Abbreviated Title: ViPOR-P in RR B-cell NHL
NIH Protocol #: 21-C-0014
Version Date: 07/20/2026
NCT Number: NCT04739813

Phase 1 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Revlimid in Combination with Polatuzumab (ViPOR-P) in Relapsed/Refractory B-cell Lymphoma

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Drug Name:	Venetoclax	Obinutuzumab	Lenalidomide (Revlimid®)	Polatuzumab	Prednisone	Ibrutinib
IND Number:	134937					
Sponsor:	Center for Cancer Research, NCI					
Manufacturer:	AbbVie, Inc.	Genentech, Inc.	Celgene Corporation	Genentech, Inc.	Generic	Generic
Supplier	Genentech, Inc.	Genentech, Inc.	Celgene Corporation	Genentech, Inc.	CC Pharmacy	CC Pharmacy

PRÉCIS

Background:

- Combination chemotherapy with rituximab has been the mainstay of treatment for CD20-positive B-cell lymphomas.
- Significant advances have been made in curing aggressive B-cell lymphomas with chemoimmunotherapy, but indolent lymphomas and relapsed/refractory aggressive lymphomas remain mostly incurable with chemotherapy alone.
- Targeted therapies, aimed at disrupting key survival pathways in lymphoid malignancies, are emerging and showing significant activity in non-Hodgkin lymphoma (NHL) in both the relapsed and first-line settings.
- Mechanistically based combinations of targeted agents are likely to benefit patients who cannot tolerate or who relapse after or are refractory to standard chemoimmunotherapy.
- ViPOR-P targets major survival pathways in B-cell lymphomas including BCL-2 (apoptosis); BTK (B-cell receptor signaling and NF-κB); Cereblon (NF-κB) and CD20 with additional genotoxic stress from the anti-mitotic antibody-drug conjugate targeting CD79b, polatuzumab.

Objectives:

- To determine the maximum tolerated dose (MTD) and the safety and toxicity profile of polatuzumab and venetoclax in combination with ibrutinib, prednisone, obinutuzumab and Revlimid® (lenalidomide) (ViPOR-P) in relapsed/refractory B-cell lymphomas
- To determine the complete response (CR) rate of ViPOR-P in relapsed/refractory non-GCB DLBCL

Eligibility:

- Individuals ≥ 18 years of age
- ECOG performance status of ≤ 2
- Histologically or cytologically confirmed relapsed and/or refractory B-cell lymphoma, excluding mantle cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Adequate organ function unless dysfunction secondary to lymphoma

Design:

- Open-label, single-center, non-randomized phase 1 study
    - Standard "3 + 3" design will be used to determine the MTD of polatuzumab and venetoclax in combination with ibrutinib, prednisone, obinutuzumab and Revlimid® (lenalidomide) (ViPOR-P) in relapsed/refractory B-cell lymphomas
    - A small expansion cohort will be treated at the MTD for a further analysis of safety and preliminary activity.
- An expansion cohort of 32 patients (including 27 new patients + 5 patients already enrolled at DL3/MTD) with non-GCB DLBCL will be treated at the MTD to determine the CR rate to ViPOR-P of this aggressive lymphoma subtype.

- Maximum 6 cycles of combination targeted therapy every 21 days.
- To explore all dose levels in the phase 1 study and to assess the CR rate in non-GCB DLBCL patients in a dose expansion at the MTD as well as to allow for the possibility of a few screen failures and inevaluable subjects, the accrual ceiling will be set at 55 patients.

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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 Objectives

- To determine the maximum tolerated dose (MTD) and the safety and toxicity profile of polatuzumab and venetoclax in combination with ibrutinib, prednisone, obinutuzumab and Revlimid® (lenalidomide) (ViPOR-P) in relapsed/refractory B-cell lymphomas
- To determine the complete response (CR) rate of ViPOR-P in relapsed/refractory non-GCB DLBCL

1.1.2 Secondary Objectives

- To determine the overall response rate (ORR) and complete response (CR) rate of ViPOR-P in relapsed/refractory B-cell lymphomas
- To assess the duration of response (DOR), event-free survival (EFS), progression-free survival (PFS) and overall survival (OS) of ViPOR-P in relapsed/refractory B-cell lymphomas

1.1.3 Exploratory Objectives

- To determine the molecular correlates of response or resistance to ViPOR-P
- To determine the rate of complete molecular remission, as determined by assays for ctDNA
- To assess the pharmacokinetics of venetoclax, ibrutinib, and lenalidomide when given in combination with prednisone, obinutuzumab, and polatuzumab (ViPOR-P)

1.2 BACKGROUND AND RATIONALE

1.2.1 General background and rationale

Aggressive B-cell lymphomas, most commonly diffuse large B-cell lymphoma (DLBCL), can be cured with combination chemoimmunotherapy (1-3); however, those with refractory disease and those with early relapse following high-dose chemotherapy and autologous stem cell transplantation (HDT/ASCT) have dismal outcomes with standard therapies, with a median survival of approximately 6 months (4). Indolent lymphomas, most commonly follicular lymphoma (FL), are generally incurable with standard combination chemoimmunotherapy with a subset of these patients having a more aggressive disease course despite standard therapy with inferior overall survival (5). Development of novel therapies is needed in order to improve outcome in these high-risk patients with poor prognosis.

Identification of key survival pathways in lymphoid malignancies and development of drugs that target those pathways has resulted in recent therapeutic advances. Novel targeted therapies have emerged that can disrupt key survival pathways in lymphoma such as regulation of apoptosis (BCL2: venetoclax), B-cell receptor signaling (BTK: ibrutinib), and NF-κB survival pathways (IRF4/SPIB: lenalidomide). Unlike combination chemoimmunotherapy which is empirically driven, mechanistically based combinations of targeted agents with synergistic activity will likely further leverage their benefits.

A major limitation of targeted therapy is the need for long-term continuous dosing schedules, which precludes combining multiple agents due to cumulative toxicity. In contrast, intermittent dosing limits toxicities and potentially allows combination targeted regimens, akin to combination

cytotoxic regimens. Indeed, if these targeted agents undermine multiple essential survival mechanisms in the tumor cells and overcome mechanisms of resistance, combination targeted treatment may significantly improve the outcome of B-cell lymphomas.

In the ongoing phase 1b/2 study of venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide (Revlimid®) (i.e., ViPOR) in relapsed/refractory B-cell lymphomas (ClinicalTrials.gov Identifier: NCT03223610), we demonstrated that the combination of ViPOR was safe without any unexpected toxicities (6, 7). Hematologic adverse events (AEs), mainly neutropenia, were most common and manageable with G-CSF support, with rare G3 (grade 3) events of febrile neutropenia or infection. Non-hematologic AEs were less common and mainly G1-2 in severity with G3 AEs occurring in ≤10% of patients and ≤3% of cycles. Furthermore, significant activity was noted across all histologic subtypes of B-cell non-Hodgkin lymphoma (NHL), most notably in those patients with the activated B-cell (ABC) subtype of DLBCL as well as those with high-grade B-cell lymphoma (HGBCL) with *MYC* and/or *BCL2* and/or *BCL6* rearrangements (i.e., "double-hit" lymphomas). Despite promising early efficacy, ViPOR showed less activity in certain lymphoma subtypes, such as the germinal center B-cell (GCB) subtype of DLBCL as well as in transformed indolent lymphomas (generally of the GCB subtype). Given the favorable safety profile of the ViPOR regimen, there is potential to further improve this regimen's efficacy in certain lymphoma subtypes through the addition of other targeted agents that may work through separate but synergistic mechanisms.

We hypothesize that the addition of the antibody-drug conjugate targeting CD79b, polatuzumab, to the ViPOR regimen will provide an additional mechanism of genotoxic stress to the lymphoma cells and thus improve the clinical activity, specifically the rate and durability of complete response (CR), of the ViPOR regimen across multiple B-cell lymphoma subtypes. The central concept stems from the effect of combination targeted agents to undermine cell survival pathways and augment sensitivity to apoptosis. Thus, we hypothesized that the genotoxic stress provided by polatuzumab may be leveraged by the increased sensitivity of the lymphoma cells to apoptosis provided by the ViPOR agents. Indeed, the addition of prednisone in the ViPOR regimen was included as an inducer of genotoxic stress and *in vitro* data in DLBCL cell lines supports this concept showing significant synergy (as measured by %Response or ΔBliss) with the combination of corticosteroids with targeted agents (**Figure 1**). Based on our *in vitro* models, the addition of further genotoxic stress via monomethyl auristatin E (MMAE, Vedotin) is highly synergistic with the targeted agents in ViPOR and forms the basis for the addition of polatuzumab in an attempt to further improve on the regimen's efficacy (**Figure 2**).

Figure 1: *In vitro* Prednisone and Prednisolone activity versus representative lymphoma cell models. Complete matrix dose response mapping (% response and ΔBliss maps) for Prednisolone in combination with Venetoclax in (HBL1) or Lenalidomide (OCI-Ly10) in indicated non-GCB DLBCL cell lines. Increasing concentrations of each drug results in greater cytotoxicity to the DLBCL cell line as demonstrated. Synergy between agents is indicated by a lower % response and negative ΔBliss. The Cmax and 30% Cmax values (Molarity values) are highlighted in the matrix plots to illustrate cellular responses to Prednisolone at concentrations achievable in humans. *Dose response curves do not span the entire dynamic range of the assay (typically plateaus between 40-60% Activity).

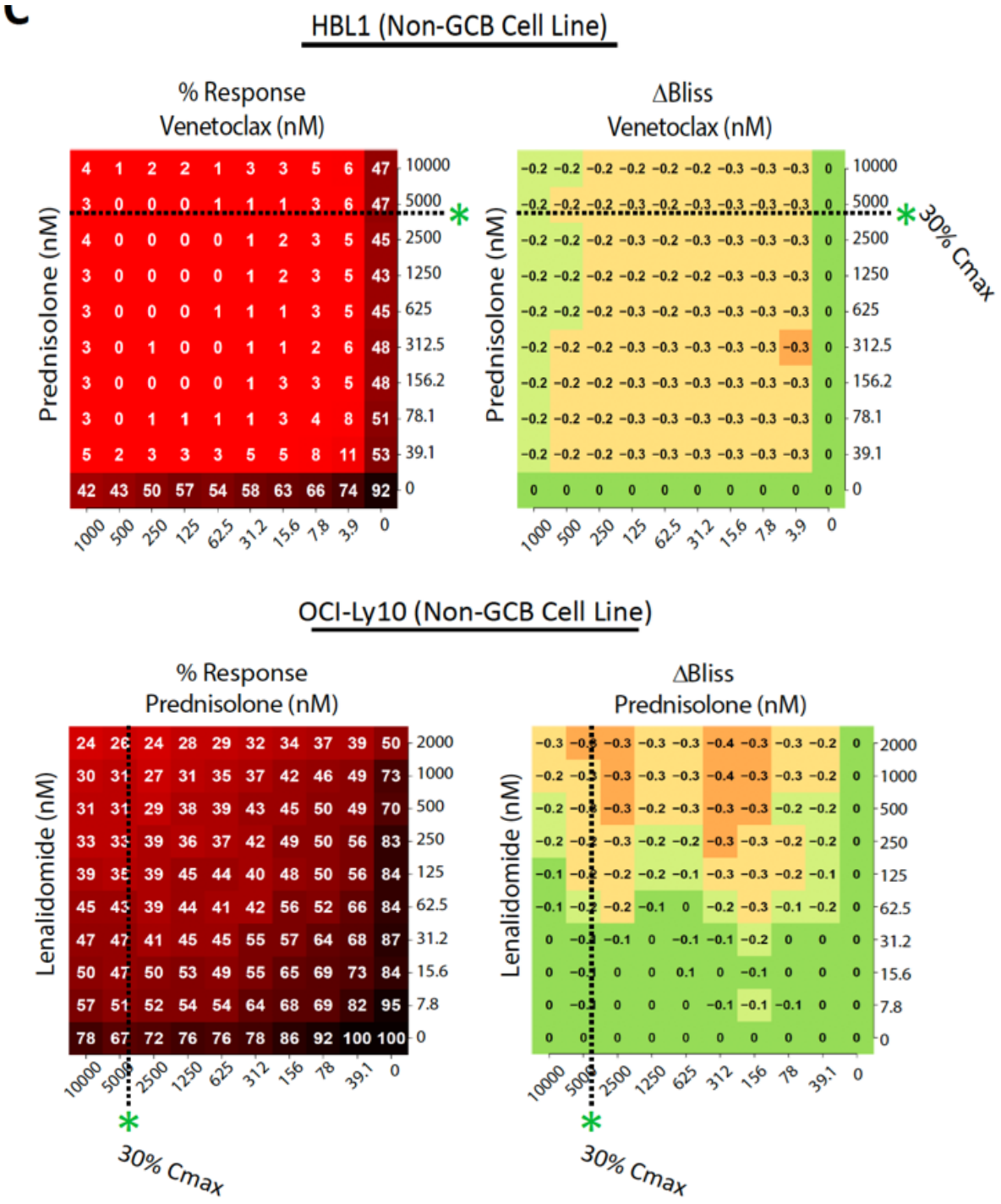
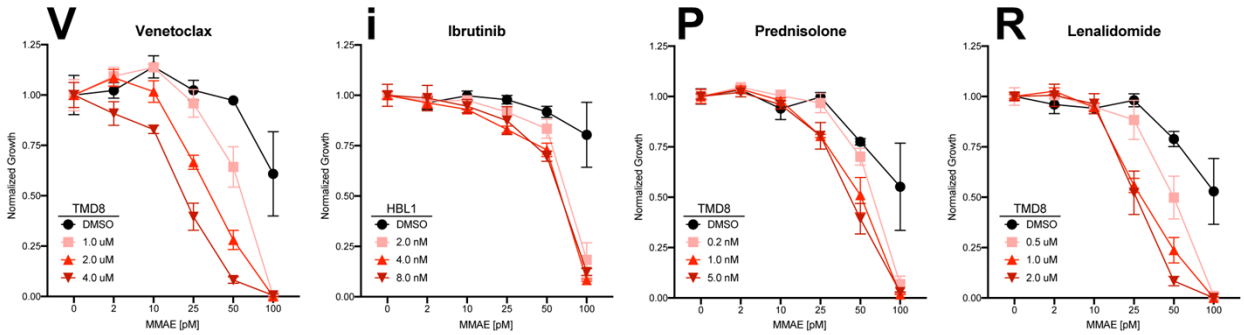

HBL1 (Non-GCB Cell Line)
% Response
Venetoclax (nM)
ΔBliss
Venetoclax (nM)
Prednisolone (nM)
30% Cmax
OCI-Ly10 (Non-GCB Cell Line)
% Response
Prednisolone (nM)
ΔBliss
Prednisolone (nM)
Lenalidomide (nM)
30% Cmax

Figure 2: **Pre-clinical synergy of ViPOR agents with Monomethyl auristatin E (MMAE, Vedotin).** Sub-optimal concentrations of ViP(O)R agents were combined with a range of MMAE concentrations and growth was measured after four days by MTS assays. Data were normalized to the signal obtained with the specified concentration of the ViP(O)R agent alone to better visualize the toxicity of combining agents. Left-shifted curves indicate super-additive or "synergistic" effects of combining agents in indicated non-GCB cell lines. Mean and standard deviation of three technical replicates are displayed.

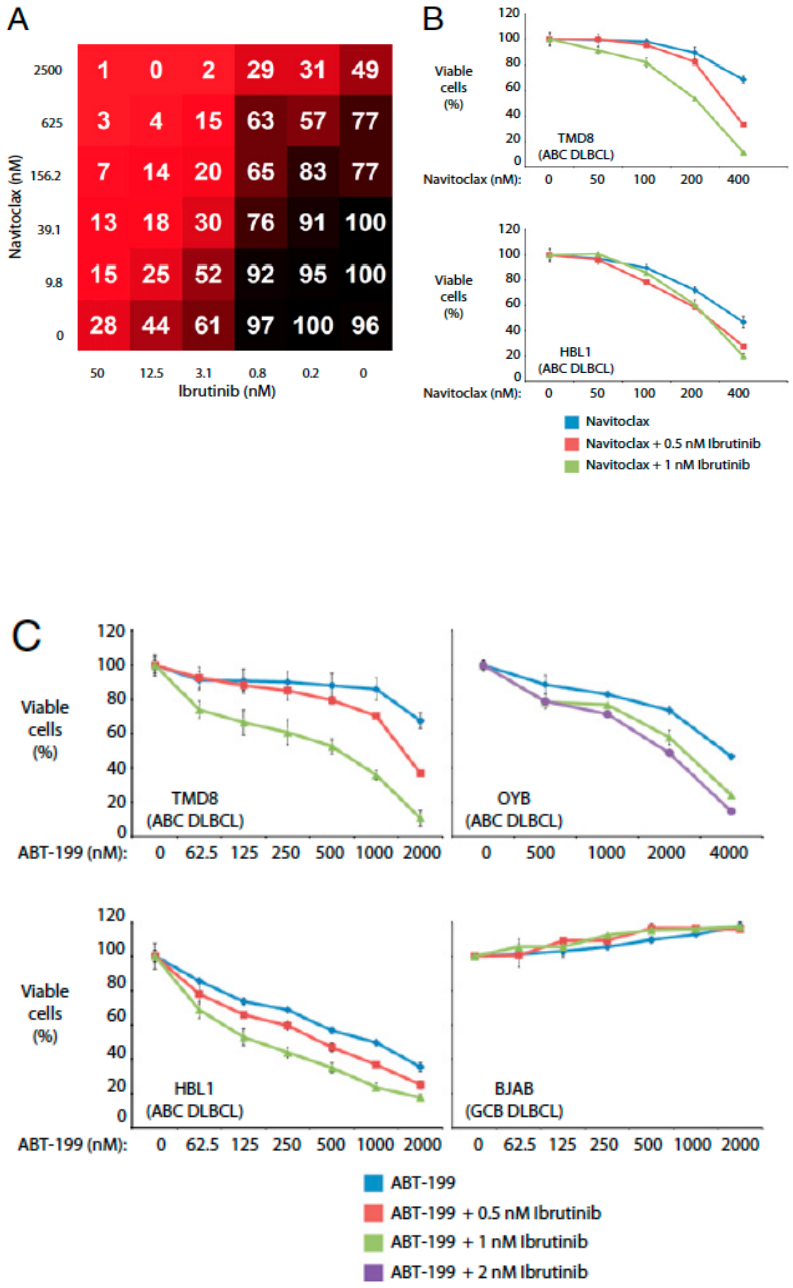


The safety and toxicity profile of polatuzumab in combination with ViPOR needs to be established. To assess this, we propose a phase 1 study of polatuzumab in combination with venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide (Revlimid®) (i.e., ViPOR-P) in relapsed/refractory B-cell lymphomas. The combination of targeted agents will be administered as 21-day cycles for up to 6 total cycles. Response assessment will be determined using the Lugano classification criteria (8) and assays for circulating tumor DNA (ctDNA) will be collected to measure minimal residual disease (MRD). Given the preferential clinical activity of Polatuzumab in ABC DLBCL when combined with front-line or later-line chemotherapy, we propose an additional expansion cohort of patients with non-GCB DLBCL at the MTD, to assess the CR rate to ViPOR-P in this molecular DLBCL subtype.

1.2.2 Pre-clinical rationale for ViPOR-P in B-cell lymphoma

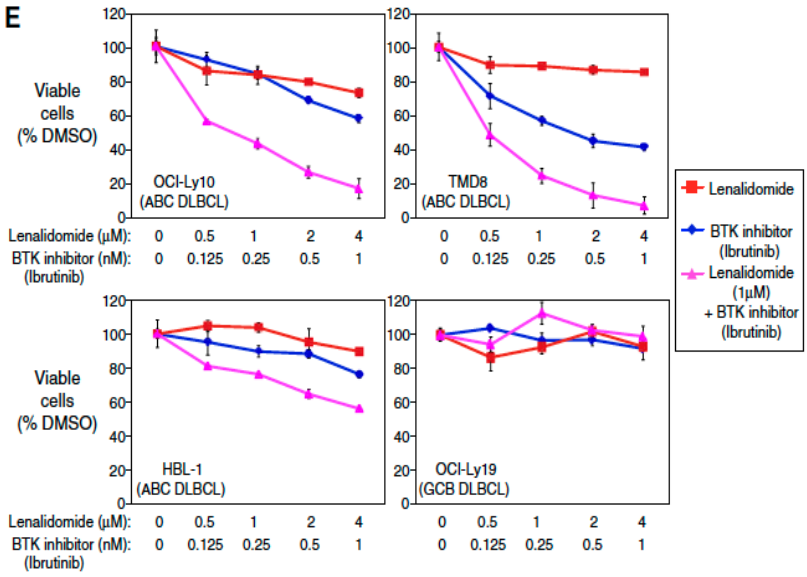
Using a high-throughput screening platform, the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, has been shown to synergistically inhibit the growth of ABC DLBCL cell lines when combined with inhibitors of the PI3K-AKT-mTOR pathway, other inhibitors of B-cell receptor (BCR) signaling, inhibitors of BCL2, as well as standard chemotherapy (9). Specifically, within the BCL2 family inhibitors, greater synergy has been observed with ibrutinib in combination with venetoclax (ABT-199) than was seen with navitoclax in all ABC DLBCL cell lines tested (**Figure 3**).

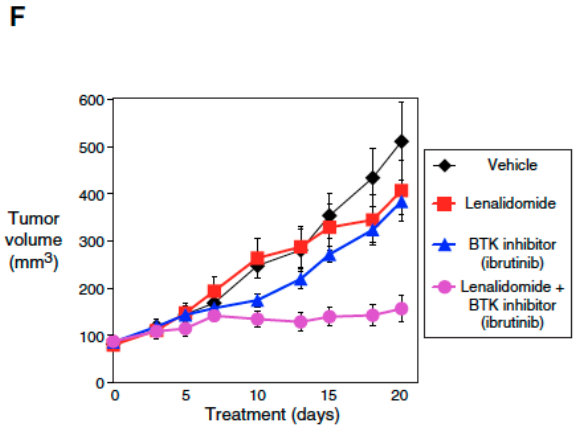
Figure 3: **Viability of lymphoma cells treated with ibrutinib plus BCL2 family inhibitors.** The combination responses for ibrutinib and navitoclax as judged by: A). 6 x 6 matrix block evaluation of ibrutinib plus navitoclax in TMD8 (non-GCB DLBCL) cells shows increased cytotoxicity (decreased viability) with increasing doses of respective targeted agents; B). MTS viability assay in 96-well plates of ibrutinib plus navitoclax in the indicated TMD8 and HBL1 non-GCB cell lines; C). MTS assay in 96-well plates of ibrutinib plus ABT-199 (venetoclax) in the indicated TMD8, HBL1, and OYB non-GCB and BJAB GCB cell lines. DLBCL cell lines were cultured in triplicate in the presence of vehicle of the indicated drug. Increasing concentrations of combination therapy results in greater cytotoxicity (decreased viability) of ABC but not GCB DLBCL cells.



Furthermore, the immunomodulatory agent (iMID) lenalidomide has also shown significant synergy with ibrutinib in killing ABC DLBCL cell lines through downregulation of IRF4 and SPIB transcription factors, leading to decreased NF-κB signaling and promotion of IFNβ production (**Figure 4**) (10).

