination strategy in terms of timing and safety.

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 RESEARCH

5.1 BIOSPECIMEN COLLECTION

Samples will be collected for exploratory objectives to evaluate biomarkers of sensitivity or resistance to study therapy. In blood, circulating tumor DNA (ctDNA) response and correlation with molecular tumor analysis is planned in addition to the other analyses described below. In tumor, analyses may include gene expression profiling for DLBCL cell-of-origin and molecular profiling for DLBCL genetic subtype. Molecular characterizations may identify altered signalling patterns or mutations that associate with response or resistance to study treatment.

Sample	Collection Details*	Time Points	Storage and Processing Laboratory/ Laboratory for Analysis
Blood Samples			
ctDNA/cfDNA, Plasma banking	2 x 10 mL Streck/BCT tube	• Baseline/Pre-Cycle 1 • Cycle 1 Day 11 • Day 1 , pre-dose of each subsequent cycle • Follow-up visits (Pre-PD) • Disease Progression/End-of-Treatment	Figg (BPC)/ Staudt/ Adaptive
Cytokines, Serum banking (exploratory-response and ctDNA)	1 x 8-10 mL SST (or red top tube)		
Peripheral blood mononuclear cells (PBMCs)	1 x 8 mL Cell Preparation Tubes (CPTs) (with sodium citrate)		
Pharmacokinetic (PK) Studies	1 x 6 mL NaHep tube 1 x 2 mL EDTA (purple top tube)	• C1D2: pre-VIP152 dose and 30 min (+/-15 min), 45 min (+/-15 min), 1- (+/-15 min), 2- (+/-15 min), 4- (+/-15 min), 6- (+/-15 min, 8- (+/-15 min), and 24-hours (+/-15 min) post-dose • C2D2: 30 min (+/-15 min), 45 min (+/-15 min), 2- (+/-15 min), and 4- (+/-15 min) hours post-VIP152 dose • C4D2: 30 min (+/-15 min), 45 min (+/-15 min), 2- (+/-15 min), and 4- (+/-15 min) hours post-VIP152 dose	Figg (BPC)/ Vincerx

Pharmacogenetic (PG) Studies	1 x 10 mL EDTA (purple top tube)	• Baseline/Pre-Cycle 1	
Tissue Samples			
Archival and/or Fresh Tissue Biopsy	FFPE (block or slides) Excision (single or multiple nodes) or core (4-6 passes); placed in formalin/FFPE and media, frozen, as appropriate	• Archival tissue will be accessed, if available • Baseline* (optional) • Disease progression/ recurrence (optional)	NCI LP/Staudt
Other Samples			
Germline DNA (exploratory – molecular correlates of response)	Blood, Buccal Swab, or Saliva (preferred)	• Baseline/Pre-Cycle 1 preferred	Figg (BPC)/Staudt

*Only to be offered if a fresh biopsy sample was not taken at screening

NOTE:

- Tubes/media may be adjusted at the time of collection based upon materials available. As written above, all blood/ tubes, aside from PK and PG samples, should remain at ambient temperature after collection and until processing. PK and PG samples should be placed on wet ice and refrigerated until processing. Processing windows: Streck tubes are generally stable for at least 7 days until processing; SST/red top tubes, NaHep, EDTA, and CPT tubes should be processed same day, whenever possible.
- Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.

5.2 SAMPLE COLLECTION, PROCESSING AND ANALYSES

5.2.1 Tissue Samples

5.2.1.1 Archival tissue

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

5.2.1.2 Lymph node excision or core needle biopsy procedure

- Participant with accessible tumor tissue who agree to have an optional biopsy performed will be 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 (FF), formalin-fixed, paraffin-embedded (FFPE) tissue, and/or viably frozen single-cell suspension.

- 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.

- **NOTE:** Image-guidance with ultrasound or other non-ionizing radiation methods may be used for tissue acquisition; image-guidance with ionizing radiation techniques (e.g., CT

guidance) may be performed for optional biopsy at baseline and time of progressive disease.

- Studies to be performed on these samples include: Whole-exome sequencing, low-pass whole-genome sequencing, RNA-sequencing and copy-number analysis for determination of molecular and genetic subtype of DLBCL as well as correlation of molecular features of disease to response or resistance to study therapy.

5.2.2 Blood Samples

5.2.2.1 Cell-free DNA (cfDNA)/Circulating Tumor DNA (ctDNA) and plasma banking

- Disposition of samples: send to Figg lab and refer to section **5.3.3** for more details on sample tracking and storage.
- Upon arrival in the BPC, samples will be centrifuged, and the plasma transferred into cryovials for storage at -80ºC until the time of analysis.
- Samples will be processed and stored by BPC until time of analysis.
- Samples will be processed and stored at BPC. Samples will then be sent to Adaptive Biotechnologies where all analyses will be performed. Analyses to be performed on these samples at Adaptive Biotechnologies include: Circulating tumor DNA (ctDNA) for amplification and sequencing of the VDJ segment of the immunoglobulin receptor as well as immunosequencing studies of the T-cell receptor repertoire. Purpose of ctDNA collection is for dynamic monitoring of treatment response during therapy and for active surveillance of disease recurrence during follow-up. Adaptive Biotechnologies will use a proprietary method (i.e., ClonoSEQ) for amplifying and analyzing immunoglobulin receptor sequences, allowing unprecedented sensitivity and specificity.
- Data from experiments conducted by Adaptive Biotechnologies using the human material will be provided to NCI and such data provided by Adaptive Biotechnologies to NCI may be used by NCI for any purpose. Only coded samples will be shared for sample storage and tracking. The samples and data will be sent to Adaptive Biotechnologies at the address listed below:

  Adaptive Biotechnologies Corp.
  1551 Eastlake Ave E
  Suite 200
  Seattle WA 98102

5.2.2.2 Cytokines, ctDNA and serum banking

- Disposition of samples: send to Figg lab and refer to section **5.3.3** for more details on sample tracking and storage.
- Upon arrival in the BPC, samples will be centrifuged, and the serum transferred into cryovials for storage at -80ºC until the time of analysis.
- Samples will be processed and stored by BPC until time of analysis.
- Samples will be processed and stored at BPC. Samples will then be sent to a collaborating lab that has yet to be determined for analyses and will be updated in a future protocol amendment, if required.
- Studies to be performed on these samples include: Cytokine analysis (e.g., IL-6, IL-10, interferon beta, TNF alpha, mutational analysis and storage of peripheral blood.