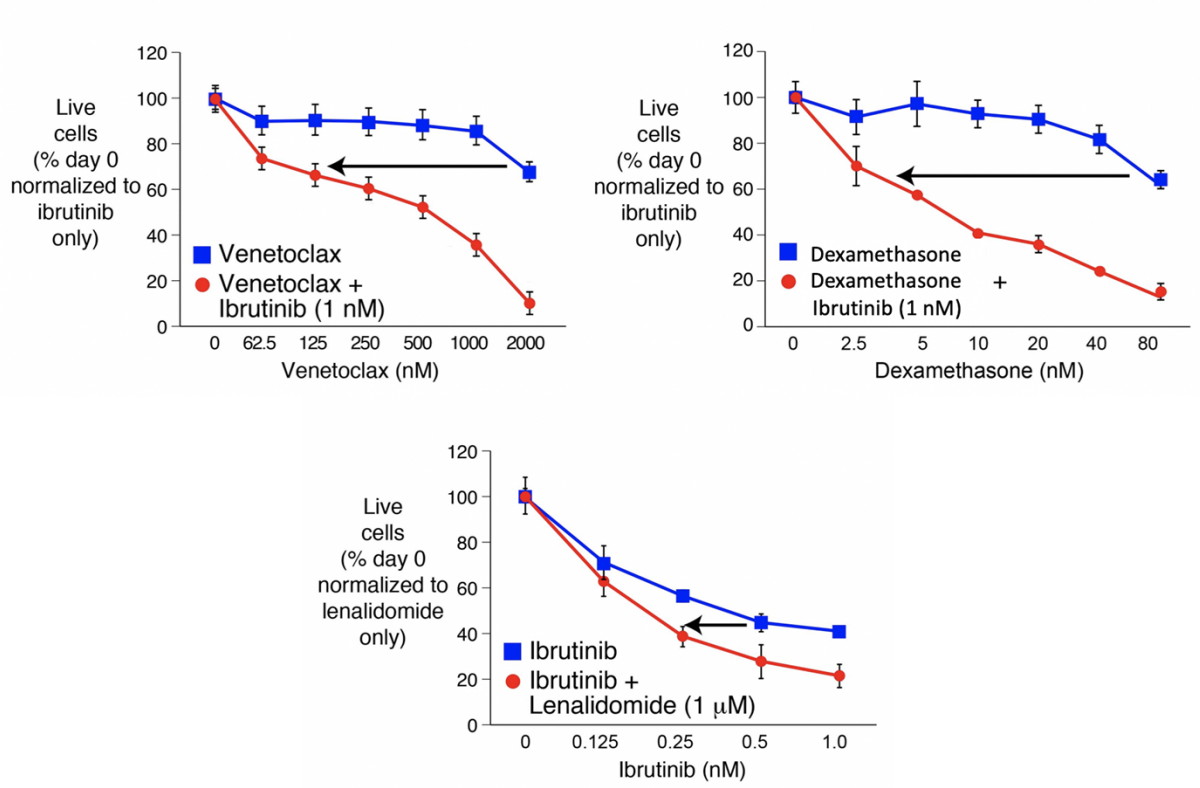
Figure 4: Synergy between Lenalidomide and Ibrutinib in ABC DLBCL. E). Viability (MTS) assay of OCI-Ly10, TMD8, and HBL-1 ABC cell lines and OCI-Ly19 GCB cell line treated with ibrutinib, lenalidomide, or both for 4 days at the concentrations indicated. Error bars show the SEM of triplicates. Increasing concentration of combination therapy results in greater cytotoxicity (decreased viability) of ABC but not GCB DLBCL cells *in vitro*; F). OCI-Ly10 ABC DLBCL cells were established as a subcutaneous tumor (average 80 mm^3) in immunodeficient mice, and then treated daily for 20 days with DMSO, lenalidomide (3 mg/kg), or lenalidomide plus ibrutinib by intraperitoneal injection. Tumor progression was monitored as a function of tumor volume. Error bars show the SEM of 5 mice per group. Combination therapy resulted in decreased tumor growth compared to either targeted agent alone *in vivo*.





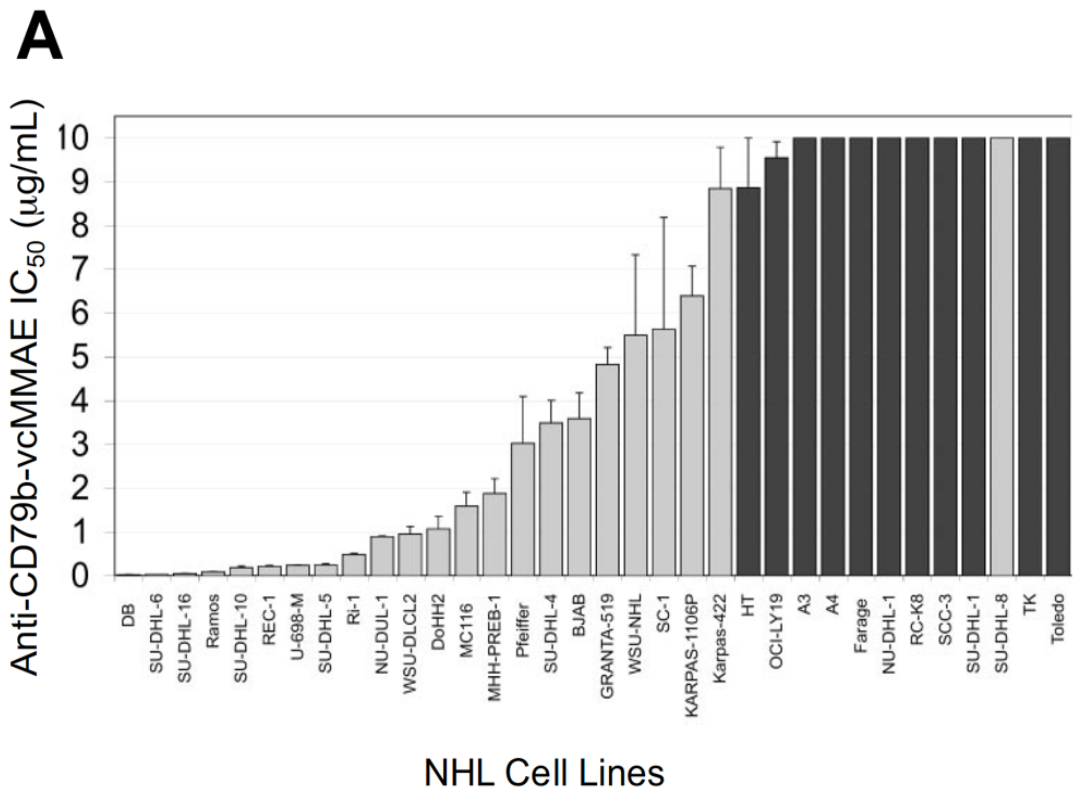
Corticosteroids, including prednisone, its active metabolite prednisolone, as well as dexamethasone, are genotoxic to DLBCL cell lines and have been shown in *in vitro* studies to synergize with several targeted agents, including venetoclax, ibrutinib, and lenalidomide (**Figure 5**) (9, 10).

Figure 5: **Pre-clinical synergy for ViPOR agents in DLBCL models.** Indicated concentrations of ViP(O)R agents were combined with ibrutinib concentrations and growth was measured after four days by MTS assays. Data were normalized to the signal obtained with the specified concentration of the ibrutinib with venetoclax, dexamethasone, or lenalidomide, alone to better visualize the toxicity of combining agents. Left-shifted curves indicate super-additive or "synergistic" effects of combining agents in indicated the non-GCB cell line, TMD8. Mean and standard error of the mean are displayed from three independent experiments.



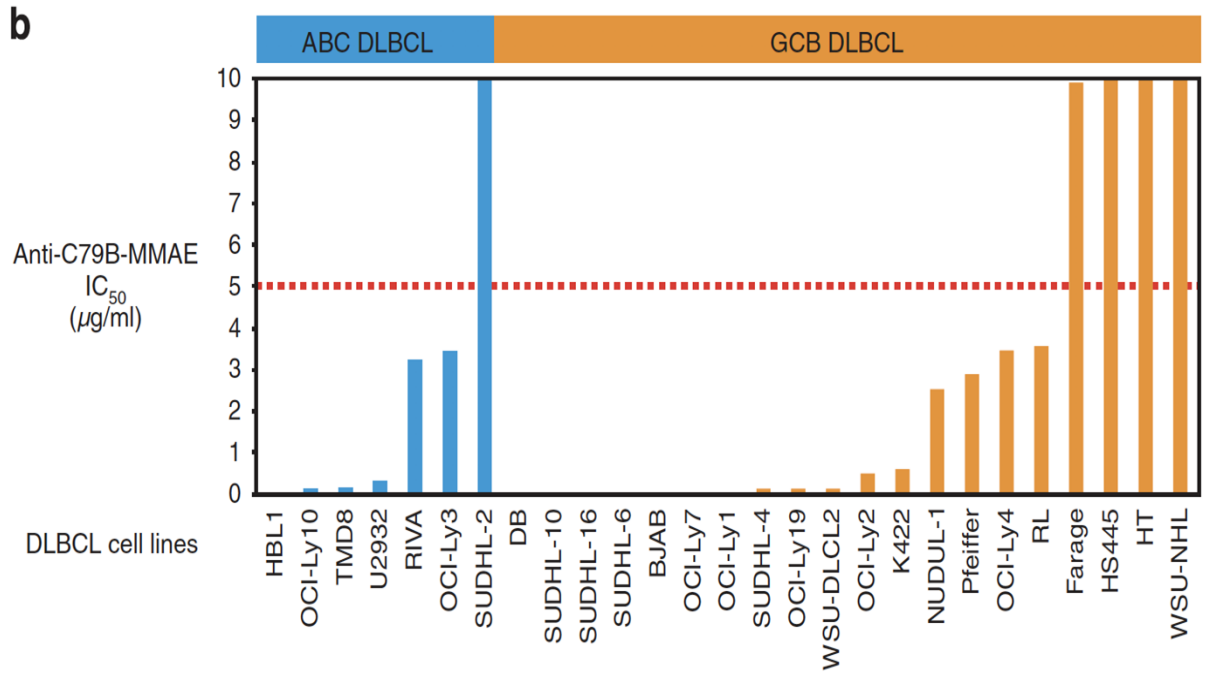
Additional genotoxic stress through targeted chemotherapy has the potential to further enhance on the clinical activity of the ViPOR regimen through synergy with the various targeted agents in ViPOR. Polatuzumab vedotin is an antibody-drug conjugate (ADC) composed of a monoclonal antibody against CD79b, a component of the B-cell receptor (BCR), covalently conjugated to the anti-mitotic cytotoxic agent monomethyl auristatin (MMAE) via a cleavable linker (11). Several pre-clinical studies have shown ADCs targeting CD79b, including polatuzumab, to be capable of target-dependent killing of various NHL cell lines and xenografts, including Burkitt lymphoma, MCL, FL, and DLBCL (**Figure 6**) (12, 13).

Figure 6: CD79b-vcMMAE *in vitro* activity across NHL cell lines. Anti-CD79b-vcMMAE demonstrates potent *in vitro* activity across NHL cell lines as indicated by a low IC_{50}. Dark and light bars indicate CD79b cell surface negative and positive cell lines, respectively, indicating cell-surface expression to be the primary predictor of response *in vitro*.



Specifically in DLBCL, 22 (81%) of 27 DLBCL cell lines tested showed toxicity following treatment with polatuzumab and preferential activity in ABC vs. GCB DLBCL cell lines was not observed (**Figure 7**) (14). Furthermore, polatuzumab induced cytotoxicity in models with and without mutations in CD79b and a strong correlation between CD79b expression was not detected indicating that the clinical activity of this agent is likely to be independent of the level of CD79b expression or CD79b mutational status.

Figure 7: Anti-CD79b-MMAE is an active agent in the treatment of DLBCL. Anti-CD79B-MMAE displays potent *in vitro* activity across ABC (blue bars) and GCB (orange bars) DLBCL cell lines. The dashed red line indicates an IC_{50} of 5 µg/ml that was used as the cutoff level to differentiate responding (lower IC_{50}) from non-responding (higher IC_{50}) cell lines.



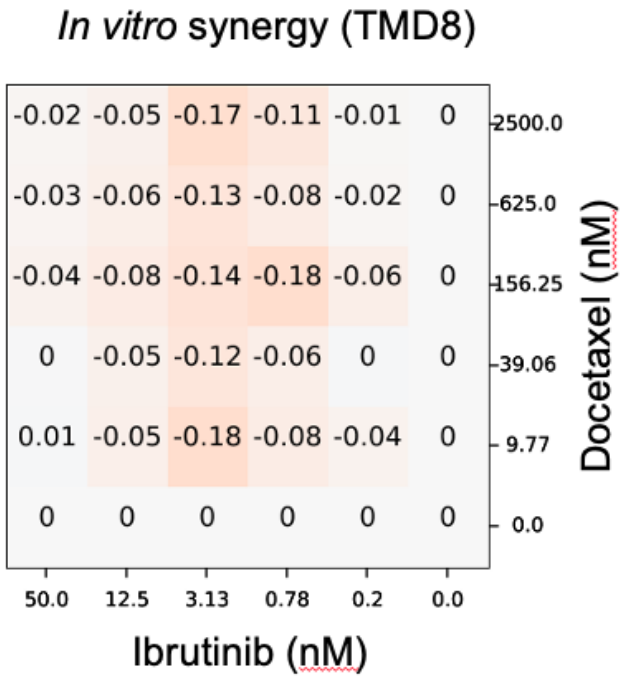
In the original high-throughput synergy screens, a separate tubulin depolymerization inhibitor (i.e., docetaxel) was shown to have significant synergy with ibrutinib in killing ABC cell lines

(

Figure 8) (9).

Figure 8: Pre-clinical synergy of Ibrutinib with Docetaxel in ABC DLBCL. Table shows top-ranked synergistic compounds with ibrutinib from a high-throughput chemical screen of ~450 agents in the non-GCB DLBCL cell line TMD8. The synergy metrics Median Exess and DBSumNeg are displayed for each ranked compound with its predicted molecular target.

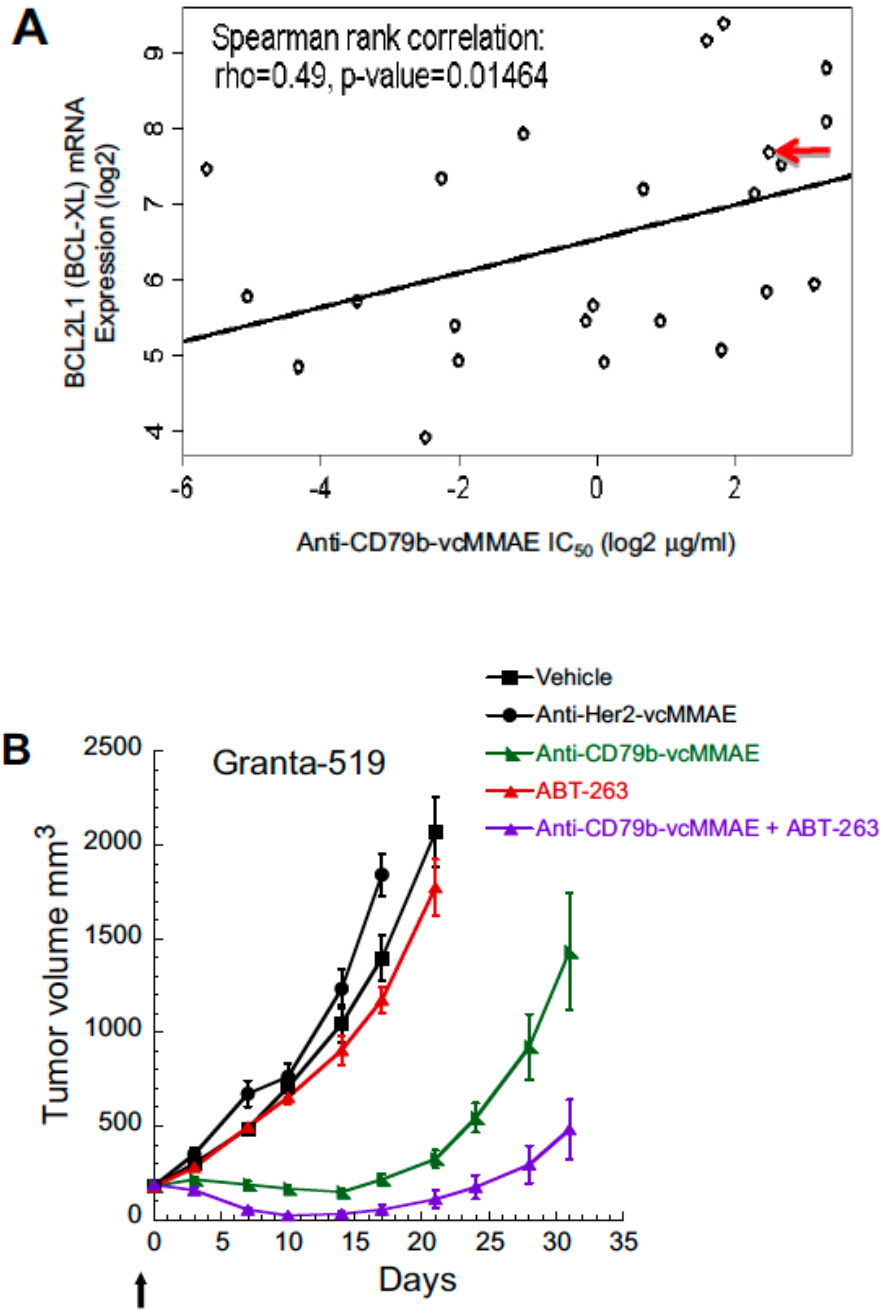
Rank	Combination Therapy	Target	Median Excess	DBSum Neg
1	Navitoclax (ABT-263)	Bcl-xL Inhibitor	91.13	-4.29
2	MK-2206	AKT Inhibitor	86.39	-3.63
3	Tipifarnib	Farnesyltransferase Inhibitor	79.29	-3.12
4	SPC-839	IKK beta Inhibitor	73.44	-2.84
5	Ispinesib	Kinesin-Like Spindle Protein Inhibitor	71.56	-2.27
6	Dexamethasone	Glucocorticoid receptor antagonist	69.86	-2.5
7	Idelalisib	PI3K-delta Inhibitor	68.3	-1.76
8	**Docetaxel**	**Tubulin depolymerization inhibitor**	**66.94**	**-1.75**
9	17-hydroxy Wortmannin	PI3K Inhibitor	66	-1.92
10	Everolimus	mTOR Inhibitor	62.91	-1.56



Furthermore, expression of BCL-XL has been correlated with reduced sensitivity to anti-CD79b-vcMMAE with *in vivo* data showing enhanced activity of polatuzumab when combined with the BCL-2 family inhibitor, ABT-263 (i.e., navitoclax) (**Figure 9**) (13). This suggests that other targeted agents with less toxicity, such as venetoclax, may synergize with polatuzumab in the treatment of NHL.

Figure 9: Gene expression profiling reveals that BCL-XL correlates with reduced sensitivity to CD79b-vcMMAE that can be overcome with ABT-263. A). BCL-XL (BCL2L1) correlates with reduced anti-CD79b-vcMMAE activity as indicated by a higher IC_{50}. Red arrow indicates Granta-519 cell

line; B). ABT-263 (navitoclax) which inhibits BCL-XL can add to the activity of anti-CD79b-vcMMAE as indicated by the decreased tumor growth with combination therapy in the Granta-519 DLBCL xenograft model despite its high BCL-XL expression.



In fact, unpublished *in vitro* data demonstrates synergy between the anti-mitotic agent MMAE and venetoclax, ibrutinib, prednisolone, and lenalidomide, indicating that polatuzumab may be a good drug candidate to synergize with the ViPOR regimen (**Figure 2**).

Based on the pre-clinical data presented above, we propose a phase 1 study to investigate the safety

and preliminary activity of venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide (i.e. ViPOR) in combination with polatuzumab in the treatment of relapsed/refractory B-cell lymphomas.

1.2.3 Clinical studies of ViPOR-P agents in B-cell lymphoma

A summary of targeted monotherapy and combination studies in B-cell NHL can be found in **Table 1** and **Table 2**

Table 1: **Targeted Monotherapy and Combination Studies in FL.**

Treatment	# Patients	ORR	CR	PFS (median)	OS (median)	Reference
Monotherapy Studies						
Venetoclax	29	38%	14%	11 m	100% (12-m)	Davids et al. JCO. 2017.
Ibrutinib	110	20.9%	11%	4.6 m	78% (12-m)	Gopal et al. JCO. 2018.
Obinutuzumab	34	38%	NA	NA	NA	Salles et al. JCO. 2013.
Obinutuzumab vs. Rituximab	149 (FL); 74 (O) 75 (R)	44.6% (O) 33.3% (R)	12.2% (O) 5.3% (R)	17.6 m (O) 25.4 m (R)	NA	Sehn et al. JCO. 2015.
Lenalidomide	22	27%	9%	NA	NA	Witzig et al. JCO. 2009.
Combination Studies						
Obinutuzumab + Lenalidomide	20	63.2%	57.9%	52.1% (3-y)	73.3% (3-y)	Morschhauser et al. Blood. 2018.
Rituximab + Lenalidomide (R^2)	22	77.3%	40.9%	NA	NA	Tuscano et al. BJH. 2014.
Lenalidomide vs. R^2	91 (All); 45 (Len) 46 (R^2)	53.3% (Len) 76.1% (R2)	20% (Len) 39.1% (R2)	1.1 y (Len) 2 y (R2)	4.5 y (Len) NR (R2)	Leonard et al. JCO. 2015.
R^2 vs. Rituximab	295 (All); 147 (R^2) 148 (Ritux)	80% (R2) 55% (Ritux)	35% (R2) 20% (Ritux)	39.4 m (R2) 13.9 m (Ritux)	95% (2-y R2) 86% (2-y Ritux)	Leonard et al. JCO. 2019.
Rituximab+ Ibrutinib+ Lenalidomide (RIL) (untreated)	22	95%	36%	80% (12-m)	NA	Ujjani et al. Blood. 2016.

Table 2: **Targeted Monotherapy and Combination Studies in DLBCL.**

Treatment	# Patients	ORR	CR	PFS (median)	OS (median)	Reference
Monotherapy Studies						
Venetoclax	34	18%	12%	1 m	32% (12-m)	Davids et al. JCO. 2017.
Ibrutinib	80	25% (All) 37% (ABC) 5% (GCB)	10% (All) 16% (ABC) 0% (GCB)	1.64 m (All) 2.02 m (ABC) 1.31 m (GCB)	6.41 m (All) 10.32 m (ABC) 3.35 m (GCB)	Wilson et al. Nature Med. 2015.
Obinutuzumab	25	32%	16%	NA	NA	Morschhauser et al. JCO. 2013.
Lenalidomide	108	28%	7%	2.7 m	NA	Witzig et al. Annals of Oncol. 2011.
	40 (All) 17 (ABC) 23 (GCB)	27.5% (All) 52.9% (ABC) 8.7% (GCB)	15% (All) 29.4% (ABC) 4.3% (GCB)	2.6 m (All) 6.2 m (ABC) 1.7 m (GCB)	NA (All) 14 m (ABC) 13.5 m (GCB)	Hernandez-Ilizaliturri et al. Cancer. 2011.
	26	19%	12%	NA	NA	Wiernik et al. JCO. 2008.
Combination Studies						
Obinutuzumab + Lenalidomide	71	35.2%	18.3%	4.1 m	10.6 m	Houot et al. Leukemia. 2018.
Rituximab + Lenalidomide (R^2)	32	28%	22%	2.8 m	10.2 m	Wang et al. Leukemia. 2013.
	23	35%	30%	34.8% (12-m)	55.1% (18-m)	Zinzani et al. Clin Lymph Myel and Leuk. 2011.
Rituximab+ Ibrutinib+ Lenalidomide (RIL)	45 (All) 17 (non-GCB) 17 (GCB)	38% (All) 65% (non-GCB) 29% (GCB)	24% (All) 41% (non-GCB) 18% (GCB)	5.5 m (All) 3.9 m (non-GCB) 5.5 m (GCB)	9.5 m (All) 10.7 m (non-GCB) 7.1 m (GCB)	Goy et al. Blood. 2019.
	89 (non-GCB)	47%	28%	5 m	14 m	Ramchandren et al. ASH. 2019

1.2.3.1 Targeted monotherapy studies in B-cell NHL

1.2.3.1.1 Venetoclax (Venclexta®)

Venetoclax is a selective small-molecule inhibitor of the anti-apoptotic protein BCL2 that has demonstrated single-agent efficacy in NHL as well as has shown synergy with other targeted agents, including ibrutinib and lenalidomide.

In the initial phase 1 study, a total of 106 patients with relapsed/refractory NHL were treated with single-agent venetoclax at target doses ranging from 200 mg to 1200 mg in dose-escalation and safety expansion cohorts (15). Venetoclax monotherapy was well tolerated overall without

evidence of clinical tumor lysis syndrome (TLS). Three patients with high-risk disease experienced laboratory TLS within 24 hours of initial dosing and all received TLS treatment and continued venetoclax as scheduled without dose interruption. Treatment-emergent AEs occurred in 97% of patients and were mainly G1-2 in severity. G3-4 AEs occurred in 56% of patients and were mainly hematologic, including anemia, neutropenia, and thrombocytopenia in 15%, 11%, and 9% of patients, respectively.

Across all patients with NHL treated on study, venetoclax monotherapy resulted in an overall response rate (ORR) of 44% with 13% CR (15). Responses were noted across all histologic subtypes including MCL (ORR 75%, CR 21%), FL (ORR 38%, CR 14%), DLBCL (ORR 18%, CR 12%), DLBCL-RT (ORR 43%, CR 0%), WM (ORR 100%, CR 0%), and MZL (ORR 67%, CR 0%). Median progression-free survival (PFS) was 6 months overall; 14 months in MCL, 11 months in FL, and 1 month in DLBCL. Overall survival (OS) at 12-months for all patients was 70%; 100% in FL, 82% in MCL, and 32% in DLBCL.

Based on this study, the MTD of venetoclax was not reached and the recommended single-agent dose of venetoclax was determined to be 1200 mg for patients with DLBCL and FL, 800 mg in MCL patients, and 600 mg in DLBCL-RT.

1.2.3.1.2 Ibrutinib (Imbruvica®)

Molecular analysis of B-cell lymphomas, especially diffuse large B cell lymphoma (DLBCL), together with functional interrogation of cell line models has uncovered a wealth of therapeutic targets for which targeted agents are available for clinical testing. One prevalent oncogenic pathway in DLBCL is constitutive B cell receptor (BCR) signaling (16). Ibrutinib is a first in class small-molecule inhibitor of Bruton's tyrosine kinase (BTK), a critical signaling kinase in the BCR pathway.

In the initial phase 1 dose escalation study, a total of 56 patients with relapsed/refractory B-cell lymphoma and CLL were treated with ibrutinib monotherapy (17). Ibrutinib monotherapy was well tolerated with no dose-limiting events and full occupancy of the BTK active site at 2.5 mg/kg/day. Dose escalation was continued up to 12.5 mg/kg/day without reaching the MTD. AEs were most frequently G1-2 in severity with G3-4 AEs most commonly hematologic, including neutropenia, thrombocytopenia, and anemia in 12.5%, 7.2%, and 7.1% of patients, respectively. ORR was 60% with 16% CR in evaluable patients with responses observed across all B-cell lymphoma subtypes. Median PFS was 13.6 months in all patients treated on study.

The phase 2 DAWN study assessed the efficacy and safety of single agent ibrutinib 560 mg PO daily in 110 patients with relapsed/refractory FL after 2 or more prior lines of therapy (18). ORR and CR rate was 20.9% and 11%, respectively, with a median duration of response (DOR) of 19.4 months. Median PFS and OS was 4.6 months and not reached, respectively, with a 30-month OS of 61%. Treatment-emergent AEs were reported in 97% of patients with ≥G3 AEs occurring in 62%. Most common AEs included diarrhea (50.9%), fatigue (40%), cough (35.5%), and muscle spasms (31.8%). G3-4 hematologic AEs included neutropenia (13.6%), anemia (9.1%) and thrombocytopenia (4.5%). Atrial fibrillation occurred in 10 patients (9%), 4 (4%) were ≥G3, and 1 patient (1%) experienced TLS.

A separate multicenter, phase 2 study evaluated the efficacy and safety of ibrutinib monotherapy (560 mg PO daily) in 63 patients with previously treated marginal zone lymphoma (MZL) (19). ORR and CR rate was 48% and 3%, respectively, in evaluable patients with 62% of responders

alive and progression-free at 18 months. Median PFS in all patients was 14.2 months with an 18-month OS of 81%. Treatment-emergent AEs ≥G3 occurred in 67% of patients with anemia (14%), pneumonia (8%), and fatigue (6%) most common. Based on the results of this study, the FDA granted accelerated approved for ibrutinib on January 19, 2017 for the treatment of patients with MZL who require systemic therapy and have received at least 1 prior anti-CD20-based therapy.

Another phase 1/2 clinical trial investigated the use of ibrutinib monotherapy (560 mg PO daily) in 80 patients with relapsed/refractory DLBCL (20). Favorable clinical activity was noted with ibrutinib, mainly in the ABC subtype of DLBCL with an ORR of 37% (CR 16%) vs. 5% (CR 0%) in patients with ABC vs. GCB DLBCL, respectively (P=0.0106). With ibrutinib monotherapy, however, most patients developed rapid treatment resistance with a median progression-free (PFS) and overall survival (OS) of only 2.02 and 10.32 months, respectively, in ABC DLBCL and 1.31 and 3.35 months, respectively, in GCB DLBCL. Albeit small numbers, patients with concurrent BCR pathway mutations in *CD79B* and $MYD88^{L265P}$ had the highest response rates (ORR 80%) with those patients having mutations in downstream regulatory components, such as *CARD11* or *TNFAIP3*, failing to respond to ibrutinib therapy (20). Based on this exploratory finding, a phase I study of ibrutinib followed by a novel immuno-chemotherapy platform (TEDDi-R) was initiated in primary CNS lymphoma, based on a high rate of BCR pathway mutations in *CD79B* and $MYD88^{L265P}$ in this disease (21). Notably, this study showed an overall response rate to ibrutinib of 83%, and provided validation for the exploratory molecular findings from the phase 2 ibrutinib study in relapsed/refractory DLBCL (20).

1.2.3.1.3 Obinutuzumab (Gazyva®)

Obinutuzumab is a glycoengineered humanized anti-CD20 type II monoclonal antibody which has shown superior activity in induction of ADCC and inducing direct cell death of lymphoma cells compared to type I antibodies in *in vitro* and preclinical studies.

In a phase 1 dose-escalating study of obinutuzumab monotherapy in patients with relapsed/refractory CD20+ indolent NHL, obinutuzumab given every 21 days for up to 8 cycles was well tolerated and demonstrated encouraging activity at doses up to 2000 mg (22). The majority of AEs were G1-2 (86%) in severity with G3-4 AEs accounting for the remaining 14% and occurring in 7 (21%) of 21 patients. Infusion-related reactions (IRRs) were the most common AE with all grade and ≥G3 IRRs occurring in 86% and 10% of patients, respectively, with most occurring during the first infusion and resolving with appropriate management. ORR and CR rate in 21 evaluable patients was 43% and 24%, respectively.

A separate phase 1 study assessed the safety and anti-tumor activity of obinutuzumab induction and maintenance therapy in patients with relapsed CD20+ NHL or CLL (23). A total of 22 patients received obinutuzumab induction (200-2000 mg) IV weekly for 4 weeks with responding patients (CR, PR or SD with clinical benefit) receiving maintenance dosing every 3 months for a maximum of 8 doses. No DLTs or unexpected AEs were observed, and IRRs were most common, with all grade and G3-4 IRRs occurring in 73% and 18% of patients, respectively. Additional AEs included infection (32%), pyrexia (23%), neutropenia (23%), headache (18%), and nausea (18%). At the end of induction therapy, ORR and CR rate was 23% and 0%, respectively. Eight (36%) patients went on to receive maintenance therapy with best ORR and CR rate to both induction and maintenance therapy 32% and 5%, respectively.

The phase II GAUGUIN study assessed the efficacy of obinutuzumab monotherapy in patients with relapsed/refractory indolent or aggressive NHL (24, 25). Patients were randomized to receive

either obinutuzumab 400 mg as a flat dose for 8 cycles (days 1 and 8 of cycle 1 and day 1 of cycles 2-8) or 1600 mg on days 1 and 8 of cycle 1 and 800 mg on day 1 of cycles 2-8. A total of 40 patients (DLBCL = 25, MCL = 15) with aggressive NHL were treated on both arms of this study, with best ORR and CR rate 37% and 16%, respectively, for the 1600/800 mg study arm and 24% and 10%, respectively, in the 400/400 mg study arm (24). Best ORR and CR rate was 32% and 16%, respectively, in DLBCL patients and 27% and 13%, respectively, in MCL patients. Median DOR was 9.8 months overall with no significant difference in median PFS between the two treatment arms (2.7 months vs. 2.6 months in the 1600/800 mg and 400/400 mg treatment arms, respectively). The most common AEs were IRRs, with all grades and G3-4 IRRs occurring in 75% and 8% of patients, respectively. The next most common AEs included asthenia (18%), anemia (15%), lymphopenia (15%), diarrhea (13%), abdominal pain (10%) and constipation (10%). A total of 40 patients (FL = 34) with indolent NHL were treated on both arms of this study, with best ORR and CR rate 64% and 23%, respectively, in the 1600/800 mg study arm and 33% and 11%, respectively, in the 400/400 mg study arm (25). Median DOR was 17.2 months with a median PFS of 11.9 months vs. 6 months in the 1600/800 mg and 400/400 mg study arms, respectively. The most common AEs were IRRs, with all grades and G3-4 IRRs occurring in 73% and 5% of patients, respectively.

The randomized phase II GAUSS study compared the efficacy of obinutuzumab induction and maintenance therapy to that of rituximab in patients with relapsed CD20+ indolent B-cell NHL (26). A total of 149 patients with relapsed FL were randomized to treatment with four weekly doses of obinutuzumab (1000 mg, N=74) or rituximab (375 mg/m2, N=75) with responding patients receiving maintenance therapy every 2 months for up to 2 years. A trend toward improved ORR (44.6% vs. 33.3%, P=0.08) and CR rate (12.2% vs. 5.3%, P=0.07) was seen with obinutuzumab therapy, however, this did not translate into an improved PFS (HR 0.93, 95%CI:0.60-1.44, P=0.74). AEs were overall balanced between the treatment arms with the exception of higher IRRs (74% vs. 51%, P=0.003) and cough (24% vs. 9%, P=0.013) with obinutuzumab therapy.

1.2.3.1.4 Lenalidomide (Revlimid®)

Lenalidomide (Revlimid®) is a novel immunomodulatory agent with antiproliferative activities that has shown efficacy both as monotherapy and in combination across a wide range of hematologic malignancies.

A phase 2 trial (NHL-001) evaluated the efficacy of lenalidomide monotherapy (25 mg PO days 1-21 every 28 days for up to 52 weeks as tolerated) in 43 patients with relapsed/refractory indolent NHL (27). ORR and CR rate was 23% and 7%, respectively, including an ORR of 27% in G1-2 FL and 22% in small lymphocytic lymphoma (SLL). Median PFS was 4.4 months for all patients. The most common G3-4 AEs were hematologic, including neutropenia (46%), thrombocytopenia (19%), and anemia (9%).

A separate phase 2, multicenter study evaluated the safety and efficacy of lenalidomide (25 mg PO days 1-21 every 27 days for up to 52 weeks as tolerated) monotherapy in 49 patients with relapsed/refractory aggressive NHL (28). ORR and CR rate was 35% and 12%, respectively, and occurred across all lymphoma subtypes including DLBCL (ORR 19%), G3 FL (ORR 60%), MCL (ORR 53%), and transformed low-grade lymphoma (ORR 33%). Median DOR was 6.2 months with a median PFS of 4.0 months. The most common G3 AEs included neutropenia (24.5%),

leukopenia (14.3%), and thrombocytopenia (12.2%) and the most common G4 AEs included neutropenia (8.2%) and thrombocytopenia (8.2%).

Another larger, international, multicenter phase 2 study evaluated the safety and efficacy of lenalidomide (25 mg PO days 1-21 every 27 days until PD or unacceptable toxicity) monotherapy in 217 patients with relapsed/refractory aggressive NHL (29). ORR was 35% with 13% CR; ORR and CR of 28% and 7% in DLBCL, 42% and 21% in MCL, 42% and 11% in G3 FL, and 45% and 21% in transformed lymphoma. Median DOR was 10.6 months with a median PFS of 3.7 months. The most common treatment-related G3-4 AEs included neutropenia (41%), thrombocytopenia (19%), and anemia (9.2%).

Specifically in DLBCL, a retrospective study of lenalidomide given at 4 academic institutions showed a significantly higher response rate and PFS in patients with a non-GCB phenotype based on immunohistochemistry (IHC) (30). In this retrospective study, 40 patients with relapsed/refractory DLBCL were included, with 23 classified as GCB-like and 17 classified as non-GCB-like according to IHC and Hans algorithm. Non-GCB patients had a significantly higher ORR (52.9% vs. 8.7%, P=0.006) and CR rate (29.4% vs. 4.3%) compared to GCB DLBCL patients treated with lenalidomide. Median PFS was also significantly improved in non-GCB patients (6.2 vs. 1.7 months, P=0.004) compared to GCB patients receiving lenalidomide; however, no difference in OS was observed between the 2 subgroups (P=0.704).

A randomized phase 2/3 trial compared the efficacy of lenalidomide versus investigator's choice in patients with relapsed/refractory DLBCL who received ≥2 prior therapies (31). DLBCL patients were stratified by DLBCL subtype by immunohistochemistry and then randomized 1:1 to lenalidomide (25 mg PO days 1-21 every 28 days) or investigator's choice (gemcitabine, rituximab, etoposide or oxaliplatin) with cross-over to lenalidomide permitted for progressive disease on investigator's choice. A total of 102 DLBCL patients (non-GCB, N=54; GCB, N=48) were treated with lenalidomide monotherapy (N=51) or investigator's choice (N=51). ORR was significantly higher with lenalidomide (27.5% vs. 11.8%, P=0.079) compared to investigator's choice with a trend toward improved CR rate (9.8% vs. 2.0%). Median PFS was also increased in lenalidomide treated patients (13.6 vs. 7.9 weeks, P=0.041), with a greater improvement in PFS seen in non-GCB DLBCL patients (15.1 vs. 7.1 weeks, P=0.021) compared to GCB DLBCL patients (10.1 vs. 9 weeks, P=0.550). No difference in OS was noted between the treatment arms both across all patients with DLBCL as well as within each DLBCL molecular subtype. Hematologic AEs with lenalidomide included neutropenia (42.6%), anemia (33.3%), thrombocytopenia (24.1%), and leukopenia (5.6%).

1.2.3.2 Combination targeted therapy studies in B-cell NHL

1.2.3.2.1 Venetoclax with Ibrutinib

A phase 2 study assessed the efficacy of the combination of ibrutinib (560 mg daily) and venetoclax (weekly ramp-up to 400 mg daily starting week 5) in 24 patients with relapsed/refractory (N=23) or untreated (N=1) MCL (32). Best ORR and CR rate as assessed by PET were both 71%, and 67% and 38% of patients were MRD negative in the bone marrow by flow cytometry or peripheral blood by ASO-PCR, respectively. DOR, PFS, and OS at 12-months was 78%, 75%, and 79%, respectively. Most AEs were low grade with the most common AEs including diarrhea (83%), fatigue (75%), and nausea/vomiting (71%). The most common ≥G3 AEs included neutropenia (33%), thrombocytopenia (17%), anemia (12%), and diarrhea (12%). Two (8%) patients, both high-risk, experienced TLS with initiation of the first dose of venetoclax

50 mg, prompting a protocol amendment to lower the starting dose of venetoclax to 20 mg daily. No further episodes of TLS occurred at this lower starting dose.

Another phase 2 study assessed the combination of ibrutinib (420 mg daily) and venetoclax (weekly dose escalation to 400 mg daily starting cycle 4) for 24 cycles in 80 older patients with high-risk CLL (33). After 12 cycles, 88% experienced CR or CR with incomplete count recovery and 61% were MRD negative in the bone marrow by flow cytometry. The most common AEs included bruising (60%), arthralgias (48%), diarrhea (41%), and nausea/vomiting (36%). The most common ≥G3 AEs included neutropenia (48%), hypertension (10%), atrial fibrillation/flutter (10%), and thrombocytopenia (2%). Three patients experienced laboratory TLS without clinical evidence of TLS.

The phase 2 CLARITY trial assessed the combination of ibrutinib and venetoclax in 53 patients with relapsed/refractory CLL (34). ORR and CR rate at 12 months was 89% and 51%, respectively, with 53% of patients achieving MRD negativity in the blood and 36% in the bone marrow. The most common AEs included neutropenia and GI events and a single case of biochemical TLS occurred.

1.2.3.2.2 Venetoclax, Ibrutinib, and Obinutuzumab

A phase 1b study assessed the safety and efficacy of the combination of sequentially administered obinutuzumab (1000 mg IV on days 1-2, 8, and 15 of cycle 1 and day 1 of cycles 2-8) followed by ibrutinib (420 mg PO daily days 1-28 of cycles 2-14) and venetoclax (weekly ramp up starting day 1 of cycle 3 to target dose of 400 mg) given in fourteen 28-day cycles in 12 patients with relapsed/refractory CLL (35). ORR was 92% with CR or CR with incomplete marrow recovery achieved in 42%. At the end of treatment, 50% of patients were MRD negative in the blood and bone marrow. Hematologic AEs were most common and included G3-4 neutropenia (33.3%), thrombocytopenia (16.7%), lymphopenia (16.7%), and lymphocytosis (8.3%). No clinically significant TLS occurred with this combination.

1.2.3.2.3 Rituximab with Lenalidomide (Revlimid®) (R^2)

The randomized phase 2 CALGB 50401 study compared the safety and efficacy of rituximab monotherapy (375 mg/m2 weekly for 4 weeks), lenalidomide monotherapy (15 mg PO days 1-21 for cycle 1 and 20 mg PO days 1-21 for cycle 2 and 25 mg PO days 1-21 for cycles 3-12) or the combination of lenalidomide with rituximab (R^2)in patients with relapsed FL after prior rituximab with a time to progression of ≥6 months from the last dose (36). The rituximab monotherapy arm was closed early due to poor accrual and 91 patients were treated with either lenalidomide monotherapy (N=45) or LR (N=46). ORR and CR rate was 53% and 20%, respectively, with lenalidomide monotherapy compared to 76% and 39%, respectively, with LR (P=0.029). Median time to progression (TTP) was significantly longer with LR (2 years vs. 1.1 years, P=0.0023) with no significant difference in OS (NR vs. 4.5 years, P=0.149). G3-4 AEs occurred in 58% and 53% of the lenalidomide and LR arms, respectively, with the most common G3-4 AEs including neutropenia (16% vs. 20%), fatigue (9% vs. 13%), and thrombosis (16% vs 4%).

The randomized phase 3 AUGMENT study assessed the safety and efficacy of lenalidomide (20 mg PO days 1-21 every 28 days of cycles 1-12) plus rituximab (375 mg/m2 days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2-5) (N=178) versus placebo plus rituximab (N=180) in 358 patients with relapsed/refractory FL (N=295) or MZL (N=63) (37). ORR was significantly higher with lenalidomide plus rituximab (78% vs. 53%, P<0.001) as was CR rate (34% vs. 18%, P=0.001)

compared to placebo plus rituximab. Median PFS was significantly improved with lenalidomide plus rituximab versus placebo plus rituximab with a HR of 0.46 (95% CI: 0.34-0.62, P<0.001) and a median PFS of 39.4 months vs. 14.1 months, respectively. No significant difference in OS was observed between the 2 treatment arms (HR 0.61, 95% CI: 0.33-1.13). Lenalidomide plus rituximab was associated with a higher rate of all grade infections (63% vs. 49%), neutropenia (58% vs. 23%), and cutaneous reactions (32% vs. 12%) compared to placebo plus rituximab. G3-4 neutropenia (50% vs. 13%) and leukopenia (7% vs. 2%) were also higher with lenalidomide plus rituximab compared to placebo plus rituximab. Based on the results of this study, on May 28, 2019 the FDA approved the combination of lenalidomide and rituximab for previously treated patients with FL and MZL.

The randomized phase 3 RELEVANCE trial compared the efficacy of the combination of rituximab plus lenalidomide (N=513) to rituximab plus chemotherapy (N=517) in 1030 patients with previously untreated FL (38). Patients randomized to rituximab plus lenalidomide received lenalidomide 20 mg per day days 2-22 every 28 days for 6 cycles followed by 10 mg per day days 2-22 every 28 days for 12 additional cycles. Patients in PR after cycle 6 could receive an additional 3-6 cycles of lenalidomide at 20 mg. Rituximab was given at 375 mg/m2 IV on days 1, 8, 15, and 22 of cycles 1 and day 1 of cycles 2-6 and then every 8 weeks for 12 cycles. Patients randomized to rituximab plus chemotherapy received investigator's choice of R-CHOP, BR, or R-CVP followed by 12 cycles of rituximab maintenance every 8 weeks. A similar rate of CR at 120 weeks was noted between the rituximab plus lenalidomide and the rituximab plus chemotherapy treatment arms (48% vs 53%, P=0.13) with no difference in 3-year PFS (77% vs. 78%, P=0.48) or OS (94% vs. 94%, P=0.63) between the arms. Rituximab plus lenalidomide resulted in a higher percentage of G3-4 cutaneous reactions (7% vs. 1%) but a lower rate of G3-4 neutropenia (34% vs. 50%) and febrile neutropenia (2% vs. 7%).

The SAKK 35/10 phase 2 trial compared the activity of a different schedule of rituximab monotherapy (375 mg/m2 IV on day 1 of weeks 1-4 and repeat weeks 12-15 in responding patients) to the combination of rituximab (same schedule) plus lenalidomide (15 mg daily for 18 weeks) in patients with previously untreated FL (39). A total of 154 patients with FL were randomized to rituximab monotherapy (N=77) or rituximab plus lenalidomide (N=77). Combination therapy resulted in a significantly higher rate of CR/CRu at 6-months (36% vs. 25%, P=0.056) and 30-months (42% vs. 19%, P=0.001) compared to rituximab monotherapy as well as a significantly longer median time to next treatment (NR vs. 2.1 years, P=0.003) and PFS (5 vs. 2.3 years, P=0.035). No difference in OS was seen between the 2 treatment arms (4-year OS 91% vs. 90%, P=0.97). G3-4 toxicity was higher with combination therapy (56% vs. 22%), mainly due to a higher rate of G3-4 neutropenia (23% vs. 7%).

The phase 2 AGMT MALT-2 study evaluated the safety and efficacy of the combination of lenalidomide (20 mg PO days 1-21 every 28 days) plus rituximab (375 mg/m2 IV day 1 of each cycle) for 6-8 cycles in 46 patients with gastric (N=14) or extra-gastric (N=32) mucosa-associated lymphoid tissue (MALT) lymphoma (40). ORR and CR rate was 80% and 54%, respectively, with combination therapy. At 27 months, 91% of patients remained progression-free with only 3 relapses noted. Non-hematologic AEs included infusion reactions (38%), musculoskeletal pain (42%), exanthema (46%), fatigue (33%), cough/respiratory infections (33%), diarrhea (23%), and vertigo (23%). G3-4 hematologic AEs included neutropenia (19%), leukopenia (4%), and anemia (2%).

In DLBCL, a single-center phase 2 trial assessed the safety and efficacy of lenalidomide (20 mg PO days 1-21 of cycles 1-4) plus rituximab (375 mg/m2 on day 1 and 21 of cycles 1-4) given every 28 days in 23 elderly patients with relapsed/refractory DLBCL (41). Responding patients received an additional 8 months of lenalidomide maintenance therapy at the same treatment schedule. ORR and CR rate at the end of induction was 35% and 30%, respectively. Disease-free survival at 1-year was 34.8% with an 18-month OS of 55.1%. The most common G3-4 AEs included neutropenia (30%), thrombocytopenia (14%), asthenia (5%), and anemia (5%).

A separate phase 2 trial assessed the efficacy of lenalidomide (20 mg PO days 1-21 every 28 days) and rituximab (375 mg/m2 weekly for cycle 1 only) in 45 patients with relapsed/refractory DLBCL (N=32), transformed lymphoma (N=9), or G3 FL (N=4) (42). ORR and CR rate was 33% and 22%, respectively, in all patients; 28% and 22% in DLBCL, 25% and 0% in G3 FL, and 55% and 33% in transformed lymphoma. Median DOR, PFS and OS was 10.2, 3.7 and 10.7 months, respectively. G3-4 AEs included neutropenia (53%), lymphopenia (40%), thrombocytopenia (33%), leukopenia (27%), and anemia (18%).