5.2.2.3 Pharmacokinetic Studies

NOTE: Select participants will undergo pharmacokinetic (PK) testing at timepoint outlined in the table in Section **5.1.** Participant selection for PK testing will depend on ensuring an adequate number of participants with full data points within each dose level to provide a complete PK analysis across all dose levels. The decision as to which participants will undergo such testing will be left to the discretion of the investigator.

NOTE: Timing of PK sample collection: Every effort will be made to collect samples for PK analysis as prescribed in the protocol above. If the timing is not strictly adhered to, it will not be considered a Protocol Deviation.

NaHep tube Processing:

- Put samples immediately on wet ice and refrigerate
- The date and exact time of each blood draw should be recorded on the sample tube and the PK sheet.
- Disposition of samples: send to Figg lab and refer to section **5.3.3** for more details on sample tracking and storage.
- Upon arrival in the BPC, samples will be centrifuged, and the plasma transferred into cryovials for storage at -80ºC until the time of analysis.
- Samples will be processed, stored, and analyzed by BPC.
- Analyses to be performed by BPC: Bioanalytical measurements of venetoclax and prednisone will be conducted on an ultra HPLC-MSMS system using validated assays for each drug developed and validated by the Clinical Pharmacology Program under the direction of Dr. Figg. The measured exposure for each drug assayed will be used to correlate to pharmacodynamic (PD) endpoints, clinical response, toxicity, and pharmacogenetic (PG) analyses. VIP152 plasma concentrations will be assessed by a validated LC/MS/MS assay by Vincerx.

EDTA tube Processing:

- Draw blood into the 2 mL K3EDTA Lavender Top Tube labeled PK (indicating appropriate PK timepoint)
- After filling the tubes, gently invert the tubes eight (8) to ten (10) times.
- Immediately after blood sampling, use aluminum foil to wrap the blood collection tubes to keep them light protected.
- Store blood sample until centrifugation in a refrigerator or in an iced water bath. When using an ice bath, cover with an opaque box or store it as long as possible in a dark environment (eg. in a cabinet). The tubes must not be exposed to daylight or neon light for more than 30 minutes and never to direct sunlight.
- Centrifuge blood sample at approximately 2000g approximately 10 minutes preferably in a pre-cooled centrifuge at approximately 4°C.
- Immediately after centrifugation, using disposable plastic transfer pipette, transfer the plasma as two aliquots into two separate brown polypropylene tubes both labeled as "**PK Plasma** " with appropriate timepoint indicated.
- Each tube must contain at least 0.4 ml of plasma.
- Discard the Lavender top tube 2mL in an appropriate medical waste container.

- Store the sample promptly and in an upright position at ≤ -20°C in a temperature-controlled freezer until shipment to QPS.
- Samples to be shipped **FROZEN** to QPS at the address listed below:

  Attn: Sample Coordination QPS, LLC
  3 Innovation Way, Suite 240
  Newark, DE 19711
  Tel: 302-369-5120
  Email: GBASCG@qps.com

- Analyses to be performed by BPC: Bioanalytical measurements of venetoclax and prednisone will be conducted on an ultra HPLC-MSMS system using validated assays for each drug developed and validated by the Clinical Pharmacology Program under the direction of Dr. Figg. The measured exposure for each drug assayed will be used to correlate to pharmacodynamic (PD) endpoints, clinical response, toxicity, and pharmacogenetic (PG) analyses. VIP152 plasma concentrations will be assessed by a validated LC/MS/MS assay by Vincerx.

5.2.2.4 Pharmacogenetic Studies

- Put samples immediately on wet ice and refrigerate.
- Disposition of samples: send to Figg lab and refer to section **5.3.3** for more details on sample tracking and storage.
- Upon arrival in the BPC, samples will be centrifuged, and the plasma transferred into cryovials for storage at -80ºC until the time of analysis.
- Samples will be processed, stored, and analyzed by BPC.
- One blood sample per participant will be collected in a purple top tube (K_2EDTA; BD Biosciences) for pharmacogenetic studies to analyze the genomic DNA and assess genotype of the most relevant drug metabolizing enzymes and transporters (DMET) in the Clinical Pharmacology Program.
- Analyses to be performed by BPC: DNA will be analyzed on a Pharmacoscan (ThermoFisher Scientific) genotyping platform that tests for 4,627 genetic variations in 1,191 drug disposition genes, including cytochrome P450s (CYPs), Glutathione transferases (GSTs), sulfotransferases (SULTs), as well as genes involved in facilitation of drug transporters, global regulation of drug metabolizing/transporting proteins, drug binding proteins, and drug targets.

5.2.2.5 Peripheral Blood MononuclearCells (PBMCs)

- Collect blood in Cell Preparation Tubes (e.g., red and green speckled top); gently invert the tubes 8-10 times immediately after collection and place on a shaker if not processed immediately.
- Disposition of samples: send to Figg lab and refer to section **5.3.3** for more details on sample tracking and storage.
- PBMCs will be isolated per routine laboratory techniques by the BPC. Samples will be sent to a collaborating lab that has yet to be determined for analyses and will be updated in a future protocol amendment, if required.

- Studies to be performed on these samples: isolation of PBMCs for RNA sequencing and microRNA sequencing in order to assess for the expression of genes in peripheral blood that correlate with clinical outcomes and disease progression.

5.2.3 Other Samples

- Germline DNA will be collected by blood, buccal swab, and/or saliva samples (preferred).
- These will ideally be collected at baseline; however, may be collected at any point on study based on supplies.
- Standardized, commercial collection kits or tubes will be used (e.g., 1 x 5-10 mL K_2EDTA tube for blood; Isohelix SK-1 for buccal swabs; Salviette/Oragene® for saliva). In the case of buccal swabs, two (2) samples may be collected in order to ensure adequate DNA collection.
- The samples will be processed and DNA extracted/isolated per kit instructions and established techniques. These will also be handled by Dr. Figg's lab (see Section **5.3.3** for contact information).
- For possible planned analyses, see Section **5.4**.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.3.1 General

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. 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. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

5.3.2 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 Participant 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.

5.3.3 Blood Processing Core/Clinical Pharmacology Program (Figg Lab)

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 blood 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

The samples will be processed, barcoded, and stored in Dr. Figg's lab until requested by the investigator.

5.3.3.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in LabMatrix utilized by the BPC. This is a secure program, with access to LabMatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LabMatrix is limited to computers specified by Dr. Figg. 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. Data will be recorded for each sample as appropriate (e.g. the participant 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 patient 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 at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

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.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the participant, if so requested). The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7**.

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 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 Phase 1/2 study are expected to include DNA/RNA sequencing of tumors, including circulating tumor (ct) DNA, and PBMCs as well as sequencing of germline DNA as a comparison. In addition, whole exome sequencing may include evaluation for known lymphoma mutations. For any genetic studies are performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the participant. This is discussed in the consent.

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

Confidentiality for genetic samples will be maintained as described (Section **5.3**). In addition, a Certificate of Confidentiality has been obtained for this study.

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. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).
Participants will be contacted at this time with a request to provide a blood 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 (at our expense) to have genetic education and counseling to explain this result. 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

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant 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.

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

6.1.1 Data Collection/Recording Exceptions

6.1.1.1 Abnormal Laboratory Values

An abnormal laboratory value will be considered an AE 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. **Note:** the investigator performing the assessment must be a licensed physician listed on the 1572.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

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_ Publication 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

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

Overall response assessments will include evaluation of physical examinations, recording of symptoms, hematological evaluations, and radiographic evaluations as per the schedule of assessments (see Study Calendar Section **3.5**). Participants will be restaged during treatment and post-treatment until year 5, or until progression. If no progression after 5 years of monitoring, the decision to continue further follow-up imaging and assessments will be left to the discretion of the investigator. Response assessments will be performed according to the Lugano Classification Response Criteria in NHL (**Appendix D**), as assessed by investigators.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of intravenous (IV) contrast.

If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results.

If independent CT and PET scanners are used, and the participant is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast.

6.3.1 Definitions

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.

Time to response: The time to response is response is defined as the time from the start of the treatment until time of first objective response.

6.3.2 Duration of Response

Duration of overall response: The duration of overall response 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).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.3 Event-Free Survival

Event-free survival (EFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, alternative therapy given (such as radiation), or death, whichever occurs first.

6.3.4 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, or death, whichever occurs first.

6.3.5 Overall Survival

Overall survival (OS) is defined as the duration of time from the date of study enrollment until death.

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/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements..

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/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.. 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/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements..

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 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. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

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 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 **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 5.0.

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.

8.2 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 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.

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.

For timeframe of recording adverse events, please refer to section **6.1**.

8.3 Reporting of Serious Adverse Events

All serious adverse events recorded from the time of first investigational product administration through 30 days after the last dose of any study drug must be reported to the sponsor with the exception of any listed in section **8.4.** Beyond 30 days after the last dose of any study drug, only serious adverse events which are related to study drug are to be recorded and must be reported to the sponsor. 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) at:

OSROSafety@mail.nih.gov. CCR SAE report form
and instructions can be found at:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions
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 is part of the study objectives (PFS), 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 **8.3**.

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreement, see Section **11.**

8.6 Reporting Pregnancy

All required pregnancy reports/follow-up to OSRO will be submitted to:
OSROSafety@mail.nih.gov. Forms and instructions can be found here:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

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 become 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 until 90 days after the last dose study drug.

8.6.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 90 days after study drug.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies occurring from the date of the first dose until 90 days after the last dose of study drug in female partners of male participants should 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 in expedited manner to the FDA in accordance to 21 CFR 31.2.32. 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 DATA SAFETY MONITORING BOARD (DSMB)

The safety oversight for this protocol will be under the direction of a DSMB composed of individuals with the appropriate expertise, including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate according to the charter which is reviewed and approved as part of the initial DSMB meeting. The charter will define the DSMB reviews for this protocol including the frequency of cumulative data reviews.
Types of DSMB reviews include:

- Initial review for a new protocol:

Review of the Protocol, ICF, presentation from the PI/designee, study-related documents, halting rules, statistical methods, set triggers for data review or analyses, establish guidelines for monitoring, and finalize Report formats.

- Cumulative data review, at least once a year but may be more frequent.
- Ad hoc review as described in the protocol when:
    - Clinical trial halting criteria are met.
    - Occurrence of a specific time point, or event described in the protocol (e.g., interim analysis, dose escalation criteria are not met resulting in a halt in enrollment)
    - At the request of the Sponsor due to a safety concern or clinical trial conduct issue

- Final review meeting at the end of the clinical trial. Additional meetings are not required unless the Sponsor requests consultation by the committee, or a potential safety concern or study-related issue arises.

Following each DSMB review, the DSMB will provide its recommendations to the Sponsor. The recommendations signed by the Committee Chair and the Sponsor determination on the recommendations signed by the OSRO Director, will be distributed to the PI for the protocol under review.