1.2.3.2.4 Obinutuzumab with Lenalidomide

The phase 1b GALEN study assessed the safety and efficacy of dose-escalated lenalidomide (10-25 mg PO days 1-21 of cycle 1 and days 2-22 of cycles 2-6) in combination with obinutuzumab (1000 mg IV days 8, 15 and 22 of cycle 1 and day 1 of cycles 2-6) every 28 days in 20 patients with relapsed/refractory FL after rituximab-containing therapy (43). Four DLTs occurred in 2 patients, all deemed unrelated to treatment, thus the MTD was not reached. The most common AEs included constipation (52.6%), neutropenia (47.4%), and asthenia (36.8%). Neutropenia accounted for 64.3% of all G3-4 AEs and was observed in 47.4% of patients. ORR and CR rate at the end of treatment was 63.2% and 57.9%, respectively. DOR, PFS and OS at 3-years was 68.4%, 52.1%, and 73.3%, respectively. Despite the absence of DLTs related to treatment, the recommended dose of lenalidomide in combination with obinutuzumab was established at 20 mg based on the risk of G3-4 neutropenia with this combination.

In the phase 2 portion of the GALEN study, 89 patients with relapsed/refractory G1-3A FL received induction therapy with lenalidomide (20 mg PO days 1-21 of cycle 1 and days 2-22 of cycles 2-6) and obinutuzumab (1000 mg IV days 8, 15, and 22 of cycle 1 and day 1 of cycles 2-6) every 28 days for 6 cycles (44). Responding patients received 1 year of maintenance lenalidomide (10 mg PO days 2-22 of cycles 7-18) with obinutuzumab (1000 mg IV day 1 on cycles 7, 9, 11, 13, 15, and 17) every 28 days for 12 cycles and 1 additional year of maintenance obinutuzumab (1000 mg IV day 1 of cycles 19-24) every 56 days for 6 cycles. In 86 evaluable patients, ORR and CR rate at end of induction was 79% and 38%, respectively. DOR, EFS, PFS, and OS at 2-years was 70%, 62%, 65%, and 87%, respectively. The most common AEs included asthenia (61%), neutropenia (43%), bronchitis (41%), diarrhea (40%), and muscle spasms (39%). The most common ≥G3 AE was neutropenia with G3 and G4 neutropenia observed in 23% and 21% of patients, respectively.

In a separate aggressive cohort of the phase 2 GALEN study, 85 patients with relapsed/refractory DLBCL (N=71), MCL (N=13), and unclassified aggressive NHL (N=1) received induction and maintenance therapy with lenalidomide and obinutuzumab (45). In DLBCL patients, ORR and CR rate at end of induction was 35.2% and 18.3%, respectively. Median PFS and OS was 4.1 months and 10.6 months, respectively. In MCL patients, ORR and CR rate at end of induction was 46.2% and 15.4%, respectively. Median PFS and OS was 5.8 months and not reached, respectively.

The most common AEs included neutropenia (54.5%), fatigue (36.4%), constipation (31.8%), and diarrhea (26.1%). The most common ≥G3 AEs included neutropenia (50%), thrombocytopenia (13.6%), and anemia (10.2%).

1.2.3.2.5 Rituximab, Ibrutinib, and Lenalidomide (RIL)

The phase 1 Alliance A051103 trial assessed the safety and activity of the combination of rituximab, ibrutinib and lenalidomide (RIL) in previously untreated patients with follicular lymphoma (46). A total of 22 patients were enrolled and DL2 (lenalidomide 20 mg days 1-21 x 18 cycles and ibrutinib 560 mg days 1-28 every 28 days until disease progression) was determined to be the recommended phase 2 dose in combination with rituximab (375 mg/m2 days 1, 8, 15 and 22 of cycle 1 and day 1 of cycles 4, 6, 8, and 10). ORR was 95% for the entire cohort with 36% CR. PFS at 12-months was 80%. Despite no protocol defined DLTs, there was a high incidence of rash noted with all grade and G3 rash observed in 82% and 36% of patients, respectively. G3-4 hematologic AEs included neutropenia (18%), thrombocytopenia (5%), anemia (5%), and lymphopenia (5%).

A separate phase 1b study evaluated the safety and activity of the combination of dose-escalated lenalidomide in combination with fixed-dose ibrutinib and rituximab (iR2) in patients with transplant-ineligible, relapsed/refractory DLBCL after at least 1 prior line of therapy (47). A total of 45 patients received iR2 and the MTD was not reached and lenalidomide 25 mg days 1-21 every 28 days was taken forward to phase 2 testing in combination with ibrutinib 560 mg days 1-28 and rituximab 375 mg/m2 on day 1 of cycles 1-6. In response-evaluable patients, ORR and CR rate was 44% and 28%, respectively. Based on cell-of-origin determined by IHC and Hans algorithm, ORR and CR rate was 65% and 41%, respectively, in non-GCB and 29% and 18%, respectively, in GCB DLBCL patients. Median DOR was 15.9 months overall; 15.9 months in non-GCB and 8.8 months in GCB DLBCL patients. Median PFS and OS was 5.5 months and 9.5 months, respectively, among all patients; 3.9 months and 10.7 months, respectively, in non-GCB and 5.5 months and 7.1 months, respectively, in GCB DLBCL patients. G3 of greater treatment-emergent AEs occurred in 76% of patients with the most frequent AEs including neutropenia (38% for ibrutinib and 40% for lenalidomide), maculopapular rash (13% for both ibrutinib and lenalidomide), and thrombocytopenia (9% for ibrutinib and 11% for lenalidomide). Treatment-related serious AEs occurred in 24% of patients and included febrile neutropenia, atrial fibrillation and dehydration in 7% of patients each.

1.2.3.2.6 ViPOR

A phase 1b/2 study of ViPOR in patients with relapsed/refractory B-cell lymphoma is currently ongoing (clinicaltrials.gov, NCT:03223610) with preliminary safety and efficacy data presented at the 15-International Conference on Malignant Lymphoma (15-ICML) and American Society of Hematology (ASH) annual meetings in 2019 and 2020 (6, 7, 48). Patients with relapsed/refractory B-cell lymphoma, excluding CLL/SLL, with adequate organ function were eligible for study. In the phase 1b portion of the study, a "3+3" design was used to determine the maximum tolerated dose (MTD) of 4 dose-levels (DLs) of dose-escalated venetoclax (200 mg, 400 mg, 600 mg, and 800 mg) PO D2-14 (starting cycle 2 for DL1) in combination with fixed-dose ibrutinib 560 mg PO D1-14, prednisone 100 mg PO D1-7, obinutuzumab 1000 mg IV D1-2, and lenalidomide 15 mg PO D1-14 in patients with non-MCL NHL. Phase 2 DLBCL and FL expansion cohorts were included at the MTD for a further analysis of safety and efficacy. A maximum of 6 cycles of ViPOR every 21 days was given unless disease progression or unacceptable toxicity. Tumor lysis

syndrome (TLS) prophylaxis with IV fluids and allopurinol was given to all patients and venous thromboembolism (VTE) prophylaxis and G-CSF use was per investigator discretion. Pre-treatment biopsies were obtained and analyzed for whole-exome sequencing, RNA-sequencing, and copy-number alterations. Baseline CT, PET, and bone marrow (BM) was performed in all patients with restaging CT scans after cycles 1, 2, 4, and 6 and PET after cycle 6 or at time of suspected complete response (CR).

At the time of most recent presentation, 58 patients had been enrolled; 20 in the phase 1b dose-escalation, 25 in the phase 2 DLBCL and 13 in the phase 2 FL dose-expansion cohorts. Histologic subtypes included diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) (N=20), follicular lymphoma (FL) (N=21), high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBCL-DH) (N=12), T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) (N=3), and marginal zone lymphoma (MZL) (N=2). Median (range) age was 58 years (29-83) with stage III/IV disease in 52 (90%), elevated LDH in 40 (69%), and $\geq$2 EN sites in 33 (57%) patients. Median (range) of prior therapies was 3 (1-9) and 27 (47%) patients were refractory to last therapy.

A single dose-limiting toxicity (DLT) of G3 intracranial hemorrhage (ICH) occurred at DL1. This event of G3 ICH occurred in a 61-year-old male with refractory non-GCB DLBCL involving the bilateral neck. The patient initiated ViPOR therapy at DL1 in early 2018 and due to disease compression, developed a left jugular vein DVT identified on CT scan of the neck about 1 week after initiation of treatment. The patient was initiated on therapeutic anticoagulation with enoxaparin 1 mg/kg subcutaneous twice daily and notably was maintained on his home dose of aspirin 81 mg by mouth daily taken for cardio prophylaxis. Due to altered mental status, a CT scan of the head was performed just over a week later demonstrated a subdural hematoma with acute components superimposed upon chronic components resulting in subfalcine and uncal herniation, and an 11 mm right-to-left midline shift. A concurrent CBC revealed a mild grade 1 thrombocytopenia with platelet count of 130 K/uL and a normal PT and aPTT at 13.5 and 34 sec, respectively. Enoxaparin and aspirin were stopped, and neurosurgery consulted. The patient underwent right parietal burr hole drainage of the subdural hematoma the next day with repeat drainage 2 days later due to increased subdural hematoma seen on follow-up CT head. Follow-up imaging repeated every few days in the following week showed expected evolution of blood products with no new hemorrhage identified. No other bleeding events or DLTs occurred on study and venetoclax 800 mg was used in expansion.

Hematologic adverse events (AEs) were most common with $\geq$G3 thrombocytopenia, neutropenia, and anemia in 52%, 52%, and 26% of patients and 23%, 22%, and 7% of cycles, respectively. G-CSF was given in 93% of patients in 90% of cycles and 3 events of G3 febrile neutropenia occurred across 267 total cycles of study therapy. Non-heme AEs were mainly G1-2 with rare G3-4 and no G5 treatment-related events. G3-4 non-hematologic AEs (% patients) included hypokalemia (19%), elevated LFTs (10%), diarrhea (7%), atrial fibrillation/flutter (5%), shingles (3%), vomiting, fatigue, fever, hypotension, UTI, dehydration, pneumoperitoneum, esophageal infection, ICH, MSSA infection, syncope, and TLS (2% each). Dose reductions and delays occurred in 21% and 29% of patients and 7% and 10% of cycles, respectively.

Of 53 patients off-therapy (33 completed all 6 cycles of therapy, 13 experienced disease progression, 5 experienced AEs resulting in study drug discontinuation, 1 withdrew consent after achieving CR following C4, and 1 was withdrawn per investigator discretion), 52 were evaluable for response with an overall response rate (ORR) of 71% (37/52) and 52% (27/52) CR, which

occurred across all DLs and NHL subtypes. In 56 evaluable patients overall (2 on active treatment), 89% (50/56) experienced tumor reduction. ORR and CR rate was 55% (17/31) and 35% (11/31) in aggressive and 95% (20/21) and 76% (16/21) in indolent NHL subtypes, respectively. Furthermore, ORR and CR rate was 64% (9/14) and 57% (8/14), respectively, in non-GCB and 47% (8/17) and 18% (3/17), respectively, in GCB DLBCL. Median TTR and DOR was 0.79 months and not reached, respectively, with 30 (73%) of 41 responses on-going. With a median potential follow-up of 14.7 months, 1-year PFS and OS was 33% and 47%, respectively, in aggressive NHL and 69% and 87%, respectively, in indolent NHL patients. Based on molecular subtype, 1-year PFS was 44% and 23%, respectively, with a 1-year OS of 59% and 38%, respectively, in non-GCB compared to GCB DLBCL.

Phase 1b/2 testing in patients with relapsed/refractory and untreated MCL as well as phase 2 testing in relapsed/refractory DLBCL and FL is currently ongoing.

1.2.4 Polatuzumab clinical studies in B-cell NHL

1.2.4.1 Summary of Polatuzumab Clinical Studies in B-cell NHL

Table 3: Polatuzumab Monotherapy and Combination Studies in FL and indolent B-cell NHL

Regimen	Dose of Pola	Phase	Disease	Patient #	ORR	CR	Reference
Polatuzumab	≤ 1.8 mg/kg	1	R/R indolent NHL	8	0%	0%	Palanca-Wessels et al. Lancet Oncol. 2015;16:704-15.
	2.4 mg/kg			15	47%	20%	
Polatuzumab + Rituximab		2	R/R FL	20	70%	45%	Morschhauser et al. Lancet Haematol. 2019;6:e254-65.
Polatuzumab + G-Len	1.4 mg/kg	½		56	76%	65%	Diefenbach et al. Blood. 2019; 134: 126 (abstract).

Table 4: **Polatuzumab Monotherapy and Combination Studies in DLBCL.**

Regimen	Dose of Pola	Phase	Disease	Patient #	ORR	CR	Reference
Polatuzumab	≤ 1.8 mg/kg	1	R/R DLBCL	12	25%	0%	Palanca-Wessels et al. Lancet Oncol. 2015;16:704-15.
	2.4 mg/kg			25	56%	16%	
Polatuzumab + Rituximab		2		39	54%	21%	Morschhauser et al. Lancet Haematol. 2019;6:e254-65.
Polatuzumab + BG	1.8 mg/kg	1/2	R/R DLBCL (transplant-ineligible)	27	41%	40%	Sehn et al. J Clin Oncol. 2020;38(2):155-65.
Polatuzumab + BR		2		40 (All)	45%	40%	
				17 (ABC)	59%	47%	
				15 (GCB)	33%	27%	
Polatuzumab + R/G-CHP		1/2	Untreated DLBCL	66 (All)	89%	77%	Tilly et al. Lancet Oncol. 2019;20:998-10.
				16 (ABC)	88%	81%	
				28 (GCB)	100%	89%	

Regimen	Dose of Pola	Phase	Disease	Patient #	ORR	CR	Reference
				7 (Uncl.)	71%	57%	

1.2.4.2 Monotherapy studies

A phase 1, multicenter study assessed the safety and preliminary activity of polatuzumab (0.1-2.4 mg/kg IV every 21 days) in patients with relapsed/refractory B-cell NHL or CLL (49). Polatuzumab vedotin was given both as monotherapy and in combination with rituximab in dose escalation and dose expansion cohorts in order to identify the MTD and R2PD in separate cohorts of NHL and CLL. A total of 95 patients were enrolled and the RP2D of polatuzumab in NHL was determined to be 2.4 mg/kg IV every 3 weeks as a single agent and in combination with rituximab 375 mg/m2. In patients treated at the RP2D of polatuzumab monotherapy, G3-4 AEs occurred in 58% of NHL patients with the most common G3-4 AEs including neutropenia (40%), anemia (11%), and peripheral sensory neuropathy (9%). In patients treated with the combination of polatuzumab and rituximab, G3-4 AEs occurred in 77% of NHL patients with the most common G3-4 AEs including neutropenia (56%), anemia (22%), and febrile neutropenia (22%). At the R2PD, ORR and CR rate was 55% and 17%, respectively, with polatuzumab monotherapy and 78% and 22%, respectively, with polatuzumab in combination with rituximab. Single agent polatuzumab demonstrated clinical activity across all NHL subtypes, including DLBCL (ORR 56%, CR 16%), indolent NHL (ORR 47%, CR 20%), and MCL (ORR 100%, CR 0%). Median DOR and PFS for NHL patients treated at the RP2D of polatuzumab monotherapy was 6.2 months and 5.7 months, respectively; 5.2 months and 5.0 months, respectively, in DLBCL and not reached and 7.9 months, respectively, in indolent NHL. Median DOR and PFS was 12.3 months and 12.5 months, respectively, in patients treated with polatuzumab in combination with rituximab. Pharmacokinetic parameters were not affected by rituximab coadministration.

In a subgroup analysis of DLBCL patients treated on the phase 1 study, clinical responses were observed across both ABC and GCB molecular subtypes of DLBCL (14). In 29 patients treated with polatuzumab at doses $\geq$ 1.8 mg/kg, 16 (55%) experienced a response to therapy with 3 (10%) achieving CR. Molecular DLBCL subtype classification was available in 15 of these patients with 4 (80%) of 5 ABC DLBCL patients responding (1 CR) and 5 (56%) of 9 GCB DLBCL patients responding (all PRs). One patient with unclassified DLBCL failed to respond to polatuzumab.

Because of the adverse event profile of polatuzumab at the 2.4 mg/kg dose, subsequent studies utilized a 1.8 mg/kg dose. The 1.8 mg/kg dose for polatuzumab is also the FDA approved dose.

1.2.4.3 Combination studies

Several studies have investigated various combinations of polatuzumab with anti-CD20 monoclonal antibodies (i.e., rituximab or obinutuzumab), combination chemotherapy, as well as targeted agents in the treatment of patients with B-cell NHL.

1.2.4.3.1 Polatuzumab with anti-CD20 therapy

The phase 2 randomized ROMULUS study evaluated the safety and efficacy of the anti-CD79b antibody-drug conjugate (ADC) polatuzumab (2.4 mg/kg IV every 21 days) compared to the anti-CD22 ADC pinatuzumab (2.4 mg/kg IV every 21 days) in combination with rituximab (375 mg/m2 IV every 21 days) for up to 1 year in 123 patients with relapsed/refractory DLBCL (N=81) and FL (N=42) (50). Of the 39 DLBCL patients treated with R-pola, ORR was 54% with a CR rate of

21%. Median DOR, PFS and OS in DLBCL patients was 13.4, 5.6, and 20.1 months, respectively. Of the 20 FL patients treated with R-pola, ORR was 70% with a CR rate of 45%. Median DOR and PFS in FL patients was 9.4 and 15.3 months, respectively, with a 2-year OS of 87.8%. G3-4 AEs occurred in 77% of DLBCL patients treated with R-pola, most commonly neutropenia (23%), anemia (8%), and diarrhea (8%). G3-4 AEs occurred in 50% of FL patients treated with R-pola, most commonly neutropenia (15%) and diarrhea (10%). Based on this study, polatuzumab was selected for further development in NHL based on its longer DOR (13.4 vs. 6.2 months in DLBCL and 9.4 vs. 6.5 months in FL) and overall favorable risk-benefit profile compared to pinatuzumab.

1.2.4.3.2 Polatuzumab with combination immunochemotherapy

The randomized phase 1b/2 GO29365 trial investigated the safety and efficacy of polatuzumab (1.8 mg/kg IV on day 2 of cycle 1 and day 1 of cycles 2-6) in combination with bendamustine and rituximab (pola-BR) or bendamustine and obinutuzumab (pola-BG) in 113 patients with relapsed/refractory DLBCL who either failed or were ineligible for ASCT (51). Pola-BR patients (N=40) had a significantly higher CR rate (40% vs. 17.5%, P=0.026) as well as improved median PFS (9.5 vs. 3.7 months, HR 0.36, P<0.001) and OS (12.4 vs. 4.7 months, HR 0.42, P=0.002) compared to patients treated with BR alone (N=40). CR rate was 29.6% in patients treated with pola-BG (N=27) with a median PFS and OS of 6.3 months and 10.8 months, respectively. Polatuzumab improved outcome in DLBCL patients regardless of COO with higher CR rate (47.1% vs. 11.1% in ABC and 26.7% vs. 11.8% in GCB) and improved median PFS (10.76 vs. 1.97 months, HR 0.20, in ABC and 2.5 vs. 1.87 months, HR 0.49, in GCB) and OS (15.38 vs. 4.73 months, HR 0.21, in ABC and 7.23 vs. 3.81 months, HR 0.57, in GCB) with Pola-BR compared to BR alone. Pola-BR resulted in higher G3-4 neutropenia (46.2% vs. 33.3%), anemia (28.2% vs. 17.9%), and thrombocytopenia (41.0% vs 23.11%), but similar G3-4 infections (23.1% vs. 20.5%) compared to BR alone. G1-2 peripheral neuropathy occurred in 43.6% of patients treated with polatuzumab and resolved in most patients. Based on this study, the FDA granted accelerated approval to polatuzumab vedotin on June 10, 2019, in combination with bendamustine and rituximab for adult patients with relapsed or refractory DLBCL NOS after at least 2 prior therapies.

A phase 1b/2 study assessed the safety and preliminary activity of polatuzumab (1.0-1.8 mg/kg IV) in combination with rituximab (R) or obinutuzumab (G) and cyclophosphamide, doxorubicin, and prednisone (CHP) in patients with untreated or relapsed/refractory NHL (phase 1b) and untreated DLBCL (phase 2) (52). A total of 85 patients were enrolled with 25 NHL patients in the phase 1b dose escalation and 57 untreated DLBCL patients in the phase 2 expansion cohorts evaluable for safety and efficacy. Due to information gained from other studies, polatuzumab doses >1.8 mg/kg were not explored and the RP2D of polatuzumab was determined to be 1.8 mg/kg IV every 3 weeks in combination with R-CHP or G-CHP. The most common ≥G3 AEs in DLBCL patients treated at the RP2D included neutropenia (30%), febrile neutropenia (18%), and thrombocytopenia (9%). Of 66 previously untreated DLBCL treated at the RP2D of polatuzumab in combination with R-CHP or G-CHP, ORR and CR rate at the end of treatment was 89% and 77%, respectively. Based on Cell of Origin (COO) by Nanostring gene expression profiling (GEP), ORR and CR rate was 88% and 81% in ABC (N=16), 100% and 89% in GCB (N=28), and 71% and 57% in unclassified (N=7) DLBCL patients. Pharmacokinetic analyses revealed no clinically relevant effects of the combination of CHP on the pharmacokinetics of the antibody-conjugated or unconjugated MMAE. Furthermore, plasma concentrations of cyclophosphamide and doxorubicin were similar prior to and after the administration of polatuzumab suggesting a low-risk of polatuzumab affecting the pharmacokinetics of these agents in combination.

Based on the above phase 1b/2 study, a double-blind, placebo-controlled, international phase 3 study was conducted in 879 patients with previously untreated intermediate-risk or high-risk DLBCL randomized 1:1 to 6 cycles of treatment with polatuzumab + R-CHP (N=440) or standard R-CHOP (N=439), both with 2 additional cycles of Rituximab monotherapy (53). After a median follow-up of 28.2 months, PFS was significantly higher in patients treated with pola-R-CHP compared to R-CHOP, with a 2-year PFS of 76.7% and 70.2% (P=0.02), respectively. There was no difference in overall survival between the two treatment arms with a 2-year OS of 88.7% and 88.6% (P=0.75) in the pola-R-CHP and R-CHOP groups, respectively. Additionally, the PFS benefit observed with pola-R-CHP was preferentially observed in the ABC subtype of DLBCL compared to those with GCB or unclassified DLBCL as well as in those patients with DLBCL NOS without double or triple-hit lymphoma.

1.2.4.3.3 Polatuzumab with anti-CD20 therapy and Lenalidomide

The phase 1b/2 GO29834 study evaluated the safety and efficacy of the combination of polatuzumab (1.4 mg/kg IV on day 1 of cycles 1-6) with obinutuzumab (1000 mg IV day 1, 8, and 15 of cycle 1, day 1 of cycles 2-6, and day 1 every 2 months for 24 months) and lenalidomide (20 mg PO days 1-21 every 28 days for cycles 1-6 then 10 mg PO days 1-21 for 12 months) in 56 patients with relapsed/refractory FL (G1-3A) (54). G3-4 AEs occurred in 79% of patients, most commonly neutropenia (50%), thrombocytopenia (23%), infections (16%), and anemia (14%). ORR and CR rate at the end of induction therapy (6 cycles) was 76% and 65%, respectively, in evaluable patients and median PFS was not reached with a median follow-up of 11.27 months.

1.2.4.3.4 Polatuzumab with anti-CD20 therapy and Venetoclax

The pro-survival BCL-2 protein family member MCL-1 has been identified as a venetoclax resistance factor in NHL cell lines and the MMAE payload of the ADC polatuzumab has been shown to promote MCL-1 degradation via the ubiquitin/proteasome system. Based on this pre-clinical rational, a phase 1b clinical trial was performed to assess the safety and preliminary efficacy of the combination of polatuzumab with obinutuzumab and venetoclax in 33 patients with relapsed/refractory FL. Preliminary results presented in abstract form at the 2020 AACR annual meeting revealed an ORR and CR rate of 76% and 56%, respectively, with all 8 patients treated at the RP2D of the regimen (venetoclax 800 mg PO + polatuzumab 1.8 mg/kg IV + obinutuzumab 1000 mg IV) achieving CR at the end of induction therapy.

1.2.4.3.5 ViPOR-P

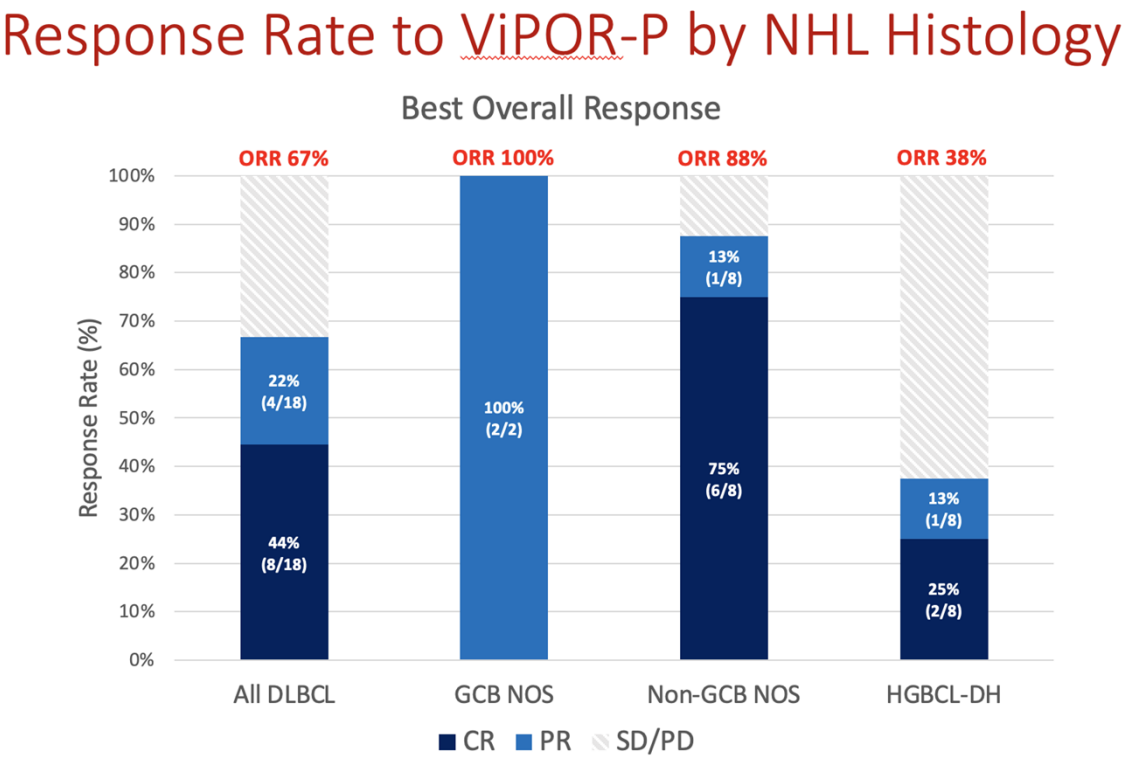
Preliminary safety and efficacy results of this ongoing phase 1study of ViPOR-P in patients with relapsed/refractory B-cell lymphoma have been presented at the American Society of Hematology (ASH) annual meeting in 2022 (55).

Fifteen (15) patients were enrolled and treated in the phase 1 dose-escalation cohort (3 at DL1, 6 at DL2, and 6 at DL3), with an additional 4 patients treated in dose expansion, for a total of 19 patients enrolled and treated. Lymphoma subtypes included 11 (58%) patients with DLBCL NOS and 8 (42%) patients with HGBCL-DH. Nine (47%) patients were non-GCB (all DLBCL NOS) and 10 (53%) were GCB (including 2 DLBCL NOS + 10 HGBCL-DH) subtype by IHC. Four (21%) patients had transformed disease. Median age was 51 (range 23-83) years, with stage III/IV disease in 79%, elevated LDH in 84%, and $\geq$2 extranodal sites of disease in 68%. Twelve (63%) patients had high-intermediate or high-risk IPI score. Median prior therapies were 2 (range 1-6), with prior BTKi in 21%, Polatuzumab in 16%, and CAR-T in 32%. Twelve (63%)

patients were primary refractory (i.e., <CR to frontline treatment) and 10 (53%) of patients were refractory (i.e., <PR) to last treatment.

One dose-limiting toxicity (DLT) of prolonged G4 thrombocytopenia occurred at DL3, but no other DLTs were noted. Polatuzumab 1.8mg/kg and Venetoclax 800mg were identified as the MTD and safe doses for use in the expansion cohort. Hematologic AEs were most common and included G3-4 (% cycles) thrombocytopenia (20%), neutropenia (13%), and anemia (5%). No cases of febrile neutropenia occurred across 75 total cycles. The only non-heme G3-4 AE occurring in >10% patients was hypokalemia (22%), with 94% of patients experiencing any grade hypokalemia requiring replacement. Other common non-heme AEs (% pts) included diarrhea (83%), increased ALT (61%), increased AST (56%), nausea (56%), increased alkaline phosphatase (50%), hypomagnesemia (39%), rash (39%), and increased bilirubin (33%). VTE occurred in 1 (6%) patient with no atrial fibrillation or major bleeding observed. No events of TLS or treatment-related mortality occurred. Dose reductions occurred in 16% of patients and 63% of patients completed all 6 cycles of study therapy. Of 16 patients off-treatment, 10 completed all 6C of therapy, 4 experienced disease progression, and 1 each came off-treatment per investigator discretion or unacceptable AE.

Of 19 enrolled patients (1 patient had not yet undergone restaging imaging), 18 are evaluable for response with tumor reduction observed in 89% (16/18) of patients and an overall response rate (ORR) and CR rate of 67% (12/18) and 44% (8/18), respectively. ORR and CR rate was 88% (7/8) and 75% (6/8), respectively, in non-GCB DLBCL NOS, 100% (2/2) and 0% (0/2), respectively, in GCB DLBCL NOS, and 38% (3/8) and 25% (2/8), respectively, in HGBCL-DH.



Of 8 total CRs, 7 (88%) are ongoing with 1 HGBCL-DH patient relapsing with indolent FL 6.5m post-treatment. With a median follow-up of 8m, 6-month PFS and OS was 71% and 68%, respectively.

Given the promising CR rate of 75% in patients with non-GCB DLBCL with ViPOR-P, an additional expansion cohort of patients with non-GCB DLBCL is being added in order to better assess the CR rate in this molecular DLBCL subtype and compare the CR rate of ViPOR-P to ViPOR in patients with non-GCB DLBCL.

1.3 JUSTIFICATION OF STUDY DESIGN

This non-randomized, single-center, open-label, phase 1study is designed to determine the maximum tolerated dose (MTD) of polatuzumab and venetoclax when given in combination with ibrutinib, prednisone, obinutuzumab and lenalidomide (ViPOR-P) for the treatment of relapsed/refractory B-cell lymphomas. A small expansion cohort at the MTD will be included for a further analysis of safety and preliminary determination of clinical activity. An additional expansion cohort of patients with non-GCB DLBCL treated at the MTD will be performed to assess the CR rate to ViPOR-P in this molecular subtype.

In the previously presented phase 1b/2 study of ViPOR in relapsed/refractory B-cell lymphomas, a solitary DLT occurred at dose level 1 with no additional DLTs encountered and thus venetoclax 800 mg days 2-14 of each cycle was taken forward in the phase 2 expansion portion of the study. Furthermore, this study demonstrated that a 12-day ramp-up of venetoclax (cycle 2 for the first patient cohort and cycle 1 for all other patient cohorts) was safe with only a single episode of tumor lysis syndrome (TLS) in a high-risk patient with transformed “double hit” DLBCL after the first dose of venetoclax (50 mg). In the phase 1b CAVALLI study, venetoclax 800 mg in combination with R-CHOP was determined to be safe in patients with relapsed/refractory B-cell NHL and venetoclax 800 mg days 4-10 of cycle 1 and days 1-10 of cycles 2-8 was taken forward in the phase 2 portion of the study in combination with R-CHOP in untreated patients with DLBCL. Three patients (5.4%), all FL and high-risk for TLS, developed laboratory TLS without clinical sequelae and none required permanent discontinuation of study therapy. Given the presence of only a single episode of TLS in the ViPOR study with venetoclax up to 800 mg given on days 2-14 of each cycle, and the safe administration of venetoclax up to 800 mg on days 4-10 of cycle 1 and days 1-10 of cycles 2-8 with R-CHOP without a ramp-up in the CAVALLI study, we propose a dose of venetoclax 600 mg given on days 2-14 of each cycle with the ViPOR-P regimen. Given the potential for overlapping hematologic toxicity, mainly neutropenia, with the addition of polatuzumab to ViPOR, a lower starting dose of venetoclax 600 mg was chosen for this study when given in combination with polatuzumab in order to mitigate the overlapping risk of neutropenia. Venetoclax dosing starts on day 2 of each cycle to allow administration of obinutuzumab on days 1 and 2 and mitigate the overlapping risk of tumor lysis syndrome (TLS).

Given the overall low rate of neutropenia seen in patients treated at DL1 and DL2 of the study when given with universal G-CSF prophylaxis and that the venetoclax dose was initially reduced from the recommended phase 2 dose of 800 mg in the original ViPOR study to 600 mg due to concerns of neutropenia which have not been encountered, an additional dose-level 3 using full dose Polatuzumab at 1.8 mg/kg IV on day 2 and Venetoclax 800 mg PO daily days 2-14 of each cycle was added as a study amendment on 10/25/2021.

All other ViPOR agents will be as per the original phase 1b/2 study including: ibrutinib 560 mg and lenalidomide 15 mg PO daily days 1-14, obinutuzumab 1000 mg IV on days 1 and 2, and

prednisone 100 mg PO daily days 1-7. A maximum of 6 cycles every 21 days will be given unless disease progression or unacceptable toxicity.

Two different dose levels of polatuzumab (1.4 mg/kg, and 1.8 mg/kg) along with two different dose levels of venetoclax (600 mg and 800 mg) will be tested in combination with fixed-dose ibrutinib, prednisone, obinutuzumab, and lenalidomide as above in patients with relapsed/refractory B-cell lymphomas.

In addition, correlative assays will investigate molecular correlates of response or resistance to ViPOR-P and will assess complete molecular remission, as determined by circulating tumor DNA (ctDNA). In tumor and other samples, analyses may include gene expression profiling, RNA-sequencing, whole-exome and/or whole-genome sequencing. These comprehensive molecular characterizations may identify altered signaling patterns or mutations that are associated with response or resistance to study therapy.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically confirmed B-cell lymphoma confirmed by the Laboratory of Pathology, NCI, as follows:

Cohorts 1 and 2:

- Aggressive B-cell lymphoma: includes DLBCL and subtypes, transformed lymphoma, Burkitt lymphoma, as well as high-grade B-cell lymphoma with *MYC* and/or *BCL2* and/or *BCL6* rearrangement(s).
- Indolent B-cell lymphoma: with the following exceptions:
  - MCL is excluded given increased risk of tumor lysis syndrome (TLS) with venetoclax compared to other non-Hodgkin lymphomas and need for venetoclax ramp-up, dose-escalation.

    CLL/SLL is excluded given alternative dosing of FDA-approved venetoclax for relapsed CLL/SLL and increased risk of TLS with CLL/SLL compared to other non-Hodgkin lymphomas.

Cohort 3:

- Non-GCB DLBCL: includes DLBCL NOS and subtypes, transformed lymphoma, THRLBCL, as well as high-grade B-cell lymphoma with *MYC* and/or *BCL6* rearrangement(s).

NOTE: Patients with known active CNS lymphoma are not eligible.

2.1.1.2 Relapsed and/or refractory disease after at least 1 prior treatment regimen, as follows:

- Aggressive B-cell lymphoma: relapsed after and/or refractory to at least 1 prior anthracycline-containing regimen
- Indolent B-cell lymphoma: relapsed after and/or refractory to at least 1 prior anti-CD20 antibody-containing regimen.

2.1.1.3 Patients must have evaluable disease by clinical exam (i.e., palpable lymphadenopathy, measurable skin lesions, etc.), laboratory assessment (i.e., lymphoma involvement of bone marrow or peripheral blood by morphology, cytology or flow cytometry), and/or

imaging (measurable lymph nodes or masses 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

NOTE: Because no dosing or adverse event data are currently available on the use of polatuzumab in combination with venetoclax, ibrutinib, obinutuzumab, prednisone and Revlimid® in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

2.1.1.5 ECOG performance status ≤2 (see **APPENDIX B**).

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

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 patients not receiving therapeutic anticoagulation
PTT/aPTT	≤1.5 X institutional ULN normal except if, in the opinion of the investigator, the aPTT is elevated because of a positive Lupus Anticoagulant, or a significant bleeding risk has been ruled out in the absence of a positive Lupus Anticoagulant
total bilirubin	≤1.5 X institutional ULN (or ≤3 X institutional ULN for patients with documented Gilberts syndrome identified by an isolated unconjugated hyperbilirubinemia in the absence of other signs of liver dysfunction and/or *UGT1A1* mutational testing)
AST(SGOT)/ALT(SGPT)	≤3 X institutional ULN
Serum creatinine	≤ 2.0 mg/dL
OR	
Creatinine clearance	≥30 mL/min/1.73 m^2 for patients with creatinine levels above 2 mg/dL NOTE: Cr Cl will be calculated with the use of the 24-hour creatinine clearance or eGRF in the clinical lab
*RBC transfusions and use of G-CSF will be allowed in order to meet eligibility parameters.	

2.1.1.7 Immune-modulating drugs (IMiDs) including Revlimid® are known to be teratogenic and potential embryo-fetal harm can be seen with use of polatuzumab, venetoclax and ibrutinib. The effects of obinutuzumab on the developing human fetus is unknown. For these reasons, individuals of child-bearing potential and individuals able to father a child must agree to use adequate contraception as described below

- For individuals of childbearing potential:
  - Agreement to remain abstinent (refrain from heterosexual intercourse) or use a

contraceptive method with a failure rate of < 1% per year as outlined below.
- Agreement to refrain from donating eggs during timelines specified below.
- Individuals of childbearing potential (ICBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10–14 days and again within 24 hours prior to prescribing Revlimid® for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS™) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking Revlimid® ICBP must also agree to ongoing pregnancy testing. See **APPENDIX G**.
- An individual is considered to be of childbearing potential if that person is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- For individuals able to father a child:
  - Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
  - With partners of childbearing potential, individuals able to father a child must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year as noted below. Individuals must refrain from donating sperm during this same period. See **APPENDIX G**.
  - With pregnant partners, individuals must remain abstinent or use a condom as noted below to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraception Requirements		
Time frame/Study Drug	**Individuals of childbearing potential**	**Individuals able to father a child**
Pre-Treatment/During Treatment	*Time frame prior to/during dosing:*	
All drugs	Begins 28 days prior to treatment	Begins on day 1
Post-Treatment	*Time frame after the last dose:*	
Venetoclax	30 days	90 days
Ibrutinib	1 months	1 months
Obinutuzumab	18 months	6 months
Revlimid®	28 days	28 days
Polatuzumab	9 months	6 months

2.1.1.8 All study participants must be registered into the mandatory Revlimid REMS™ program and be willing and able to comply with the requirements of Revlimid REMS™. **NOTE:** Individuals of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS™ program.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

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:

- Patients who are actively receiving any other investigational agents.
- Any chemotherapy or anti-cancer antibodies within 2 weeks. **NOTE:** Short courses of corticosteroids or palliative XRT prior to enrollment are permitted within the 2-week washout period.
- Radio- or toxin-immunoconjugates within 10 weeks.
- Previous treatment with more than one of the study agents (i.e., polatuzumab, venetoclax, ibrutinib, or Revlimid®), excluding prior prednisone or anti-CD20 antibody treatment.
- 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.
- 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 subject at unacceptable risk of participation in the opinion of the PI (e.g., alopecia).

2.1.2.2 Patients requiring the use of warfarin are excluded because of potential drug-drug interactions that may potentially increase the exposure of warfarin.

2.1.2.3 Patients requiring the following agents to the first dose of venetoclax or ibrutinib are excluded, as noted:

- Strong CYP3A inhibitors (see **APPENDIX C**) within 7 days
- Strong CYP3A inducers (see **APPENDIX C**) within 7 days

NOTE: Moderate CYP3A inhibitors and inducers should be used with caution (see Section **4.1.9**) and an alternative medication used, whenever possible.

2.1.2.4 Uncontrolled intercurrent illness including, but not limited to the following that may limit interpretation of results or that could increase risk to the patient at the discretion of the investigator:

- Symptomatic congestive heart failure, unstable angina pectoris, or uncontrolled cardiac arrhythmia
- Uncontrolled and/or symptomatic thyroid disease
- 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 Cycle 1, Day 1;
- 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:
  - Patients who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation
  - Patients with occult or prior HBV infection (defined as positive hepatitis B surface antigen (HBsAg) or positive hepatitis B core antibody (HBcAb) and with negative HBsAg) may be included if HBV DNA is undetectable (i.e., "none detected" in copies/mL or IU/mL). These patients must be willing to undergo HBV DNA testing during treatment and in surveillance for at least 12 months after completion of study therapy.
- Malabsorption syndrome or other condition that precludes enteral route of administration
- Psychiatric illness/social situations that would limit compliance with study requirements

2.1.2.5 Pregnant individuals, or individuals who intend to become pregnant during the study, are excluded from this study because Revlimid® has known teratogenic effects and polatuzumab, venetoclax, ibrutinib and obinutuzumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, nursing should be discontinued if the individual is treated on study.

2.1.2.6 HIV-positive patients are ineligible because of the potential for pharmacokinetic interactions with venetoclax, ibrutinib and Revlimid® and combination antiretroviral therapy. In addition, these patients are at increased risk of lethal infections when treated

with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

2.1.2.7 Evidence of active tumor lysis syndrome based on laboratory assessment

2.1.2.8 History of recent major surgery within 6 weeks prior to the start of Cycle 1, Day 1 other than for diagnosis

2.1.2.9 History of other active malignancy that could affect compliance with the protocol or interpretation of results

- Patients with a history of curatively treated basal or squamous cell carcinoma or stage 1 melanoma of the skin as well as any in situ carcinoma are eligible.
- Patients with a malignancy that has been treated with curative intent will also be eligible. Individuals in documented remission who are not receiving active treatment prior to enrollment may be included at the discretion of the investigator.

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

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 patients screened in the lymphoid malignancies' clinic of the National Institutes of Health. These will include both referrals from outside physicians as well as patient 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 subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- 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 subject has signed the study consent on which screening activities will be performed

Assessments and procedures to confirm study eligibility should be completed within 28 days prior to the start of study treatment (unless otherwise noted). See also the Schedule of Assessments provided in **APPENDIX A**.

2.2.2.1 Clinical Assessments

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

- Complete medical history, including: all active conditions considered to be clinically significant by the treating investigator
- Physical examination, including: height (screening only), weight, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status using the ECOG scale

2.2.2.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- CBC with differential
- Chemistry panels (as noted) or specific analyte required for eligibility, including: Creatinine and potassium (i.e., or Acute Care Panel); calcium and phosphate (i.e., or Mineral Panel); ALT, AST, total bilirubin (i.e., or Hepatic Panel); and, 24-hour urine creatinine clearance (if needed to measure CrCl in cases where serum creatinine >2.0 mg/dl)
- Others: Lactic dehydrogenase (LDH) and Uric acid
- Coagulation panel, including: PT/INR and aPTT
- Thyroid function, including: thyroid stimulating hormone (TSH); if abnormal, other testing may be done at the discretion of the investigator (e.g., T3 and/or T4)
- Urinalysis
- 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)
    - Patients who are HBsAg positive or HBcAb positive are required to have viral load testing by HBV PCR. If HBV DNA > 100 IU/mL they are ineligible and should be referred to hepatology for HBV treatment prior to study enrollment. If HBV DNA < 100 IU/mL they should have repeat testing approximately 2 weeks later and if continued positivity should be referred to hepatology for HBV treatment prior to study enrollment (See Section **4.1.7**).
    - Patients 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 study therapy.
- Urine and/or serum HCG in individuals of childbearing potential (within 10-14 days prior to initiation of Revlimid® and again within 24 hours prior to within initiation of Revlimid®
    - A pregnancy test (urine or serum) with a sensitivity of 25 mIU/mL must be done in accordance with Celgene Revlimid REMS™ guidelines for individuals of childbearing potential (ICBP) only. If the pregnancy test is positive, the subject is not eligible.
    - A ICBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months)

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, MRI and/or PET instead and should continue to be measured by CT, MRI and/or PET 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 or as clinically indicated)

2.2.2.4 Other Assessments and Procedures

- Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit)
- Electrocardiogram (EKG)
- Venous Thromboembolism Risk Assessment
  - The subject's risk for development of venous thromboembolism (VTE) will be assessed. General risk factors for subjects with cancer include, but are not limited to: underlying disease, family history, age, obesity, immobilization, hormonal therapy, central venous catheter, recent DVT, sex, renal dysfunction and certain chemotherapy-based regimens. It is not known whether prophylactic anticoagulation or anti-platelet therapy prescribed in conjunction with Revlimid® may lessen the potential for venous thromboembolism. It is up to the discretion of the Investigator after consideration of the subject's individual risk/benefit profile whether to institute VTE prophylaxis using a permitted concomitant medication (see Section **4.1.8**). It is recommended that protocol appropriate VTE prophylaxis be used in subjects considered at high-risk for thrombosis; however, they will not specifically be considered ineligible for participation due to high risk.
  - This assessment must be performed at the Screening Visit and may be performed anytime thereafter as appropriate. Refer to Section **3.3** for dose modification in the event a VTE occurs while on treatment.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

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

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries

from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an eligibility criterion (e.g., laboratory parameter) may be rescreened.

2.3.2 Treatment Assignment Procedures

2.3.2.1 Cohorts

Number	Name	Description
1	Indolent and Aggressive B-cell Lymphoma: Dose Escalation	Relapsed/refractory indolent and aggressive B-cell lymphoma after 1 prior treatment regimen (closed as of 02/15/2023)
2	Indolent and Aggressive B-cell Lymphoma: Dose Expansion	Relapsed/refractory indolent and aggressive B-cell lymphoma after 1 prior treatment regimen (closed as of 02/15/2023)
3	Non-GCB DLBCL: Dose Expansion	Relapsed/refractory non-GCB DLBCL after 1 prior treatment regimen (up to 32 evaluable patients at the MTD – includes 25 new patients in addition to 7 patients already enrolled in cohorts 1 (DL3) and 2 with non-GCB DLBCL)

2.3.2.2 Arms

Number	Name	Description
1	Experimental Treatment: Dose Escalation	Venetoclax (PO) at escalating doses (2 dose levels) on days 2-14, ibrutinib (PO) 560mg on days 1-14, prednisone (PO) 100mg on days 1-7, obinutuzumab 1000mg (IV) on days 1 and 2, lenalidomide (PO) 15mg on days 1-14, and polatuzumab (IV) at escalating doses (2 dose levels) on day 2 of each 21-day cycle (maximum 6 cycles) to determine MTD of polatuzumab and venetoclax
2	Experimental Treatment: Dose Expansion	Venetoclax (PO) at the MTD days 2-14, ibrutinib (PO) 560mg on days 1-14, prednisone (PO) 100mg on days 1-7, obinutuzumab 1000mg (IV) on days 1 and 2, lenalidomide (PO) 15mg on days 1-14, and polatuzumab (IV) at the MTD of each 21-day cycle (maximum 6 cycles)

2.3.2.3 Arm Assignment

Patients in cohort 1 are assigned to arm 1, and patients in cohorts 2 and 3 are assigned to arm 2.

2.4 BASELINE EVALUATION

The following 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 (**APPENDIX A**) for tests required within 7 days of first dose of study drug (pre-C1D1 assessments); tests performed as part of Screening/Baseline do not need to be repeated if they were performed within the specified window.

It should be noted that some patients 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 patient 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.

2.4.1 Clinical Evaluations

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

2.4.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- CBC with differential
- Chemistry panels, including: Acute Care Panel (sodium, potassium, chloride, CO_2, glucose, BUN, creatinine), Mineral Panel (serum calcium, phosphate, magnesium and albumin), Hepatic Panel (alkaline phosphatase, ALT, AST, total and direct bilirubin), and 24-hour urine creatinine clearance (if needed to measure CrCl)
- Others: LDH, Uric acid, Total protein, and Beta-2 microglobulin
- Quantitative PCR analysis (blood): EBV, CMV
- Lymphocyte Phenotype: T, B and NK cell subsets. **NOTE:** The blood sample(s) for T/B/NK cell count (i.e., CD3+, CD4+, CD8+, CD19+, CD16/56+) must be taken; percentages and absolute counts of CD3+, CD4+, CD8+, CD19+, and CD16/56+ cells will be collected.
- Required within 24 hours:
  - Urine and/or serum HCG in ICBP (see Section **2.1.1.7** for requirements)

2.4.3 Other Procedures

- Registration into the Revlimid REMS™ program
- Bone marrow aspiration and biopsy. **NOTE:** A unilateral bone marrow aspirate and biopsy must be obtained up to 28 days prior to the first administration of study drug. Subjects who have a bone marrow aspirate and biopsy result since completion of their last therapy may use those bone marrow results, provided the biopsy/aspirate was done <28 days prior to first dose of study drug.