8.9 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
- that 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) Sponsor 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 will be 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 take place at the study site(s). Monitoring visit reports will describe visit activities, observations, findings of protocol non-adherence and associated action items or follow-up required for resolution of findings. Monitoring reports will be distributed to the study PI, NCI CCR QA, coordinating center (if applicable) and the OSRO 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		
Phase 1: To determine the MTD, RP2D, and the safety and toxicity profile of the combination of VIP152 with venetoclax and prednisone (VVIP) in relapsed/refractory lymphoid malignancies	Adverse events assessed during the first 22 days of treatment for unsolicited events, and on Day 9 and 15 of Cycle 1 for solicited events	Standard endpoint for phase I trial, see Section **3.1.1**
Phase 2: To determine the CR rate of the combination of VIP152 with venetoclax and prednisone (VVIP) in R/R lymphoid malignancies	Complete response (CR) rate after cycles 6 and 12 of therapy (+/-7 days)	Standard endpoints for cancer clinical trials.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To assess the activity (ORR, TTR, DOR, EFS, PFS and OS) of VIP152 in combination with venetoclax and prednisone (VVIP) in relapsed/refractory lymphoid malignancies	- Overall survival (OS)- median, assessed during treatment and after completion of therapy until death or last follow-up q3, 4, 6 and 12 months for post-treatment years 1, 2, 3, and 4-5, for up to 5 years after the last participant has enrolled on study - Event free survival (EFS)- median, assessed during treatment and after completion of therapy until alternative treatment, relapse/progression, death or last follow-up q3, 4, 6 and 12 months for post-treatment years 1, 2, 3, and 4-5, respectively, for up to 5 years after the last participant has enrolled on study - Progression free survival (PFS) - median, assessed during treatment and after completion of therapy until relapse/progression, death or last follow-up q3, 4, 6 and 12 months for post-treatment years 1, 2, 3, and 4-5, respectively, for up to 5 years after the last participant has enrolled on study - Duration of Response (DOR)- median, assessed during therapy and after completion of therapy until progression or last follow-up q3, 4, 6 and 12 months for post-treatment years 1, 2, 3, and 4-5, respectively, for up to 5 years after the last participant has enrolled on study - Time to Response (TTR)- median, assessed during therapy and after completion of therapy from initiation of therapy to first response q3, 4, 6 and 12 months for post-treatment years 1, 2, 3, and 4-5, respectively, for up to 5 years after the last participant has enrolled on study - Overall Response Rate (ORR) assessed after cycles 6 and 12 of therapy (+/-7 days)	Standard endpoints for cancer clinical trials. Success of regimens will be determined by these endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary/Exploratory		
To assess the ORR and CR rate to VVIP rechallenge in participants who achieve CR, discontinue therapy after 12 cycles and subsequently relapse more than 6 months after initial study drug discontinuation	- Overall Response Rate (ORR) after rechallenge assessed after cycles 6 and 12 of therapy (+/-7 days) - CR after rechallenge assessed after cycles 6 and 12 of therapy (+/-7 days)	Standard endpoints for cancer clinical trials
To assess circulating tumor DNA (ctDNA) response and correlate with molecular tumor analysis	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 for **5.1** collection timepoints.	Exploratory analysis
To evaluate biomarkers of sensitivity or resistance to VIP152, venetoclax and prednisone		
To assess the pharmacokinetics and pharmacogenomics of VIP152, venetoclax, and prednisone when given in combination		

10.2 SAMPLE SIZE DETERMINATION

10.2.1 Phase 1

The trial will begin with a Phase 1 evaluation of the combination of agents, with VIP152 and venetoclax evaluated at four dose escalation levels. Using a standard 3+3 design, up to 4 x 6=24 participants may be required for the Phase 1 portion of the trial.

10.2.2 Phase 2

For the Phase 2 portion of the trial, participants will be accrued in three cohorts:

- Cohort 1: R/R MYC-rearranged DLBCL/HGBCL
- Cohort 2: R/R non-GCB DLBCL (no MYC rearrangement)
- Cohort 3: R/R PTCL

The following are the sample size determination rules for each of the four cohorts based on the rate of CR from historic studies of venetoclax monotherapy in DLBCL (see Section **1.2.2.1.2**) and other FDA-approved targeted therapies for PTCL (see Section **1.2.1.2**):

10.2.2.1 MYC-rearranged DLBCL/HGBCL

In participants with MYC-rearranged DLBCL/HGBCL, it will be desirable if the fraction who experience a CR after 6 cycles of VVIP therapy were at least 20%. To obtain an acceptable

outcome with small numbers of participants, the trial will be conducted using a Simon two-stage optimal design which will have as its objective to rule out a 12% CR rate (p0=0.12) in favor of an improvement of the CR rate to 30% (p1=0.30). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta=0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 10 evaluable participants, and if 0 or 1 of the 10 have a CR after 6 cycles of VVIP therapy, then no further participants will be accrued in this cohort. If 2 or more of the first 10 participants have a CR after 6 cycles of VVIP therapy, then accrual would continue until a total of 29 evaluable participants have been treated. As it may take up to several months to determine if a participant has experienced a CR, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. In addition, if needed to allow time to evaluate the CR rate of the first stage, the study will allow up to 2 additional participants to be accrued pending determination of the CR rate in the initial 10 participants enrolled in the cohort. These 2 participants would not be included among the initial 10, but rather are a limited size addition and considered part of an intended second stage to permit evaluation without substantial disruption to accrual within the cohort. If there are only 1-5 participants with a CR after 6 cycles of VVIP therapy out of 29 participants, this would be an uninterestingly low CR rate. If there were 6 or more of 29 (20.7%) who experienced a CR after 6 cycles of VVIP therapy, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (12% CR rate), the probability of early termination is 65.8%.