2.4.4 Research Correlates

NOTE: See Section **5** for additional information. The following sample types will be collected for correlative research studies:

- Samples collected for germline DNA: i.e., blood, buccal swab, or saliva (preferred) (no time limit; may be collected after enrollment/registration)

- Blood Samples (See Section **5**)
- Tumor Samples – Archival: Tissue from original diagnosis or other procedures for routine care will be accessed for research correlates, if available.
- Tumor Samples – Fresh Biopsy: OPTIONAL
  - Patients with accessible tumor tissue who agree to have an optional biopsy performed will be biopsied at least 3 days prior to treatment. For these biopsies, fresh frozen and/or formalin-fixed, paraffin-embedded (FFPE) tissue will be collected.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

To determine the maximum tolerated dose (MTD), and the safety and toxicity profile of polatuzumab and venetoclax in combination with ibrutinib, prednisone, obinutuzumab and Revlimid® (i.e., ViPOR-P) in relapsed/refractory B-cell lymphomas, a phase 1, open-label, non-randomized, single-center study will be conducted at the NCI. A standard "3 + 3" design will be used to determine the MTD of polatuzumab and venetoclax in combination with fixed-dose ibrutinib, prednisone, obinutuzumab and Revlimid®. A small expansion cohort of patients will be treated at the MTD for a further assessment of safety and preliminary estimate of clinical activity. An additional expansion cohort of non-GCB DLBCL patients treated at the MTD will be conducted to assess the CR rate of ViPOR-P in this molecular DLBCL subtype.

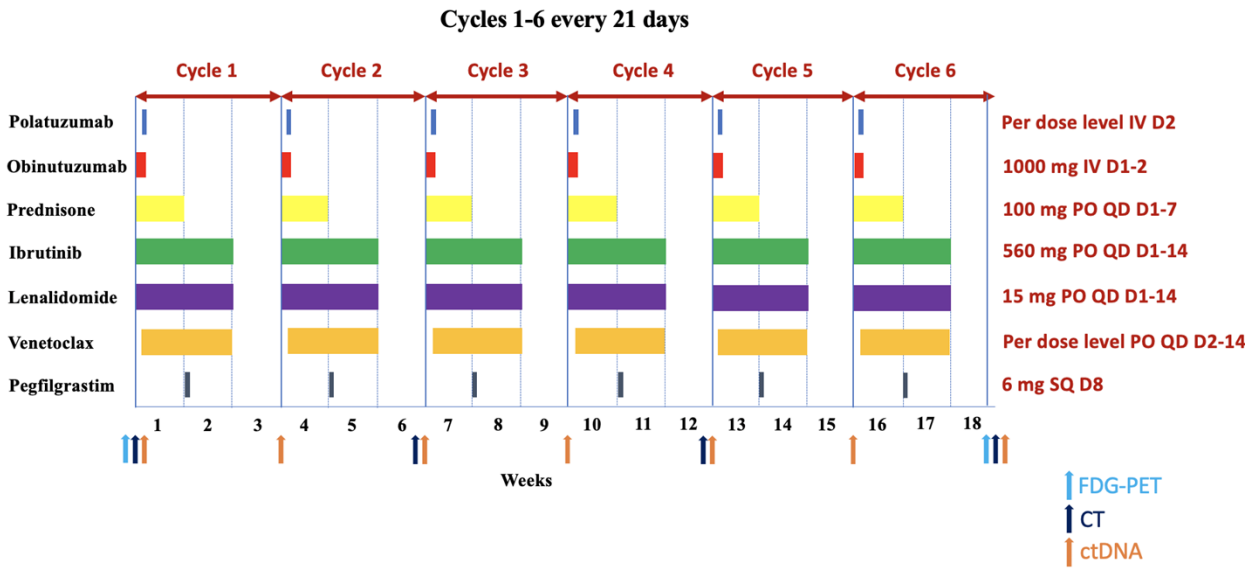
A maximum of 6 cycles of combination targeted therapy will be given every 21 days:

- Venetoclax per dose level by mouth daily (PO QD) days 2-14 (see **Table 5**)
- Ibrutinib 560 mg by mouth daily (PO QD) days 1-14
- Prednisone 100 mg by mouth daily (PO QD) days 1-7
- Obinutuzumab 1000 mg IV days 1 and 2
- Lenalidomide 15 mg by mouth daily (PO QD) days 1-14
- Polatuzumab per dose level IV on day 2 (see **Table 5**)

Study treatment will continue for up to a maximum of 6 cycles and as long as:

- Subject is deriving clinical benefit (complete remission [CR], partial remission [PR], or stable disease [SD]) and
- Subject is not experiencing any unacceptable toxicity
- Off protocol therapy criteria in Section **3.9.1** are not met

It is anticipated that treatment will be given primarily on an outpatient basis; however, treatment is required to be initiated as inpatient in patients at high-risk of tumor lysis syndrome (TLS). 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 patient monitoring/follow-up, patient/scheduling convenience, etc.); see also Section **6.1.1**.



Subjects will be restaged after cycles 2, 4, and 6 of treatment, and then every 3, 4, 6, and 12 months during post-treatment years 1, 2, 3, and 4-5 respectively (see Section **3.5.2** for more information and applicable windows). After 5 years of monitoring, the decision to continue further surveillance imaging will be left to the discretion of the investigator.

3.1.1 Dose-Limiting Toxicity

A DLT (Dose-Limiting Toxicity) is defined as an adverse event (AE) that occurs within the first 21 days of Cycle 1 of treatment for all patients in the dose-escalation cohort (i.e., Cycle 1 Day 1 to Cycle 2 Day 1 pre-dose) that meets the DLT definition, is clinically relevant, and considered at least possibly related to study drug in the opinion of the investigator.

A DLT is defined as any of the following: Grade 3 or higher adverse event at least possibly related to study drug and occurring during the DLT window 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 subject does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity improves to < grade 3 within ≤ 3 days
- 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
- Grade 3 infusion related reaction
- Treatment delay of Cycle 2 ≤ 7 days for non-hematologic toxicity

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
- Grade 3 thrombocytopenia not associated with grade 2 or greater bleeding
- Grade 3 anemia persisting for ≤ 7 days
- Treatment delay of Cycle 2 for ≤ 7 days for hematologic toxicity

3.1.2 Dose Escalation

Dose escalation of polatuzumab and venetoclax in combination with fixed doses of ibrutinib, prednisone, Obinutuzumab and Revlimid® will proceed in cohorts of 3-6 patients. The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during the DLT evaluation window(s), or the dose below that at which at least 2 (of ≤6) patients have DLT. If a patient 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.

Dose level 3 defines the maximum administered dose (MAD) in this study. If in dose level 3, DLTs occur in <33% of the subjects, then the MTD will not be identified. In that case, the MAD of 1.8 mg/kg of polatuzumab and 800 mg of venetoclax from dose level 3 will be used for further study.

Given concerns regarding compromised efficacy with polatuzumab doses <1.4 mg/kg when given as monotherapy or in combination with anti-CD20 antibody therapy, if dose escalation of polatuzumab to ≥1.4 mg/kg is not tolerated based on observance of DLTs, reduced dosing of one or more of the ViPOR agents will be considered with reescalation of polatuzumab in a protocol amendment.

Table 5: Polatuzumab dose escalation schedule

Dose Level (DL)	Dose of Polatuzumab Agent	Dose of Venetoclax Agent
Level 1	1.4 mg/kg IV on day 2	600 mg PO days 2-14
Level 2	1.8 mg/kg IV on day 2	600 mg PO days 2-14
Level 3	1.8 mg/kg IV on day 2	800 mg PO days 2-14

Table 6: Dose escalation will follow the rules outlined below:

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter up to 3 patients 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 patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
1 out of 3	Enter up to 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Up to three (3) additional patients will be entered at the next lowest dose level if only 3 patients 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 patients must be entered at the recommended phase 2 dose. **NOTE:** If ≤1 out of 6 patients with DLT occurs at DL3, the MTD will not have been identified and DL3 will be declared the MAD for further study.

Subjects 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 Day 1 of Cycles 1-6

- Premedication, approximately 30-60 minutes prior to obinutuzumab:
  - Acetaminophen 650 mg PO
  - Diphenhydramine 50 mg PO
  - Prednisone 100 mg PO
- Obinutuzumab 1000 mg IV rate escalated infusion[a]
- Ibrutinib 560 mg PO[c]
- Lenalidomide 15 mg PO[d]

3.2.2 Day 2 of Cycles 1-6

- Premedication, approximately 30-60 minutes prior to obinutuzumab:
  - Acetaminophen 650 mg PO
  - Diphenhydramine 50 mg PO
  - Prednisone 100 mg PO
- Obinutuzumab 1000 mg IV rate escalated infusion[a]
- Polatuzumab per dose level IV infusion[e]
- Venetoclax per dose level PO[b]
- Ibrutinib 560 mg PO[c]
- Lenalidomide 15 mg PO[d]

3.2.3 Days 3-7 of Cycles 1-6

- Prednisone 100 mg PO daily
- Venetoclax per dose level PO daily[b]
- Ibrutinib 560 mg PO daily[c]

- Lenalidomide 15 mg PO daily[d]

3.2.4 Days 8-14 of Cycles 1-6

- Venetoclax per dose level PO daily[b]
- Ibrutinib 560 mg PO daily[c]
- Lenalidomide 15 mg PO daily[d]

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

[b] Venetoclax tablets should be taken orally once daily with a meal and water. Do not chew, crush or break tablets.

[c] Ibrutinib capsules should be taken orally with a glass of water, with or without food. Do not open, break or chew the capsules.

[d] Lenalidomide capsules should be swallowed whole with water, with or without food. Capsules should not be opened, broken or chewed.

[e] Polatuzumab will be administered as a 90-minute infusion during initial dosing and patients should be monitored during the infusion and for infusion-related reactions for a minimum of 90 minutes following completion of the initial dose. If the previous infusion was well-tolerated, subsequent doses may be administered as a 30-minute infusion and patients should be monitored during the infusion and for a minimum 30 minutes following completion of subsequent doses. Monitor patients closely for signs/symptoms of infusion reaction and interrupt/discontinue infusion for any signs of a reaction and contact the investigator.

NOTE: All oral study medications, including pre-medications, may be given together when administered on the same day. Pre-medications may be adjusted at the discretion of the investigator.

Patients will be encouraged to complete and return a drug diary as a memory aid to help document the date and time of all self-administered study drugs (**APPENDIX D**). 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. Please refer to CCR SOP #PM-8 for further information regarding drug accountability for self-administered medications.

3.3 DOSE MODIFICATIONS

The following sections detail dose modifications guidelines for each individual drug of the ViPOR-P regimen based on documented toxicity. It is the responsibility of the investigator to determine the most likely agent responsible for the observed toxicity and follow dose modification guidelines in the appropriate section listed below. Dose reductions for multiple study agents based on the same toxicity is not necessary and dosing should be modified only for the most likely offending agent identified by the investigator.

3.3.1 Exceptions During DLT Evaluation Window

In general, dose modifications should follow the schedule and guidelines below with the exception of the DLT evaluation window. Dose modifications should be avoided during the DLT evaluation window (i.e., cycle 1, day 1 to cycle 2, day 1 pre-dose for Cohort 1) in order to allow identification of toxicities. A patient who experiences a DLT should be removed from protocol therapy (see Section **3.9.1**) unless the investigator feels it is in the patient's best interest to remain on study.

In the case of a DLT 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 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 subject meets criteria to receive study drug as planned.

3.3.3 Dose Modifications

A dose delay of 14 days is generally permitted for study therapy to allow recovery of hematologic toxicities to Grade ≤ 2 or non-hematologic toxicities to Grade ≤ 1; however, delay of up to 6 weeks may be allowed at the discretion of the investigator. Actions for recurrent hematologic adverse events are described in the tables for each drug in the sections below. If treatment is delayed for more than 6 weeks (except for hepatitis B reactivation), the patient should be withdrawn from study treatment except in exceptional circumstances. Patients 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 (see Section **3.6**). At the discretion of investigator, dose-modification guidelines should be evaluated and revised, as appropriate, based on the risk associated with the regimen employed.

3.3.3.1 Dose Modifications for Venetoclax and Obinutuzumab

Sample guidelines for dose delay and modification of venetoclax and obinutuzumab are shown in **Table 7**. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment. No dose modifications of obinutuzumab are allowed, only dose delays. Venetoclax dose may be re-escalated (even to the full dose) at the discretion of the investigator. See **Table 8** for the dose levels for venetoclax dose reduction.

Table 7: Guidelines for Dose Delay or Modification of Venetoclax and Obinutuzumab

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 and obinutuzumab. • Administer growth factors (e.g., G-CSF for neutropenia as indicated). -If ANC < 1000/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If ANC < 1000/μL for > 7 days, reduce the dose of venetoclax by 1 dose level. • For subsequent episodes, 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 and obinutuzumab until resolution.
Thrombocytopenia: • Grade 3 (decrease to <50,000/ μL) associated with > Grade 2 bleeding, OR • Grade 4 (decrease to <25,000/ μL) with or without bleeding	• Hold further doses of venetoclax and obinutuzumab. -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 patient 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.
Severe thrombocytopenia (platelets < 10,000/μL) and/or symptomatic bleeding in patients who are not receiving concomitant anticoagulants or platelet inhibitors	• Hold further doses of obinutuzumab in case of severe thrombocytopenia (platelets < 10,000/μL) or symptomatic bleeding (irrespective of platelet count) until it resolves.

Event(s)	Dose Delay or Modification
Thrombocytopenia with platelets < 20,000/μL and/or symptomatic bleeding in patients who are receiving concomitant anticoagulants or platelet inhibitors[a,b]	• Hold further doses of obinutuzumab in case of platelets < 20,000/μL or symptomatic bleeding (irrespective of platelet count) until it resolves. -For patients who are receiving concomitant anticoagulant when thrombocytopenia with platelets < 20,000/μL develops, adjust the dose or hold the drug per investigator discretion.[a] -For patients who are on platelet inhibitors when thrombocytopenia with platelets < 20,000/μL develops, consider temporarily holding their use.[b]
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay.
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.
Grade 3 or 4 tumor lysis syndrome (TLS)	• Hold further doses of venetoclax and obinutuzumab. -If resolution of TLS occurs within 24-48 hours, venetoclax may be resumed at the full dose. -If TLS persists for > 48 hours, reduce the dose of venetoclax by 1 dose level. -In patients who meet criteria for clinical TLS, venetoclax should be restarted at a lower dose following TLS resolution. -Obinutuzumab may be restarted at full dose upon TLS resolution. No dose modifications for Obinutuzumab are allowed. • 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.

[a]If the patient's clinical condition requires the use of concomitant anticoagulants, the patient is at increased risk of bleeding when thrombocytopenia with platelets < 20, 000/μL develops. When possible, replace prior therapy with vitamin K antagonists with low-molecular weight heparin before Cycle 1, Day 1.

[b]Clinical decision-making may be adjusted depending on the patient-specific assessment of benefit and risk.

Table 8: Venetoclax Dose Reduction

Dose Reduction	Venetoclax Dose
1	600 mg
2	400 mg
3	200 mg
4	100 mg
5	Discontinue venetoclax

3.3.3.2 Dose Modifications for Ibrutinib

Sample guidelines for dose delay and modification of ibrutinib are shown in **Table 9**. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment. Ibrutinib dose may be re-escalated (even to the full dose) at the discretion of the investigator. See **Table 10** for the dose levels for ibrutinib dose reduction.

Table 9: Guidelines for Dose Delay or Modification of Ibrutinib

Event(s)	Dose Delay or Modification
Neutropenia: • Grade 3 (ANC <1,000/μL) for ≥ 7 days, OR • Grade 4 (ANC <500/μL) for any duration	• Hold further doses of ibrutinib. • Administer growth factors (e.g., G-CSF for neutropenia as indicated). - If ANC < 500/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. - If ANC < 500/μL for > 7 days, reduce the dose of ibrutinib by 1 dose level. • For subsequent episodes, further dose reduction of ibrutinib 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 ibrutinib. Decisions must be made in consultation with and with approval of the Principal Investigator.
Febrile neutropenia or neutropenia with infection	• Hold further doses of ibrutinib 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 ibrutinib. - If platelet count < 50,000/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. - If platelet count < 50,000/μL for > 7 days, reduce the dose of ibrutinib by 1 dose level. • For subsequent episodes, further dose reduction of ibrutinib and consideration of drug discontinuation will be considered. • If the patient 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 ibrutinib. 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.
Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy	• Hold further doses of ibrutinib. - If improves to ≤ Grade 2 in ≤ 7 days, administer full dose of study treatment for the next cycle. - If improves to ≤ Grade 2 in > 7 days, reduce the dose of ibrutinib by 1 dose level. • For subsequent episodes, further dose reduction of ibrutinib and consideration of drug discontinuation will be considered.
Grade 3 or 4 atrial fibrillation/flutter or persistent atrial fibrillation/flutter of any grade	• Hold further doses of ibrutinib. • Initiate medical management of atrial fibrillation/flutter. • Consider the risks and benefits of restarting ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (See Section **4.1.8**).
Any other Grade 4 toxicity or unmanageable Grade 3 toxicity attributed to ibrutinib	• Hold further doses of ibrutinib. - If improves to ≤ Grade 2 in ≤ 7 days, administer full dose of study treatment for the next cycle. - If improves to ≤ Grade 2 in > 7 days, reduce the dose of ibrutinib by 1 dose level. • For subsequent episodes, further dose reduction of ibrutinib and consideration of drug discontinuation will be considered.

Table 10:Ibrutinib Dose Reduction

Dose Reduction	Ibrutinib Dose
1	420 mg
2	280 mg
3	140 mg
4	Discontinue ibrutinib

3.3.3.3 Dose Modifications for Lenalidomide

Sample guidelines for dose delay and modification of lenalidomide are shown in **Table 11**.The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment. Lenalidomide dose may be re-escalated (even to the full dose) at the discretion of the investigator. See

Table 12 for the dose levels for lenalidomide dose reduction.

Table 11: Guidelines for Dose Delay or Modification of Lenalidomide

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 lenalidomide. • Administer growth factors (e.g., G-CSF for neutropenia as indicated). -If ANC < 1000/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If ANC < 1000/μL for > 7 days, reduce the dose of lenalidomide by 1 dose level. • For subsequent episodes, further dose reduction of lenalidomide 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 lenalidomide. Decisions must be made in consultation with and with approval of the Principal Investigator.
Febrile neutropenia or neutropenia with infection	• Hold further doses of lenalidomide 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 lenalidomide. -If platelet count < 50,000/µL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If platelet count < 50,000/µL for > 7 days, reduce the dose of lenalidomide by 1 dose level. • For subsequent episodes, further dose reduction of lenalidomide and consideration of drug discontinuation will be considered. • If the patient 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 lenalidomide. 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.
Rash: • Any Grade desquamating (blistering), OR • Grade 4 non-blistering	• Discontinue lenalidomide.
Thromboembolic event ≥ Grade 3	• Hold further doses of lenalidomide. • Initiate therapeutic anticoagulation as clinically indicated, please evaluate interactions with other study drugs. • Resume lenalidomide without dose modifications at Day 1 of next cycle if benefit of therapy outweighs bleeding risk.
Hyperthyroidism or hypothyroidism ≥ Grade 2	• Hold further doses of lenalidomide. • Evaluate etiology & initiate appropriate therapy. • Reduce lenalidomide by 1 dose level at Day 1 next cycle. Start new cycle when patient meets cycle initiation criteria (see Section **3.3.2**).
Creatinine Clearance <60 mL/min (CrCl, Cockcroft-Gault)	• Hold further doses of lenalidomide. • Reduce lenalidomide according to recommendations below based upon CrCl at Day 1 of next cycle if patient meets cycle initiation criteria (see Section **3.3.2**). -CrCl 30–60 mL/min: 10 mg every 24 hours -CrCl <30 mL/min (not requiring dialysis): 15 mg every 48 hours -CrCl <30 mL/min (requiring dialysis): 5 mg every 24 hours (on dialysis days, administer the dose following dialysis) • If CrCl becomes >60mL/min for a minimum of 2 cycles, may re-escalate to the prior dose at investigator's discretion.

Event(s)	Dose Delay or Modification
Any other Grade 4 toxicity or unmanageable Grade 3 toxicity attributed to lenalidomide	• Hold further doses of lenalidomide. -If improves to ≤ Grade 2 in ≤ 7 days, administer full dose of study treatment for the next cycle. -If improves to ≤ Grade 2 in > 7 days, reduce the dose of lenalidomide by 1 dose level. • For subsequent episodes, further dose reduction of lenalidomide and consideration of drug discontinuation will be considered.

Table 12: Lenalidomide Dose Reduction

Dose Reduction	Lenalidomide Dose
1	10 mg
2	5 mg
3	Discontinue lenalidomide

3.3.3.4 Dose Modifications for Polatuzumab

Sample guidelines for dose delay and modification of polatuzumab are shown in **Table 13**. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment. Polatuzumab dose may be re-escalated (even to the original full dose) at the discretion of the investigator. See **Table 14** for the dose levels for polatuzumab dose reduction

Table 13: Guidelines for Dose Delay or Modification of Polatuzumab

Event(s)	Dose Delay or Modification
Grade 2 or 3 peripheral neuropathy	• Hold further doses of polatuzumab. -If improves to ≤ Grade 1 in ≤ 14 days, reduce the dose of polatuzumab by 1 dose level. -If improves to ≤ Grade 1 in > 14 days, discontinue polatuzumab. • For subsequent episodes, further dose reduction of polatuzumab and consideration of drug discontinuation will be considered.
Grade 4 peripheral neuropathy	• Discontinue polatuzumab.

Event(s)	Dose Delay or Modification
Grade 1 to 3 infusion-related reaction (IRR)	• Interrupt polatuzumab and give supportive treatment. • For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, discontinue polatuzumab. • For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, discontinue polatuzumab. • Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. • For the next cycle, infuse polatuzumab over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
Grade 4 infusion-related reaction (IRR)	• Stop polatuzumab infusion immediately. • Give supportive treatment. • Discontinue polatuzumab.
Neutropenia: • Grade 3 (ANC <1,000/μL) on Day 1, OR • Grade 4 (ANC <500/μL) on Day 1	• Hold further doses of polatuzumab. • Administer growth factors (e.g., G-CSF for neutropenia as indicated). -If ANC < 1000/μL for ≤ 7 days, administer full dose of study treatment for the next cycle. -If ANC < 1000/μL for > 7 days, reduce the dose of polatuzumab by 1 dose level. • For subsequent episodes, further dose reduction of polatuzumab 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 polatuzumab. Decisions must be made in consultation with and with approval of the Principal Investigator.
Febrile neutropenia or neutropenia with infection	• Hold further doses of polatuzumab until resolution.
Thrombocytopenia: • Grade 3 (decrease to <50,000/ μL) on Day 1 OR • Grade 4 (decrease to <25,000/ μL) on Day 1	• Hold further doses of polatuzumab. -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 polatuzumab by 1 dose level. • For subsequent episodes, further dose reduction of polatuzumab and consideration of drug discontinuation will be considered. • If the patient 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 polatuzumab. Decisions must be made in consultation with and with approval of the Principal Investigator.

Event(s)	Dose Delay or Modification
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 polatuzumab	• Hold further doses of polatuzumab. -If improves to ≤ Grade 1 or baseline in ≤ 14 days, administer full dose of study treatment for the next cycle. -If improves to ≤ Grade 1 in > 14 days, reduce the dose of polatuzumab by 1 dose level. • For subsequent episodes, further dose reduction of polatuzumab and consideration of drug discontinuation will be considered.