10.2.2.2 Non-GCB DLBCL (no MYC-rearrangement)

In participants with non-GCB DLBCL without MYC rearrangements it will be desirable if the fraction who experience a CR after 6 cycles of VVIP therapy were at least 20%. To obtain an acceptable outcome with small numbers of participants, the trial will be conducted using a Simon two-stage optimal design which will have as its objective to rule out a 12% CR rate (p0=0.12) in favor of an improvement of the CR rate to 30% (p1=0.30). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta=0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 10 evaluable participants, and if 0 or 1 of the 10 have a CR after 6 cycles of VVIP therapy, then no further participants will be accrued in this cohort. If 2 or more of the first 10 participants have a CR after 6 cycles of VVIP therapy, then accrual would continue until a total of 29 evaluable participants have been treated. As it may take up to several months to determine if a participant has experienced a CR, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. In addition, if needed to allow time to evaluate the CR rate of the first stage, the study will allow up to 2 additional participants to be accrued pending determination of the CR rate in the initial 10 participants enrolled in the cohort. These 2 participants would not be included among the initial 10, but rather are a limited size addition and considered part of an intended second stage to permit evaluation without substantial disruption to accrual within the cohort. If there are only 1-5 participants with a CR after 6 cycles of VVIP therapy out of 29 participants, this would be an uninterestingly low CR rate. If there were 6 or more of 29 (20.7%) who experienced a CR after 6 cycles of VVIP therapy, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (12% CR rate), the probability of early termination is 65.8%.

10.2.2.3 PTCL

In participants with PTCL it will be desirable if the fraction who experience a CR after 6 cycles of VVIP therapy were at least 20%. To obtain an acceptable outcome with small numbers of participants, the trial will be conducted using a Simon two-stage optimal design which will have

as its objective to rule out a 12% CR rate (p0=0.12) in favor of an improvement of the CR rate to 30% (p1=0.30). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta=0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 10 evaluable participants, and if 0 or 1 of the 10 have a CR after 6 cycles of VVIP therapy, then no further participants will be accrued in this cohort. If 2 or more of the first 10 participants have a CR after 6 cycles of VVIP therapy, then accrual would continue until a total of 29 evaluable participants have been treated. As it may take up to several months to determine if a participant has experienced a CR, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. In addition, if needed to allow time to evaluate the CR rate of the first stage, the study will allow up to 2 additional participants to be accrued pending determination of the CR rate in the initial 10 participants enrolled in the cohort. These 2 participants would not be included among the initial 10, but rather are a limited size addition and considered part of an intended second stage to permit evaluation without substantial disruption to accrual within the cohort. If there are only 1-5 participants with a CR after 6 cycles of VVIP therapy out of 29 participants, this would be an uninterestingly low CR rate. If there were 6 or more of 29 (20.7%) who experienced a CR after 6 cycles of VVIP therapy, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (12% CR rate), the probability of early termination is 65.8%.

10.2.3 Participant Accrual

The trial may require up to 24+29+29+29=111 evaluable participants. To allow for a small number of inevaluable participants and screen failures (15 screen failures and 4 inevaluable), the accrual ceiling will be set at 130 participants. It is expected that up to 1.5-2.5 years may be required to accrue the Phase 1 participants and the first stage of each of the four two-stage designs. The accrual rate in the second stage of each two-stage design will depend on the success identified during in the first stage.

10.3 POPULATIONS FOR ANALYSES

10.3.1 Evaluable for toxicity

Any participant who receives at least one dose of any study agent will be evaluable for toxicity within the appropriate dose level or in the expansion cohort. The DLT evaluation period will be the first cycle (i.e., cycle 1, day 1 to cycle 2, day 1 pre-dose).

10.3.2 Evaluable for objective response

All participants who have received at least 1 cycle of therapy and have had their disease re-evaluated will be considered evaluable for response to combination VVIP therapy. Participants need to have completed baseline and follow-up scans for inclusion in response evaluations, except that any participants noted to have clinical progression without the follow-up scan will be noted as being non-responders. Participants need to have completed baseline and follow-up scans following cycle 1 of therapy to be evaluable for response to the combination therapy. (**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

In the Phase 1 dose-escalation cohort, the DLTs at each dose level will be reported according to type of toxicity identified at each dose level.

In the Phase 2 expansion cohorts, the ORR and CR rate will be estimated based on participants treated at the RP2D, separately by cohort along with a two-sided 95% confidence interval.

10.4.2 Analysis of primary endpoints

10.4.2.1 Phase 1 dose-escalation

The DLTs at each dose level will be reported according to type of toxicity identified at each dose level. Final analysis will be made at least 30 days after the last participant completes therapy. Any participants who are not evaluable for the toxicity evaluation will be replaced.

10.4.2.2 Phase 2 dose-expansion

The CR rate will be estimated based on participants treated at the RP2D, separately by cohort along with a two-sided 95% confidence interval.

10.4.3 Analysis of secondary endpoints

The ORR will be estimated based on participants treated at the RP2D, separately by cohort along with a two-sided 95% confidence interval.

TTR, DOR, EFS, PFS and OS will be determined separately by cohort using the Kaplan-Meier method. The median and a 95% confidence interval will be reported for each cohort.

10.4.4 Safety analyses

The primary endpoint is determination of DLTs. The toxicity grades identified will be reported by dose level. All participants who receive at least 1 dose of study medication will be evaluable for safety (see Section **6.3.1**).

10.4.5 Baseline descriptive statistics

Participant characteristics will be provided by cohort.

10.4.6 Planned Interim analyses

10.4.6.1 Phase 1 to Phase 2 Interim analysis

After 6 participants have completed the required DLT assessment period at the MTD or MAD (either completing the DLT evaluation period or experiencing DLT) with no more than 1 participant experiencing DLT, a report including the supporting safety data and delineation of each criterion met, will be provided to the Sponsor (OSROSafety@nih.gov) before additional participants will be enrolled into the study. The Dose Escalation Determination form on the sponsor website: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions may be used for this purpose.

If more than 1 participant has experienced DLT at DL1, no further accrual will occur.

10.4.6.2 Interim efficacy analysis

As indicated in section **10.2.2**, enrollment for efficacy evaluation will take place in 2 stages for each cohort. Specifically, the second stage of each cohort will be conducted only if there are at least 2 of 10 participants with a complete response (Cohorts 1-3, NHL) after 6 cycles of study therapy.