Table 14: Polatuzumab Dose Reduction

Dose Reduction	Polatuzumab Dose
1	Decrease 1 dose level from starting assigned dose level
2	Discontinue polatuzumab
NOTE: Table 5 lists the polatuzumab dose levels for this study. Polatuzumab 1.4 mg/kg (DL1) is the lowest dose level in this study. If further dose reductions are required for patients treated at this dose, polatuzumab should be discontinued.	

3.4 PROTOCOL STOPPING RULE

If >1 treatment-related death occurs in the dose-expansion cohort, then further accrual to this cohort will be suspended until a full review of safety is performed with the study sponsor.

3.5 ON STUDY EVALUATIONS

Study drug treatment should be continued until disease progression, unacceptable treatment-related toxicity or other reasons outlined in Section 3.9, or a maximum of 6 cycles each 21 days, whichever occurs first.

Refer to the Study Calendar (APPENDIX A) for a complete list of procedures to be performed at each scheduled study visit. Any additional assessments may be done as clinically indicated; including, but not limited to repeat EKG, venous thromboembolism risk assessment.

NOTE: Laboratory results from outside NIH are accepted unless otherwise requested or specified by the investigator due to safety concerns.

3.5.1 Pregnancy Testing

Individuals of childbearing potential (ICBP) with regular or no menstruation must have a pregnancy test weekly for the first 21 days and then every 21 days while on lenalidomide therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 (+2 days) post the last dose of lenalidomide.

A ICBP with irregular menstruation must have a pregnancy test weekly for the first 21 days and then every 14 days while on lenalidomide therapy (including breaks in therapy), at discontinuation

of lenalidomide and at Day 14 (+/-1 day) and Day 28 (+2 days) following lenalidomide discontinuation.

3.5.2 Response Assessments

Subjects will be restaged at the following time points. For additional details on response criteria, see Section **6.3**:

- After cycle 2 (up to 7 days prior to cycle 3, day 1 pre-dose)
- After cycle 4 (up to 7 days prior to cycle 5, day 1 pre-dose)
- After cycle 6 (cycle 6, day 21 +/- 7 days)
- Post-treatment in follow-up prior to disease progression as described in Section **3.6.2**

NOTE: For patients who continue on active treatment, refer to the Study Calendar (**APPENDIX A**) 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 patient 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 patient'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 unless felt to be clinically indicated.

3.5.3 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:

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

3.5.4 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)
- Bone marrow aspirate/biopsy (only if biopsy at screening was positive)

The following assessments should also be performed:

- Symptom-guided clinical assessment with physical exam and performance score
- CBC with differential
- Acute care and mineral panels
- Hepatic panel and total protein
- LDH and uric acid
- PT/INR and PTT
- TSH
- EBV and CMV PCR
- T/B/NK cell count
- Research blood samples (see Section **5**)
- Optional tumor biopsy (if accessible tumor)

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.

3.6 POST-TREATMENT EVALUATIONS

When a subject completes all 6 cycles of treatment or discontinues early, all applicable activities scheduled for the End of Treatment Visit should be performed at the time of discontinuation (see **APPENDIX A**). Any adverse events which are present at the time of discontinuation should be followed in accordance with the safety requirements outlined in Section **7**.

Regardless of a patient's disease status, follow-up must continue for at least 3 years after the last dose of study drug to meet the reporting requirements of the industry supporters (e.g., for purposes of reporting of secondary malignancies; see Section **8.5**).

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

3.6.1 Safety Follow-Up Visit

The safety follow-up visit should occur 30 days (-2/+7 days) after the last dose of study drug; note required pregnancy testing at about 14 and 28 days for applicable ICBP:

- ICBP with regular or no menstruation must have a pregnancy test at discontinuation of lenalidomide and at Day 28 (+2 days) post the last dose of lenalidomide.
- ICBP with irregular menstruation must have a pregnancy test at discontinuation of lenalidomide and at Day 14 (±1 day) and Day 28 (+2 days) following lenalidomide discontinuation.

All other required testing is as noted in the Study Calendar (**APPENDIX A**).

3.6.2 Follow-Up Visits – Prior to Disease Progression

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

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

- Every 3 months during post treatment year 1 (+/- 14 days)
- Every 4 months during post treatment year 2 (+/- 14 days)
- Every 6 months during post treatment year 3 (+/- 21 days)
- Every 1 year during post treatment years 4-5 (+/- 28 days)

All required testing is as noted in the Study Calendar (**APPENDIX A**).

After 5 years of monitoring without disease progression the decision to continue further surveillance imaging, including any assessments and procedures, will be left to the discretion of the investigator.

At the time of suspected or confirmed disease progression, the above assessments should be performed as well as the tests listed in Section **3.5.4**, as applicable.

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

Once subjects 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. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination, whichever occurs first.

3.7 STUDY CALENDAR

Please refer to **APPENDIX A** which lists all the scheduled assessments in a summarized table form.

3.8 COST AND COMPENSATION

3.8.1 Cost

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by an insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.8.2 Compensation

No direct compensation will be provided on the study.

3.8.3 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.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, every effort must be made to have all subjects complete a safety visit approximately 30 (-2/+7) days following the last dose of study therapy. Additional safety visits and follow-up will continue as per Section **3.6**.

3.9.1 Criteria for removal from protocol therapy

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

- Completion of protocol therapy
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Delay of treatment for more than 6 weeks (except for hepatitis B reactivation), unless it is felt by the Principal Investigator to be in the patient's best interests to remain on study in exceptional circumstances.

- Unacceptable adverse event(s) (see Sections **3.1.1**, and **3.3**), unless it is felt by the Principal Investigator to be in the patient's best interests to remain on study in exceptional circumstances (e.g., discontinue offending study agents while continuing others).
- Patient 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
- Patient requires a prohibited concomitant medication
- Pregnancy
- Investigator's decision to withdraw the subject
- Study is cancelled for any reason

All subjects, 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.

3.9.2 Off-Study Criteria

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

- Screen failure and/or failure to maintain eligibility (i.e., between enrollment/confirmation of eligibility 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 subject in the opinion of the investigator (Section **2.4**)
- Participant requests to be withdrawn from study
- Subject is lost to follow-up
- Death
- Study is cancelled for any reason

3.9.3 Study Cancellation

Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- The Manufacturers decides to stop development of study drug(s)

3.9.4 Lost to Follow-up

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

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

- The team will attempt to contact the participant and reschedule the missed visit within 5 business days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if

necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 PERMITTED THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator.

4.1.1 Growth Factors

Patients will be monitored for the development of treatment-emergent neutropenia per protocol-specified laboratory testing.

G-CSF prophylaxis is recommended for all patients receiving treatment with ViPOR-P. Prophylaxis with long-acting G-CSF (e.g., pegfilgrastim) should be administered on day 8 (+/-1 day) of each treatment cycle. Additional supplementation of long-acting G-CSF with short-acting G-CSF (e.g., filgrastim) is permitted for severe or prolonged neutropenia at the discretion of the investigator. Daily short-acting G-CSF (e.g., filgrastim) may also be used as prophylaxis at the discretion of the investigator. If short-acting G-CSF is utilized, patients should receive their first dose of G-CSF starting on day 8 (+/-1 day) of each treatment cycle and daily dosing should be continued until the patient completes their day 14 study drugs and their absolute neutrophil count (ANC) is >5000.

4.1.2 Prophylaxis of Pneumocystis Jiroveci (Previously Pneumocystis Carinii)

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

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

Treatment will begin with initiation of treatment (cycle 1, day 1) and will be stopped upon completion of therapy (cycle 6, day 21) unless continued administration beyond this point is deemed necessary based on inadequate immune reconstitution.

PJP prophylaxis may be held or discontinued per investigator discretion if adverse events or potential adverse pharmacokinetic or pharmacodynamic interactions are observed with prophylaxis and the study agents (e.g., cytopenias interfering with study drug administration or escalation). If PJP prophylaxis is held or discontinued, patients will still be able to continue study therapy after a further discussion of the risks and benefits of continued study therapy in the absence of PJP prophylaxis. Documentation of this discussion and recommendation for PJP prophylaxis will be noted in the patient's medical record.

4.1.3 Tumor Lysis Syndrome

Patients will be monitored closely for laboratory evidence of tumor lysis syndrome (TLS) prior to and during study treatment. Perform tumor burden assessment with CT scan and CBC with WBC

differential, assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing chemistry abnormalities prior to initiation of study treatment. Elective admission for fluid hydration, correction of electrolyte abnormalities and closer monitoring is permitted at the discretion of the investigators and will not be considered an SAE.

Patients 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. Patients will receive prophylaxis as outlined in the guidelines below prior to the first cycle of therapy which includes venetoclax; this can be discontinued during subsequent cycles if there is no clinical or laboratory evidence of TLS as deemed by the investigator. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per **APPENDIX E**.

Guidelines:
TLS, including fatal TLS, is a risk for patients with NHL who are treated with high cell-killing agents, including venetoclax and obinutuzumab. 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 study therapy. 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 pretreatment 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 patients and correct pre-existing chemistry abnormalities prior to initiation of study treatment.

All patients 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 14 days of therapy) or rasburicase IV (for those high-risk patients 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 patient should receive additional prophylactic treatment and hydration before the initiation of dosing.

Guidelines for Hospitalization Due to TLS Risk:
Patients 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 patients 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 ≥ 5 cm

- Patients with highly proliferative tumors such as those with high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements

In addition to characteristics requiring hospitalization, other patient 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 patients exhibiting these characteristics, but these and any other factors considered relevant to TLS should be considered in an overall assessment of the patient's state and their risk of TLS. Investigators should use their judgment in assessing TLS risk for their patients and may optionally hospitalize any patient they consider to be at risk for TLS for closer monitoring; elective admission will not be considered an SAE.

Hospitalization Procedures:
For patients requiring hospitalization, hospitalization will begin 1 day prior to the first dose of venetoclax and continue for a minimum of 24 hours after 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 patient 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 patients who are hospitalized for TLS monitoring should 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 patient developed a change related to TLS. Laboratory results of the 24-hour post-dose must be reviewed before receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per **APPENDIX E**.

Guidelines for TLS prophylaxis and elective admission for hydration and closer monitoring is not limited to the cycle involving initiation of venetoclax and can be considered for any other cycle if deemed necessary by the investigators.

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.

4.1.5 Hormone-Replacement Therapy

Patients 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 at the discretion of the investigator.

Patients 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.

4.1.7 Monitoring and Treatment for Hepatitis B Reactivation

Patients 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 especially when combined with novel agents like ViPOR-P. Patients may be included in the study provided that they have an undetectable HBV DNA level prior to starting therapy.

These patients 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 patients 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 ≤ 100 IU/mL, the patient should be retested within 2 weeks. If the assay is still positive, study treatment must be held, and the patient should be immediately referred to a gastroenterologist or hepatologist for management.

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

4.1.8 Venous Thromboembolism Prophylaxis

The use of lenalidomide has been associated with the development of venous thromboembolism, including deep venous thrombosis and pulmonary embolism. Ibrutinib has been associated with increased risk of bleeding, including serious intracranial hemorrhage. VTE risk assessment will be performed in all patients at screening and the risks and benefits of anticoagulation with aspirin or low molecular weight heparin will be assessed by the investigators and discussed with the patient.

4.1.9 Prophylaxis of Herpesvirus

High-risk patients with prior HSV infection should receive prophylaxis for herpesvirus during study therapy administration. Standard prophylaxis in these patients will include either acyclovir 400 mg three to four times daily or valacyclovir 500 mg two to three times daily.

When herpesvirus prophylaxis is given, treatment will begin with initiation of treatment (cycle 1, day 1) and will be stopped upon completion of therapy (cycle 6, day 21) unless continued administration beyond this point is deemed necessary based on inadequate immune reconstitution.

Herpesvirus prophylaxis may be held or discontinued per investigator discretion if adverse events or potential adverse pharmacokinetic or pharmacodynamic interactions are observed with prophylaxis and the study agents (e.g., cytopenias interfering with study drug administration or escalation). If herpesvirus prophylaxis is held or discontinued, patients will still be able to continue

study therapy after a further discussion of the risks and benefits of continued study therapy in the absence of antiviral prophylaxis. Documentation of this discussion and recommendation for herpesvirus prophylaxis will be noted in the patient's medical record.

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 patient 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.
- Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of Venetoclax and throughout study drug administration.

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

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

4.2.1 CYP3A Inhibitors/Inducers

Venetoclax and ibrutinib are 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 subject for toxicity and follow dose modification guidance as needed (Section **3.3**). Subjects should avoid grapefruit and Seville oranges during treatment, as these contain moderate inhibitors of CYP3A.

Co-administration of venetoclax or ibrutinib 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.

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

https://drug-interactions.medicine.iu.edu/main-table

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

Results from human in vitro studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be

subject to P450-based metabolic drug interactions (please see lenalidomide prescribing information).

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. Patients on this study will be undergoing frequent imaging for response evaluation and the investigators will also evaluate these imaging studies for potential infectious complications, including possible invasive fungal infection. Further clinical work-up may include, but is not limited to, peripheral blood analysis for fungal blood markers and/or bronchoscopy with 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 and/or ibrutinib therapy. Azole treatment during the days the patient is not receiving study therapy is permitted as long as enough time is permitted for the azole therapy to be out of the patient's system prior to initiation of the next cycle of study therapy that includes venetoclax and/or ibrutinib. Furthermore, azoles with less CYP3A inhibition such as itraconazole may be consider 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 patients 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.

4.2.4 Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be used with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section **4.4**.

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

4.3 PROHIBITED THERAPY

4.3.1 Prohibited Therapy

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

Use of the following therapies is prohibited during the study:

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

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

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

It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label.

4.3.2 Live-Virus Vaccines

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment or at any time during study therapy and are not recommended until B-cell recovery post completion of study therapy.

4.4 GUIDELINES FOR IBRUTINIB MANAGEMENT WITH SURGERIES OR PROCEDURES

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguinous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

5 CORRELATIVE STUDIES FOR RESEARCH

Please note that tubes and media referenced below in sections **5.1** and **5.2** may be substituted based on availability with the permission of the PI or laboratory investigator.

5.1 BIOSPECIMEN COLLECTION

Samples will be collected for exploratory objectives to evaluate for potential biomarkers of sensitivity or resistance to ViPOR-P therapy. In blood, serum and plasma samples will be collected to assess circulating tumor DNA (ctDNA) response and correlate with molecular tumor analysis. In tumor and other samples, analyses may include gene expression profiling, RNA-sequencing, whole-exome and/or whole-genome sequencing. These comprehensive molecular characterizations may identify altered signaling patterns or mutations that are associated with response or resistance to study therapy.

Sample	Collection Details*	Time Points*	Supervising Laboratory/ Investigator*
Blood Samples			
ctDNA/cfDNA, Plasma banking	2 x 10 mL Streck/BCT tube	• Baseline/Pre-Cycle 1 • On Treatment: Pre-cycle of every cycle • Response Assessments/ Follow-Up: Each disease re-assessment and at disease progression/ recurrence	Biospecimen Processing Core (BPC)/Staudt /Adaptive
Cytokines, Serum banking	1 x 8-10 mL SST (or red top tube)		
Peripheral blood mononuclear cells (PBMCs)	2 x 8 mL Cell Preparation Tubes (CPTs) (with sodium citrate)		
Pharmacokinetic (PK) Studies	1 x 6 mL NaHep tube	• C1D2: pre-dose and about 0.5 (+/-15min), 1 (+/-15min), 2 (+/-15min), 4 (+/-15min), 6 (+/-15min), and 24 (+/-15min) hours post-dose • C1D8: pre-dose (just before C1D8 dose taken) and about 2 (+/-15min) hours post-dose	
Pharmacogenetic (PG) Studies	1 x 10 mL EDTA (purple top tube)	• Baseline/Pre-Cycle 1	
Other Samples			
Germline DNA	Blood, Buccal Swab, or Saliva (preferred)	• Baseline/Pre-Cycle 1	BPC/Staudt
Tissue Samples			

Sample	Collection Details*	Time Points*	Supervising Laboratory/ Investigator*
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 • Optional biopsy at baseline and at disease progression/ recurrence	NCI LP/Staudt

* For all Baseline/Pre-Cycle 1-collection can be up to 7 days prior to C1; for all subsequent cycles – collection can be up to 3 days prior to the cycle.

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. The PK sample timepoints are suggested and not required. 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.
- The location of specimen processing or analysis may be adjusted with the permission of the PI or laboratory investigator.

5.2 SAMPLE COLLECTION, PROCESSING AND ANALYSES

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

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

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 patient consent.

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 BPC and refer to section **5.3.2** 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 and serum banking

- Disposition of samples: send to BPC and refer to section **5.3.2** 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 patients will undergo pharmacokinetic (PK) testing at timepoint outlined in the table in Section **5.1**. Patient selection for PK testing will depend on ensuring an adequate number of patients with full data points within each dose level to provide a complete PK analysis across all dose levels. The decision as to which patients will undergo such testing will be left to the discretion of the investigator.

- 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 BPC and refer to section **5.3.2** 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 ibrutinib, lenalidomide, and venetoclax will be conducted on an ultra HPLC-MSMS system using validated assays for each drug developed and validated by the Clinical Pharmacology Program. The measured exposure for each drug assayed (ibrutinib, lenalidomide, and venetoclax) will be used to correlate to pharmacodynamic (PD) endpoints, clinical response, toxicity, and pharmacogenetic (PG) analyses.

5.2.2.4 Pharmacogenetic Studies

- Put samples immediately on wet ice and refrigerate.
- Disposition of samples: send to BPC and refer to section **5.3.2** 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 patient 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 Mononuclear Cells (PBMCs)

- Gently invert the tubes 8-10 times immediately after collection and place on a shaker if not processed immediately.
- Disposition of samples: send to BPC and refer to section **5.3.2** 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 the BPC (see Section **5.3.2** for contact information).
- For possible planned analyses, see Section **5.4**.

5.3 Storage, Use, and Sharing of Specimens and Data (Including for Secondary Research)

5.3.1 Sample Tracking and Processing

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

5.3.2 Biospecimen Processing Core/Clinical Pharmacology Program

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

For sample pickup, page 102-11964.

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

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

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

5.3.3 Sample Storage and Disposition

Barcoded samples are stored in barcoded boxes according to stability requirements. Access to stored clinical samples is restricted. Unless other permission is obtained, samples are only to be used for research purposes associated with this trial (as per the IRB-approved protocol) by investigators named on the protocol. It is the responsibility of the Principal Investigator to ensure that samples are being used in a manner consistent with IRB approval.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of a sample tracking database (e.g., 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, to correlate results with sample characteristics.

5.3.4 Protocol Completion/Secondary Use/Sample Destruction

Any specimens remaining at the completion of the protocol will be stored indefinitely in the conditions described above. The study will remain open so long as sample or data analysis continues. All samples and data from consenting participants will be stored in identifiable format 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.

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 participant's samples and data will be excluded from future distributions, but those which 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**.

With the permission of the participant, specimens and data collected on this study, identifiable through a code available to the study team, will be stored indefinitely and used for secondary research, including genetic research. Furthermore, the data and/or specimens, may be shared with other investigators in identifiable or coded (code key not available to recipient) format for secondary research. Any investigator conducting secondary research in human subjects will seek either additional regulatory approval or exemption for research as appropriate.

Data will also be shared in public database per the study's data sharing plan in compliance with NIH policies.

In addition, specimens/data may be anonymized and further research, including genetic research, conducted at the site or other institutions without participant consent. Participants will be informed that the possibility for this type of research exists.

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 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 and/or whole genome 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 subject. 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

Subjects 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. Subjects will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to have genetic education and counseling as described below

5.4.4 Genetic Counseling

Subjects will be contacted with a request to provide a sample to be sent to a CLIA certified

laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject 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 subject 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.

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

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be expeditiously reported per requirements in **7.2.1**

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 patient's outcome.

6.2 HUMAN DATA SHARING, INCLUDING GENOMIC DATA SHARING, AND PUBLICATION

6.2.1 NIH Data Management and Sharing Policy and NIH Genomic Data Sharing Policy

Compliance

This study will comply with the NIH Data Management and Sharing (DMS) Policy, which applies to all new and ongoing NIH-funded research in the IRP, as of January 25, 2023, that is associated with a ZIA, with a clinical protocol that undergoes scientific review and/or will involve genomic data sharing.

This study will comply with the NIH Genomic Data Sharing (GDS) Policy, which applies to all new and ongoing NIH IRP-funded research, as of January 25, 2015, that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

6.2.2 NIH Public Access Policy Compliance

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

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 **APPENDIX A**). Subjects 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 surveillance 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, as assessed by investigators (see **APPENDIX F**)(8).

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 subject 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

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

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at https://irbo.nih.gov/hrpp-policy-guidelines/.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

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

7.3 NCI CLINICAL DIRECTOR REPORTING

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

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

To report these deaths, please send an email describing the circumstances of the death to at 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 patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

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 patient 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.

7.4.2 Safety Monitoring Committee (SMC)

This protocol will be periodically reviewed by an intramural Safety Monitoring Committee comprising of physicians, biostatisticians and a lay member selected based on experience, area of expertise, reputation for objectivity, absence of conflicts of interest and knowledge of or experience with clinical trial research.

Initial review will occur as soon as possible after the decision to incorporate SMC review. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC based on the risks presented in the study. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period.

The SMC will operate under the rules of an approved charter that will be written and reviewed at the organization meeting of the SMC. Each review will focus on unexpected protocol-specific safety issues that are identified during the conduct of the clinical trial.

Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

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

- Death,
- A life-threatening adverse event (see **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 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.

8.1.6 Adverse Events of Special Interest (AESI)

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

AESIs for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3x ULN in combination with total bilirubin > 2x ULN
    - Treatment-emergent ALT or AST > 3x ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

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

Venetoclax AESIs are:

- All TLS (any grade)

Obinutuzumab AESIs are:

- All TLS (irrespective of seriousness, causality or severity)
- Second Malignancies

Polatuzumab AESIs are:

- All TLS (any grade)
- Second malignancies

All new/secondary malignant tumors including solid tumors, skin malignancies and hematologic malignancies that occur during study treatment and for as long as a subject continues protocol-specified follow-up, including post-progression follow-up for overall survival, will be considered an AESI.

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 (return to baseline or stabilization), seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal

investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution (return to baseline or stabilization).

SAEs will be:

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

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

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. 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 via an electronic SAE reporting system (e.g. HiLIT). In the event of system downtime or issues, SAE reports will be submitted using the CCR SAE Report form to the sponsor at: NCIOSROSafety@mail.nih.gov. CCR SAE report form and instructions can be found at: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

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

8.4 Waiver of Expedited Reporting to CCR

As death and hospitalization due to disease progression are part of the study objectives, and captured as an endpoint in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

The Sponsor might request case summaries for those events if, upon review, the Sponsor determines that an aggregate safety report is required (21CFR312.32(c)(1)(iv)).

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreements; reporting requirements to Genenetch will be according to the respective SDEA/CTA and reporting requirements to Celgene will be according to the CTA.

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

8.6.1 Maternal exposure

If a patient 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.

If a female subject becomes pregnant while receiving the study therapy or within 30 days after the last dose of venetoclax, 9 months after the last dose of polatuzumab, or 18 months after the last dose of Obinutuzumab, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should be obtained if possible.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study treatment and for 6 months after study drug.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies 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.

If the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 6 months after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should be obtained if possible.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

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

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

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or

protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

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

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

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- 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) and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

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

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

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

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the 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 STATISTICAL OBJECTIVES

- Primary Endpoints
  - MTD and the safety and toxicity profile of polatuzumab in combination with venetoclax, ibrutinib, prednisone, obinutuzumab and Revlimid® (ViPOR-P) in relapsed/refractory B-cell lymphomas
  - Complete response (CR) rate of ViPOR-P in relapsed/refractory non-GCB DLBCL
- Secondary Endpoints
  - ORR and CR rate of ViPOR-P in relapsed/refractory B-cell lymphomas
  - DOR, EFS, PFS and OS of ViPOR-P in relapsed/refractory B-cell lymphomas

10.2 SAMPLE SIZE DETERMINATION

10.2.1 Dose-escalation

During the dose-escalation portion of the study, two dose levels of polatuzumab (1.4 mg/kg and 1.8 mg/kg) and two dose levels of venetoclax (600 mg and 800 mg) with up to 6 patients each in dose level will be tested yielding a maximum of 18 patients.