After the completion of disease assessment in cycle 6 (or earlier if progression confirmed sooner) in the 10th evaluable participant in each cohort, an analysis will be conducted. As addressed in section **10.2.2,** up to 2 participants in the cohort being analyzed may be enrolled as the analysis is conducted. A brief interim analysis report will be created to document the number of responses in the first stage for the cohort under review, and will be reviewed by the PI and study team. The interim analysis report will be provided to study sponsor prior to continuation of accrual. Alternatively, if the required number of responses is observed before that time, the interim analysis report may be generated, reviewed and provided to the study sponsor at that point without restrictions to accrual. The interim analysis report will also be provided to the DSMB at the time of DSMB review.

10.4.7 Interim safety analysis

Notable toxicities of venetoclax-based combination regimens include the development of clinical tumor lysis syndrome (TLS) as well as increased infectious complications that can be life-threatening or fatal. As an additional measure of safety across the entire study population, study-wide stopping rules for prohibitive toxicities throughout the duration of study treatment will be utilized as per below:

- If within the first 25 total participants who have been treated on study, 3 or more have experienced grade 3-4 clinical TLS or grade 4 infectious complications -or- if after 26 or more participants have been treated on study the cumulative incidence of grade 3-4 clinical TLS or grade 4 infectious complications exceeds 10%, then further enrollment to study will be held pending an amendment to modify study treatment.
- If anytime 1 or more within the first 25 participants, 2 or more within the first 50 patients, 3 or more within the first 75 participants, or 4 or more of all study participants treated experience a grade 5 treatment-emergent adverse event (TEAE), then further enrollment to study will be held pending an amendment to modify study treatment.

All SAEs and grade 5 TEAEs will be expeditiously reported to the study sponsor (CCR) and DSMB as directed in Sections **8.3** . With any grade 5 TEAE, a temporary pause in enrollment will be considered, with resumption of study enrollment after thorough discussion and evaluation with the study sponsor (CCR) and DSMB. The sponsor may also consult with Vincerx Pharma (regarding VIP152 safety trends) as necessary.

10.4.8 Subgroup analyses

Analyses will be done according to disease cohort.

10.4.9 Tabulation of individual participant data

None are planned.

10.4.10 Analysis of exploratory endpoints

Any analyses performed on the exploratory objectives are done without any formal adjustment for multiple comparisons but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 Cooperative Research and Development Agreement

This study has been approved by Vincerx (CRADA #03459) who will provide study drug for the participants enrolled on the study and funding to purchase commercial supply of venetoclax (presently manufactured by AbbVie).

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale For Participant Selection

All participants from both genders and 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, these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated. In addition, pregnant individuals and individuals unwilling 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 mature lymphoid malignancies 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. **NOTE:** Because no dosing or adverse event data are currently available on the use of VIP152 and venetoclax in participants <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

12.3 Risk/Benefit Assessment

12.3.1 Known Potential Risks

12.3.1.1 Study Drug Risks

The main risks associated with the study agents include hematologic side effects (neutropenia, thrombocytopenia, anemia and leukopenia), gastrointestinal (diarrhea, nausea, vomiting, constipation), constitutional (fatigue) 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. Additional toxicity may be seen with the combination of these study agents that was not seen with monotherapy or prior combination trials. See Section **14**.

12.3.1.2 Biopsy risks

The risks associated with biopsies are pain, redness, welling, bruising and/or 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.

12.3.1.3 Conscious sedation

The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

12.3.1.4 Risks of Imaging

CT, PET, and/ or MRI scans may be used to monitor a participant's disease on this study. 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 addition, there is a risk of kidney damage from the contrast agent (gadolinium) used for the MRI scan. 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.

12.3.1.5 Radiation

This study will involve radiation from the following sources:

- Up to 10 CT scans of neck, chest, abdomen, and pelvis including 1 done at screening
- Up to 3 whole body 18F-FDG PET/CT scans including 1 done at screening
- Up to 2 CT scans for CT-guided biopsies

The maximum exposure in one year is 18.2 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 1.8 out of 100 (1.8%) and of getting a fatal cancers is 0.9 out of 100 (0.9%).

12.3.1.6 Risks related to blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting, blood clot formation at the needle insertion site or infection of the vein. The maximum amount of blood that will be drawn at a single timepoint on study is approximately 95 mL. The maximum amount of blood that will be drawn over 8 weeks on the study is approximately 616.5 mL.

12.3.1.7 Risk of Urine Collection

There are no physical risks associated with urine collection.

12.3.1.8 Risks of EKG and ECHO

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

12.3.1.9 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.

12.3.1.10 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. Subjects will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with subject'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, subjects will be notified of any medically significant and actionable incidental findings. Study results will not be shared with subjects.

12.3.2 Known Potential Benefits

Venetoclax has shown clinical activity both as monotherapy and as combination therapy in participants with relapsed or refractory lymphoid malignancies It is possible that the combination of venetoclax and VIP152 may synergistically enhance the anti-tumor activity of the other with the hope of increasing efficacy of these agents and decreasing the development of treatment resistance.

12.3.3 Assessment of Potential Risks and Benefits

A number of clinically appropriate strategies to minimize risks to participants have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. 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.

12.4 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant 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

local policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

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://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions.

*Please note that consent for treatment must be obtained by a designated appropriately licensed study investigator (e.g., MD, NP, PA, DO). However, study investigators not falling into this category (e.g. RNs) who are designated as able to obtain consent, may do so for non-treatment procedures such as screening.

For the optional research biopsies on the protocol, the participant will consent at the time of the procedure (via clinical procedure consent form). If the participant refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

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, associate investigators, 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 National Cancer Institute 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/each 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 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(s) 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/ DEVICE INFORMATION

14.1 VENETOCLAX

14.1.1 Source

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 Toxicity

Please see venetoclax prescribing information for details. The major adverse events observed in clinical studies are TLS, neutropenia, infections, embryo-fetal toxicity and concerns over immunization with live attenuated vaccines.

14.1.3 Formulation and Preparation

Venetoclax comes in 10 mg, 50 mg and 100 mg tablets. Excipients include: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, calcium phosphate dibasic. In addition, the 10 mg and 100 mg tablet coating contains iron oxide yellow, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc; the 50 mg tablet coating contains iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

14.1.4 Stability and Storage

Venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Each bottle will be labeled per local regulatory requirements. A desiccant canister may be included in the bottle. The tablets must be stored in original container at or below 30°C (86°F). If supplied with a desiccant, the desiccant canister should be returned to the bottle directly after each tablet removal.

14.1.5 Administration Procedures

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold, and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions. Venetoclax should be administered with a meal.

Venetoclax should be taken with a meal and may be administered with prednisone. 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.

All participants must receive prophylaxis for TLS (see Sections **4.1.3** and **Appendix C**) prior to the initiation of venetoclax.

14.1.6 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 **Appendix B**, and Sections **4.2.1** and **4.3**). Please refer to the package insert and PDR for full drug interactions and toxicities.

14.2 PREDNISONE

14.2.1 Source

Prednisone is commercially available 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 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.

14.2.3 Formulation and Preparation

Prednisone is commercially available in oral pill and liquid formulations; it is intended that we will exclusively use the pill formulation in this study. All formulation excipients are compendial and are commonly used in oral formulations.

14.2.4 Stability and Storage

Prednisone will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All supplied drug will be dispensed in child-resistant packaging.

Please refer to the package insert for additional guidance on drug preparation, handling and storage.

14.2.5 Administration Procedures

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

14.3 VIP152

14.3.1 Source

VIP152 will be provided by Vincerx and supplied to the participants enrolled on the study by the NIH clinical center pharmacy department.

14.3.2 Toxicity

See Section **1.2.2.2.1**. Generally, in phase 1 dose escalation studies, the most commonly reported toxicities were neutropenia and gastrointestinal toxicity. The observed toxicity seen so far has been manageable with anti-emetics and G-CSF.

14.3.3 Formulation and Preparation

VIP152 drug substance is a white to slightly colored solid. It is practically insoluble in water, slightly soluble in 0.1 M hydrochloric acid (HCl) and ethanol and soluble in polyethylene glycol (PEG) 400. The solid drug substance is insensitive to thermal stress, non-hygroscopic and not sensitive to light.

A sterile IV solution of VIP152 with a nominal concentration of 2.5 mg/mL has been developed. The solution is provided in 20 mL brown glass vials closed with a rubber stopper and a flanged closure; each vial contains a nominal fill volume of 16.0 mL. The solution may be diluted prior to administration using physiological saline solution (0.9% NaCl solution) for injection down to a concentration of 0.10 mg/mL.

14.3.4 Stability and Storage

The transport and storage conditions at 2-8°C and protection from strong light are required. Please refer to pharmacy manual for details.

14.3.5 Administration Procedures

Please refer to pharmacy manual to administration procedures.

14.3.6 Incompatibilities

VIP152 is a small molecule administered via IV and is primarily metabolized by cytochrome P450 3A4 (CYP3A4). Concomitant use of VIP152 and strong inducers or inhibitors of CYP3A is contraindicated (see **Appendix B**, Sections **4.2.1** and **4.3**). Please refer to the VIP152 IB for full drug interactions and toxicities.

14.4 Additional Information

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section **3.3**. Treatment will continue for up to 12 cycles of treatment [in those who achieve CR], up to a maximum of 24 total cycles of treatment, until disease progression, or other reason for treatment discontinuation as outlined in Section **3.7**.

Investigators are prohibited from supplying study drug to any participants not properly enrolled in this study or to any physicians or scientists except those designated as sub-investigators on Food and Drug Administration (FDA) Form 1572. The investigator must ensure that participants receive study drug only from personnel who fully understand the procedures for administering the drug.

All doses of oral study drugs taken in the clinic or day hospital should be taken from the bottle dispensed to the participant. Unused tablets/capsules dispensed during previous visits must be returned to the site and drug accountability records must be updated; returned supply must not be re- dispensed to anyone. Participants should return all used bottles to the site when they receive new study drug.

For the purpose of drug accountability of oral agents, empty bottles and returned drug may be handled per local institution policy; unless otherwise noted above or in an applicable Pharmacy Manual.

14.5 Vysis LSI MYC Break Apart Rearrangement Probe Kit

MYC rearrangement FISH testing is performed using the Vysis LSI MYC Break Apart Rearrangement Probe (Abbott Molecular, Inc.) in the Chromosome Pathology Section, Laboratory of Pathology, CCR, NCI. This kit is not FDA approved. It is being used as a treatment determining in-vitro diagnostic device in this study. According to 21 CFR 812.3(m), a significant risk device presents a potential for serious risk to the health, safety and welfare of a participant and meets the significant risk criteria listed in the table below along with the sponsor's conclusions with regard to the applicability of these criteria to the current study. The device has been assessed by the sponsor as non-significant risk per the below.

Significant Risk Criteria	Applicable to current study	Justification
Is an implant	No	The Vysis LSI MYC Break Apart Rearrangement Probe Kit is not introduced into the participant.
Is used in supporting or sustaining human life	No	The device is diagnostic.
Is of substantial importance in diagnosing mitigating or	No	While the device is diagnostic, we do not believe it presents a potential for serious

Significant Risk Criteria	Applicable to current study	Justification
treating disease or preventing impairment of human health		risk to the health and welfare of the participant. The assessment of MYC rearrangement is only used to help to increase the possibility that all persons enrolling on the study might derive benefit from study therapy.
Otherwise poses a risk	No	Testing will be performed on archival samples or on fresh sample that is collected at screening for confirmation of diagnosis. No additional collection of sample will occur for purposes of MYC testing.

15 REFERENCES

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16 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
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large cell lymphoma
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
BV	Brentuximab vedotin
CAP	CT chest, abdomen, and pelvis
CCR	Center for Cancer Research
CDA	Confidential Disclosure Agreement
CFR	Code of Federal Regulations
CI	Confidence Interval
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
CNS	Central nervous system
CNSL	CNS lymphomas
COO	Cell of Origin
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
EATL	Enteropathy-associated T-cell lymphoma

Abbreviation	**Term**
EBV	Epstein Barr Virus
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EKG	Electrocardiogram
ENKL	Extranodal NK/T cell lymphoma, nasal type
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
ICBP	Individuals of childbearing potential
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
GCB	Germinal Center B-cell
GDS	Genomic Data Sharing
GEP	Gene Expression Profiling
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
G-CSF	Granulocyte-colony-stimulating factor
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
HGBCL	High grade B-cell lymphoma
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
IMiD	immunomodulatory agent (IMiD)
IMV	Interim Monitoring Visit
IND	Investigational New Drug
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

Abbreviation	Term
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
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
OSRO	Office of Sponsor and Regulatory Oversight
PCR	Polymerase chain reaction
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
PTCL	Peripheral T-cell Lymphoma
PT	Prothrombin time
PTT	Partial thromboplastin time
QA	Quality Assurance
QC	Quality Control
R/R	Relapsed/Refractory
SAE	Serious Adverse Event/Serious Adverse Experience
SAV	Site Assessment Visit
SIV	Site Initiation Visit
SD	Stable Disease
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
TCM	T-cell malignancies
TLS	Tumor Lysis Syndrome
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
US	United States
WBRT	Whole brain radiation
WHO	World Health Organization
VIPOR	Venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide
VVIP	Venetoclax, VIP152, prednisone
VTE	Venous thromboembolism

17 APPENDIX

17.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

17.2 APPENDIX B: INHIBITORS AND INDUCERS OF CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section **4.2.1** _bookmark52and **4.3** on instructions for concomitant use of CYP3A inhibitors and inducers with study medications.

Inhibitors of CYP3A		**Inducers of CYP3A**
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE SAQUINAVIR TELITHROMYCIN **Moderate inhibitors:** aprepitant erythromycin diltiazem fluconazole grapefruit juice Seville orange juice verapamil	**Weak inhibitors:** cimetidine **All other inhibitors:** amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit telaprevir troleandomycin voriconazole	Carbamazepine Efavirenz Nevirapine Barbiturates Glucocorticoids Modafinil Oxcarbarzepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

17.3 APPENDIX C: ELECTROLYTE IMBALANCES MANAGEMENT AND TUMOR LYSIS SYNDROME PREVENTION

NOTE: The following are recommendations for initial management of electrolyte imbalances and prevention of Tumor Lysis Syndrome (TLS).

First Dose of Venetoclax or Dose Increase

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the participant should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
    - If resolution of TLS occurs within 24-48 hours, venetoclax may be resumed at the same dose.
    - If TLS persists for >48 hours, venetoclax should be restarted at a lower starting dose.
    - In participants who meet criteria for clinical TLS, venetoclax should be restarted at a lower dose following TLS resolution.
- Nephrology (or acute dialysis service) should be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not < 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

Table 10:Management of Electrolyte Imbalances

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform immediate ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform immediate ECG and commence telemetry. • Nephrology assessment with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. – If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 μmol/L)	• Consider rasburicase (dose per institutional guidelines). – If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour.

Abnormality	Management Recommendations
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose per institutional guidelines). – If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Participant symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus > 10 mg/dL) • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours.

Ongoing Dosing of Venetoclax

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose increase (e.g., 48 or 72 hours) are as below. **NOTE:** If the participant is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit participant for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.

  Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (**Table 10**)

- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of TLS prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (**Table 10**).

17.4 APPENDIX D: LUGANO CLASSIFICATION CRITERIA

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

17.5 APPENDIX E: STUDY DRUG DIARY

Participant ID: _____ Cycle: _____

Instructions:

- Use this diary to record all doses of oral study medication taken.
- You should bring this study drug diary and each of your study medications (including leftover pills and empty bottles) with you to each clinic visit.
- Contact us if you have any side effects or before starting any new medications or over-the-counter drugs.
- If you have questions at any time, please contact your doctor or nurse.

Study Drugs:
The study medications should be taken as follows, the dose of each will be assigned to you by your doctor:

V = Venetoclax	Venetoclax tablets should be taken with a glass of water and food
VI =VIP152	VIP152 is given by IV, in the clinic
P = Prednisone	Prednisone tablets should be taken with a glass of water with or without food
	NOTE: All oral study medications may be taken together; with food on days when taken together.

Additional Information:

- Each of the study drugs should be taken at about the same time each day, with or without food as described above (see example below).
- If you do not remember to take all or any of the medications on any day, please tell us. Do not make-up the dose or take extra the following day to make-up for the missed dose.
- If you vomit after taking a dose, you should not take another dose that day.

STAFF USE ONLY
Date returned/reviewed: _____ Staff member: _____

Notes/Comments:

Study Drug Diary:

These are examples of how you might take the study drugs:

- Day -1: Please drink 2 to 3 liters (e.g., 4 to 6, 16 oz. bottles) of water at home.
- Day 1: Take the venetoclax and prednisone with water when instructed, with or without food.
- Day 2: In clinic, take the venetoclax and prednisone with water and food when instructed. About 30-60 minutes later, receive the VIP152 infusion.
- Days 3 through 8: Take the venetoclax and prednisone with water and food (e.g., with breakfast).
- Day 9: In clinic, take the venetoclax and prednisone with water and food when instructed. About 30-60 minutes later, receive the VIP152 infusion.
- Day 10: Take the venetoclax and prednisone with water and food (e.g., with breakfast).
- Days 12-21: No study drugs are taken on these days.

Please record the dose/number of pills of each study drug taken in the table below:

Cycle Day	Date	Study Drugs				Comments
		Venetoclax	Prednisone	VIP152	Pegfilgrastim	
		V	P	VI		
-1		NO DRUG				Fluid Intake
1				NONE	NONE	
2				IV in clinic	NONE	
3				NONE	NONE	
4				NONE	NONE	
5				NONE	NONE	
6				NONE	NONE	
7				NONE	NONE	
8				NONE	NONE	
9				IV in clinic	NONE	
10				NONE	NONE	
11		NONE	NONE	NONE		
12-21	NO DRUG					