As of Amendment Version 04/03/2023, 15 patients were required to complete Cohort 1 portion of the study. No patients experienced a protocol defined DLT at DL1 and thus 3 patients were treated at this dose level. DL2 was expanded to 6 patients per protocol given the amendment incorporating a new DL3 was not yet approved, and no patients experienced a protocol defined DLT at DL2. One patient treated at dose level 3 experienced a DLT of prolonged grade 4 thrombocytopenia and thus this dose level was expanded to 6 evaluable patients. No additional patients experienced a DLT and thus DL3 was determined to be the MTD/RP2D to be used in expansion.

10.2.2 Dose-expansion

During the dose-expansion portion of the study, an additional 10 patients will be enrolled and treated at the MTD for polatuzumab and venetoclax in a dose expansion group for further analysis of safety and determination of efficacy.

As of 02/15/2023, a total of 8 patients (5 HGBCL-DH and 3 non-GCB DLBCL) have been enrolled and treated in cohort 2 of the study. Given the preferential early activity of ViPOR-P in patients with non-GCB DLBCL, cohort 2 will be closed as of 02/15/2023 and only patients with non-GCB DLBCL will be enrolled in cohort 3 of the study.

10.2.3 Non-GCB DLBCL cohort

At the MTD up to a total of 32 patients with non-GCB DLBCL will be enrolled in a dose expansion group for further analysis of safety and determination of efficacy as described below; this 32 will include the 7 patients already treated at DL3/MTD who have non-GCB DLBCL:

In participants with non-GCB DLBCL, it will be desirable if the fraction who experience a CR after 6 cycles of ViPOR-P therapy were at least 70%. 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 50% CR rate (p0=0.50) in favor of an improvement of the

CR rate to 70% (p1=0.70). 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 12 evaluable participants, including 7 non-GCB DLBCL patients from cohorts 1 (DL3) and 2, and if 6 or fewer of the 12 have a CR after 6 cycles of ViPOR-P therapy, then no further participants will be accrued in this cohort. If 7 or more of the first 12 participants have a CR after 6 cycles of ViPOR-P therapy, then accrual would continue until a total of 32 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 12 participants enrolled in the cohort. These 2 participants would not be included among the initial 12 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 19 or fewer participants with a CR after 6 cycles of ViPOR-P therapy out of 32 participants, this would be an uninterestingly low CR rate. If there were 20 or more of 32 (62.5%) who experienced a CR after 6 cycles of ViPOR-P therapy, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (50% CR rate), the probability of early termination is 61.3%

10.2.4 Following IRB approval of Amendment Version 04/03/2023:

The accrual ceiling will be set at 55 patients. This will account for the 15 patients treated in dose-escalation (cohort 1), 8 patients treated in the dose-expansion (cohort 2), and 25 additional non-GCB patients (4 already treated in cohort 1 (DL3) and 3 non-GCB patients from cohort 2 will be included in the 32 total non-GCB patients in cohort 3) in the non-GCB DLBCL portions of the study while still allowing for a few inevaluable patients and potential screen failures (4 screen failures, 3 inevaluable). Approximately 2-3 patients per month each are anticipated to be enrolled on study. Thus, approximately 1.5-2.5 years will be required to enroll all 55 potential patients. Study follow-up will be for at least 1 year after the last subject received the first dose of study medication thus approximately 2.5-3.5 years is required from screening of the first patient to end of study.

10.3 POPULATION FOR ANALYSIS

Any patient 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.

Patients need to have completed baseline and follow-up scans for inclusion in response evaluations, except that any patients noted to have clinical progression without the follow-up scan will be noted as being non-responders.

10.3.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of first dose of study drug.

10.3.2 Evaluable for objective response

All patients who have received at least one cycle of therapy and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (**NOTE:** Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.4 STATISTICAL ANALYSES

10.4.1 General approach

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

In the dose expansion group, the ORR and the CR rate will be estimated based on patients treated at the MTD, all patients and by subtype (aggressive vs. indolent disease), along with a two-sided 95% confidence interval.

In the non-GCB DLBCL dose expansion group, the CR rate will be estimated based on patients treated at the MTD along with a two-sided 95% confidence interval.

10.4.2 Analysis of primary endpoint

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 patient completes therapy. Any patients who are inevaluable for the toxicity evaluation will be replaced.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 12 months after the last patient is enrolled.

Dose-expansion

The CR rate will be estimated based on non-GCB DLBCL patients treated at the MTD, along with a two-sided 95% confidence interval.

10.4.3 Analysis of secondary endpoints

In the dose expansion group, the ORR and the CR rate will be estimated based on patients treated at the MTD, all patients and by subtype (aggressive vs. indolent disease), along with a two-sided 95% confidence interval.

DOR, EFS, PFS and OS will be determined, all patients and by subtype (aggressive vs. indolent disease), beginning at the on-study date, using the Kaplan-Meier method. The median and a 95% confidence interval will be reported for each.

10.4.4 Safety analyses

The primary endpoint is determination of DLTs. The toxicity grades identified will be reported by dose level.

10.4.5 Baseline descriptive statistics

Patient characteristics will be provided.

10.4.6 Interim analyses

None are planned.

10.4.7 Subgroup analyses

Analyses will be done according to disease subtype (aggressive vs. indolent disease).

10.4.8 Tabulation of individual patient data

None are planned.

10.4.9 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 CLINICAL TRIAL AGREEMENTS

This study has been approved by both Genentech (CTA #1222-21), and Celgene (CTA #01221-21) who will provide study drug for the patients enrolled on the study.

Genentech has authorized provision of venetoclax (presently manufactured and provided directly by AbbVie) and will provide obinutuzumab and polatuzumab. Celgene will provide lenalidomide.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

All subjects from both sexes and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in the protocol. Subjects 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, pregnant or nursing mothers are excluded because of the potential teratogenic effects of therapy.

12.2 PARTICIPATION OF CHILDREN

Subjects under the age of 18 are excluded because recurrent B-cell lymphomas are rare in young patients, and the inclusion of an occasional younger patient will not provide generalizable information that would justify their inclusion on this study.

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

12.3.1.2 Risks of Tissue Biopsy

The risks associated with biopsies are pain and bleeding at the biopsy site. In order to minimize pain, local anesthesia and/or 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 Risk of Urine Collection

There are no physical risks associated with urine collection.

12.3.1.5 Risks of EKG

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

12.3.1.6 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.

12.3.1.7 Risks of Blood Sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting. Up to 96 ml of blood may be collected at any visit, but no more than 408 ml per 8 weeks period.

12.3.1.8 Risks of Imaging

CT, PET, and/ or MRI scans may be used to monitor a patient's disease on this study. CT and PET scans expose a patient to radiation; the amount depends on the number of body areas scanned. In addition, CT, PET and MRI scans involve use of contrast (oral and/or IV). An IV line may need to be inserted for administration of the contrast agent and can cause pain at the site where the IV is placed. There is also a small risk of bruising or infection. If a contrast agent is given with the scan there is a small risk of having a reaction to the contrast. In the small group of patients 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.

12.3.1.9 Risks of Radiation Exposure

This study will involve radiation from the following sources:

- Up to 6 CT scans of chest, neck, abdomen pelvis
- Up to 2 whole body 18F-FDG PET/CT scans
- Up to 2 CT scans for CT-guided biopsies

The maximum exposure in one year is 11.8 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 1.2 out of 100 (1.2%) and of getting a fatal cancer is 0.6 out of 100 (0.6%).

12.3.2 Known Potential Benefits

Polatuzumab, venetoclax, ibrutinib, prednisone, obinutuzumab and lenalidomide have all shown clinical activity either as monotherapy or combination therapy in patients with relapsed or refractory B-cell lymphomas. See Section **1.2.3** and **1.2.4** for benefits of the study agents in the treatment of B cell lymphomas.

12.3.3 Assessment of Potential Risks and Benefits

It is possible that the combination of these therapies may synergistically enhance the anti-lymphoma activity of the others and with the hope of increasing efficacy of the agents and decreasing the development of treatment resistance.

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

12.4 CONSENT PROCESS AND DOCUMENTATION

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

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. 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 with a signature on the electronic document as described below. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

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

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

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

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

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

12.5 INCLUSION OF WOMEN AND MINORITIES
Participants of all sexes and members of all races are eligible for this trial.

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 NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

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

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

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

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

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 VENETOCLAX (IND #134937)

14.1.1 Source, Acquisition and Accountability

Venetoclax is a commercially available agent but will be provided by Genentech to the NCI for

dispensing to the study participants as per an arranged research agreement.

14.1.2 Toxicity

Please refer to the toxicity data presented in the background for clinical safety of venetoclax in NHL as well as risks associated with the combination of venetoclax with other study drugs (Sections **1.2.3.1.1**, **1.2.3.2.1**, **1.2.3.2.2**, **1.2.3.2.6** and **12.3.1.1)**.

Table 15: Venetoclax adverse events

Very Common, may be serious >10%:	• Neutropenia • Lymphopenia • Anemia • Thrombocytopenia • Nausea • Fatigue • Diarrhea • Infection (e.g., upper respiratory infection, pneumonia, urinary tract) • Emesis • Cough • Peripheral edema • Musculoskeletal pain
Common , may be serious, 1% - 10%:	• Febrile neutropenia • Constipation • Pyrexia • Chemical imbalance in blood (Hyperuricemia, hypo/hyperkalemia, hypocalcemia, hyperphosphatemia) • Back pain • Headache • Creatinine increased • Dizziness • Hypoxia • Tumor Lysis Syndrome • Sepsis
Uncommon ≤1%:	• Hepatic failure • Second primary malignancy

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 contain 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.

Only 100mg tablets will be used in this study.

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 at 15°C–25°C (59°F–77°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
Venetoclax should be taken with a meal and may be administered with ibrutinib, prednisone, and lenalidomide. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient 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 subjects in bottles. All doses of venetoclax taken in the clinic or day hospital should be taken from the bottle dispensed to the subject. Unused venetoclax tablets dispensed during previous visits must be returned to the site and drug accountability records (Section **3.2**) must be updated. Returned tablets must not be re-dispensed to anyone. Subjects should return all used bottles to the site when they receive new study drug.

All patients must receive prophylaxis for TLS (see Sections **4.1.3**, and **4.1.8**, and **APPENDIX E**) 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 C**, Sections **4.2.1** and **4.3**). Please refer to the package insert and PDR for full drug interactions and toxicities.

14.2 IBRUTINIB

14.2.1 Source, Acquisition and Accountability
Ibrutinib is a commercially available agent and will be purchased by the CCR and supplied to the patients enrolled on the study by the NIH Clinical Center Pharmacy Department.

14.2.2 Toxicity

The most common (≥20%) adverse reactions are thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising, nausea, pyrexia, muscle spasms, stomatitis, hemorrhage, abdominal pain, pneumonia, and headache.

Serious adverse reactions include infections, cardiac arrhythmias, cardiac failure and sudden death, hypertension, second primary malignancies, hepatotoxicity, including drug-induced liver injury, and Tumor Lysis Syndrome (TLS).

Please refer to product information for additional details.

Also see Section **1.2.3** for additional information.

14.2.3 Formulation and Preparation
Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All

formulation excipients are compendial and are commonly used in oral formulations.

14.2.4 Stability and Storage
Ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

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

14.2.5 Administration Procedures
Ibrutinib is administered orally with approximately 8 ounces (240 mL) of water. Ibrutinib may be taken with or without food and may be administered with venetoclax, prednisone, and lenalidomide. Grapefruit or Seville orange juice should be avoided due to CYP3A inhibition. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

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

14.2.6 Incompatibilities
Ibrutinib is a small molecule administered orally and is primarily metabolized by cytochrome P450 3A4 (CYP3A4). Concomitant use of ibrutinib and strong inducers or inhibitors of CYP3A is contraindicated (see **APPENDIX C**, Section **4.2.1** and **4.3**). Please refer to the package insert and PDR for full drug interactions and toxicities.

14.3 PREDNISONE

14.3.1 Source, Acquisition and Accountability
Prednisone is a commercially available agent and will be purchased by the CCR and supplied to the patients enrolled on the study by the NIH Clinical Center Pharmacy Department.

14.3.2 Toxicity

The most common adverse reactions may include edema, glucose intolerance, hypertension, behavioral and mood changes (euphoria, insomnia, mood swings, personality changes, severe depression, psychosis), increased appetite, and weight gain.

Additional serious adverse reactions include immunosuppression and increased risk of infection, hypokalemia, gastrointestinal perforation, osteoporosis, eye disorders (cataracts, infection, glaucoma), negative effects on growth and development in children and adolescents.

Please refer to product information for additional details.

14.3.3 Formulation and Preparation
Prednisone is supplied as 2.5 mg, 5 mg, 10 mg, and 50 mg tablets. Additional strengths are also available although not likely utilized as part of this trial.

14.3.4 Stability and Storage

Store at 15 - 30˚C, protected from moisture and light.

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

14.3.6 Incompatibilities

Please refer to product information for additional details.

14.4 OBINUTUZUMAB (IND #134937)

14.4.1 Source, Acquisition and Accountability

Obinutuzumab is a commercially available agent but will be provided by Genentech to the NCI for dispensing to the study participants as per a previously arranged research agreement.

14.4.2 Toxicity

Please refer to the toxicity data presented in the background for clinical safety of obinutuzumab in as well as risks associated with the combination of obinutuzumab with other study drugs (Sections **1.2.3.1.3**, **1.2.3.2.2**, **1.2.3.2.4**, **1.2.3.2.6** and **12.3.1.1**).

Table 16: Obinutuzumab adverse events

Very Common, may be serious >10%:	• Neutropenia • Thrombocytopenia • Anemia • Febrile Neutropenia • Generalized Weakness, Asthenia, Fatigue • Infusion Reaction or Allergic Reaction • Pyrexia • Nausea • Emesis • Infection, Upper Respiratory Infection, Sinusitis and Urinary Tract Infection • Cough • Rhinitis • Arthralgia, Back Pain, Myalgia, Pain in Extremity, Chest Wall Pain • Pruritis • Diarrhea • Constipation • Decreased Appetite • Herpes Zoster Infection, Herpes Simplex Infection • Headache • Alopecia • Insomnia
Common may be serious 1-10%:	• Granulocytopenia, Leukopenia, Lymphopenia • Pharyngitis • Hemorrhoids • Dyspepsia • Basal Cell Carcinoma, Squamous Cell Carcinoma

	• Rhinorrhea • Arrhythmia • Weight Gain • Anxiety, Mental Depression • Incontinence Urinary, Dysuria • Hypertension • Tumor Lysis Syndrome • Electrolyte Imbalance electrolyte imbalance - hypocalcemia, hypophosphatemia, hypokalemia, hyponatremia, hyperuricemia, alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased
Rare but Serious:	• Atrial fibrillation, atrial flutter • Progressive Multifocal Leukoencephalopathy • Hepatitis B reactivation • Gastrointestinal perforation • Neutropenia • Febrile neutropenia • Thrombocytopenia • Disseminated Intravascular Coagulation

14.4.3 Formulation and Preparation

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

14.4.4 Stability and Storage

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For further instructions, as well as information on in-use stability, see the packaging label.

14.4.5 Administration Procedures

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

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

All patients must receive prophylaxis for TLS (see Sections **4.1.3**, and **4.1.8**, and **APPENDIX E**) prior to the initiation of obinutuzumab.

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

14.5 LENALIDOMIDE (IND #134937)

14.5.1 Source, Acquisition and Accountability
Lenalidomide is a commercially available agent but will be provided by Celgene to the NCI for dispensing to the study participants as per a previously arranged research agreement.

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this study at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Revlimid REMS™ program of Celgene Corporation. Per standard Revlimid REMS™ requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this study, and all research subjects enrolled into this study, must be registered in and must comply with all requirements of the Revlimid REMS™ program.

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

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

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

14.5.2 Toxicity
There are boxed warnings for lenalidomide, embryo-fetal toxicity (please see **APPENDIX G**), hematologic toxicity and venous thromboembolism. Lenalidomide can cause significant neutropenia and thrombocytopenia.

In addition, there are warnings regarding allergic reactions, tumor lysis syndrome, tumor flare reaction and second primary malignancies.

Allergic reactions: Hypersensitivity, anaphylaxis, angioedema, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

Tumor lysis syndrome: Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These subjects should be monitored closely, and appropriate precautions taken.

Tumor flare reactions: Serious tumor flare reactions have occurred during investigational use of lenalidomide for chronic lymphocytic leukemia and lymphoma.

Adverse Events: Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized

pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures. Other rare or uncommon serious related adverse events are gastrointestinal hemorrhage (Uncommon), small intestinal obstruction (Rare), chest pain (Rare), hepatocellular injury (Rare), decreased appetite (Uncommon), peripheral neuropathy (Uncommon), hypoxia (Rare), and pleuritic pain (Rare).

Second new cancers: Higher incidences of second primary malignancies, including acute myelogenous leukemia (AML) and Hodgkin lymphoma, have been observed in controlled trials of patients with multiple myeloma receiving lenalidomide in addition to melphalan and stem cell transplantation.

Please refer to the lenalidomide IB and package insert for a complete listing of all toxicities. See Section **1.2.3** for additional information.

14.5.3 Formulation and Preparation

Lenalidomide (REVLIMID®) will be supplied as capsules for oral administration by Celgene Corporation.

Lenalidomide will be shipped to the pharmacy at the study site in individual bottles or blister packs. Bottles or blister packs will contain a sufficient number of capsules to last for 1 cycle of dosing. Lenalidomide must be dispensed in the original packaging with the label clearly visible. **Only enough lenalidomide for 1 cycle of therapy may be provided to the subject each cycle.**

The Investigator or designee is responsible for taking an inventory of each shipment of lenalidomide received on the drug accountability form.

14.5.4 Stability and Storage

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Please see local prescribing information for Revlimid® for detailed instructions on storage conditions and stability.

14.5.5 Administration procedures

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

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

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

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

14.5.6 Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug

received and comparing it with the accompanying study drug accountability form. The Investigator or designee will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

14.5.7 Unused study drug supplies
Celgene recommends destruction of unused study drug on-site. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

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

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

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

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

14.6 POLATUZUMAB (IND #134937)

14.6.1 Source, Acquisition and Accountability
Polatuzumab is a commercially available agent but will be provided by Genentech to the NCI for dispensing to the study participants as per a previously arranged research agreement.

14.6.2 Toxicity
Please refer to the toxicity data presented in the background for clinical safety of polatuzumab in as well as risks associated with the combination of polatuzumab with other study drugs (Section **1.2.4**).

Table 17: Polatuzumab adverse events

Likely:	• Neutropenia • Thrombocytopenia • Anemia • Peripheral sensory and motor neuropathy • Diarrhea • Pyrexia • Decreased appetite • Fatigue, asthenia • Infections including pneumonia, upper respiratory tract infection, COVID, urinary tract infection, skin infection,

	fungal pneumonia, herpes simplex, herpes zoster, or cytomegalovirus infection • Emesis • Weight decrease • Electrolyte imbalance (hypokalemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hypophosphatemia) • Alanine transferase increased, aspartate transaminase increased, total bilirubin increased • Lymphopenia, leukopenia, febrile neutropenia • Nausea • Constipation
Less Likely:	• Arthralgia • Pneumonitis • Sepsis • Lipase increased • Conjunctival hemorrhage, lacrimation increased, diplopia, blepharitis, retinal hemorrhage, blurred vision • Cough, dyspnea • Abdominal pain • Rash, pruritic • Dry skin • Myalgia • Mucositis • Peripheral Edema • Chills • Progressive Multifocal Leukoencephalopathy • Abnormal kidney function tests, serum creatinine increased • Arrhythmia • Tumor lysis syndrome (TLS) • Gastrointestinal hemorrhage • Tissue death at the injection site caused by drug leakage (Infusion site extravasation injury)

14.6.3 Formulation and Preparation

Polatuzumab vedotin for injection is supplied as a sterile, white to grayish-white, preservative-free, lyophilized powder, which has a cake-like appearance, for intravenous infusion after reconstitution and dilution. After reconstitution with 7.2 mL of Sterile Water for Injection, USP, the final concentration is 20 mg/mL with a pH of approximately 5.3. Each single-dose vial delivers 140 mg of polatuzumab vedotin-piiq, polysorbate-20 (8.4 mg), sodium hydroxide (3.80 mg), succinic acid (8.27 mg), sucrose (288 mg).

The POLIVY vial stoppers are not made with natural rubber latex.

Reconstitute and further dilute POLIVY prior to intravenous infusion.

POLIVY is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose, the total volume of reconstituted POLIVY solution required, and the number of POLIVY vials needed.
- Reconstitute each 140 mg POLIVY vial by using a sterile syringe to slowly inject 7.2 mL of Sterile Water for Injection, USP with the stream directed toward the inside wall of the vial to obtain a concentration of 20 mg/mL of polatuzumab vedotin-piiq.
- Swirl the vial gently until completely dissolved. *Do not shake*.
- Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Do not use if the reconstituted solution is discolored, is cloudy, or contains visible particulates. *Do not freeze or expose to direct sunlight.*
- If needed, store unused reconstituted POLIVY solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 48 hours or at room temperature (9°C to 25°C, 47°F to 77°F) up to a maximum of 8 hours prior to dilution. Discard vial when cumulative storage time prior to dilution exceeds 48 hours.

Dilution

- Dilute polatuzumab vedotin-piiq to a final concentration of 0.72–2.7 mg/mL in an intravenous infusion bag with a minimum volume of 50 mL containing 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.
- Determine the volume of 20 mg/mL reconstituted solution needed based on the required dose.
- Withdraw the required volume of reconstituted solution from the POLIVY vial using a sterile syringe and dilute into the intravenous infusion bag. Discard any unused portion left in the vial.
- Gently mix the intravenous bag by slowly inverting the bag. *Do not shake*.
- Inspect the intravenous bag for particulates and discard if present.

- If not used immediately, store the diluted POLIVY solution as specified in the Table below. Discard if storage time exceeds these limits. *Do not freeze or expose to direct sunlight*.

Diluted POLIVY Solution Storage Conditions Diluent Used to Prepare Solution for Infusion	**Diluted POLIVY Solution Storage Conditions***
0.9% Sodium Chloride Injection, USP	Up to 24 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
0.45% Sodium Chloride Injection, USP	Up to 18 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
5% Dextrose Injection, USP	Up to 36 hours at 2°C to 8°C (36°F to 46°F) or up to 6 hours at room temperature (9 to 25°C, 47 to 77°F)

* To ensure product stability, do not exceed specified storage durations.

- Limit transportation to 30 minutes at 9°C to 25°C or 12 hours at 2°C to 8°C (refer to instructions below). The total storage plus transportation times of the diluted product should not exceed the storage duration specified in the Table above.
- Agitation stress can result in aggregation. Limit agitation of diluted product during preparation and transportation to administration site. Do not transport diluted product through an automated system (e.g. pneumatic tube or automated cart). If the prepared solution will be transported to a separate facility, remove air from the infusion bag to prevent aggregation. If air is removed, an infusion set with a vented spike is required to ensure accurate dosing during the infusion.
- No incompatibilities have been observed between polatuzumab and intravenous infusion bags with product contacting materials of polyvinyl chloride (PVC) or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). No incompatibilities have been observed with infusion sets or infusion aids with product-contacting materials of PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), fluorinated ethylene propylene (FEP), or polytetrafluorethylene (PTFE), or with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).

Administration

- Administer polatuzumab as an intravenous infusion only.
- Polatuzumab must be administered using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2-or 0.22-micron pore size) and catheter.
- Do not mix polatuzumab with or administer as an infusion with other drugs.

14.6.4 Stability and Storage

Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not use beyond the expiration date shown on the carton. Do not freeze. Do not shake.

For further instructions, as well as information on in-use stability, see the packaging label.

14.6.5 Administration Procedures

Polatuzumab will be administered by IV on Day 2 of each 21-day treatment cycle (Cycles 1–6). Premedication will be used to reduce the risk of infusion related reactions (IRRs) as outlined in Section **3.2**. See also above Section **14.6.4**. The initial dose of polatuzumab will be administered over 90 minutes and patients will be monitored for IRRs during the infusion and for a minimum of 90 minutes following completion of the initial dose. If the previous infusion was well tolerated, the subsequent dose of polatuzumab may be administered as a 30-minute infusion and patients should be monitored during the infusion and for at least 30 minutes after the completion of the infusion.

If a planned dose of polatuzumab is missed, administer as soon as possible. Adjust the schedule of administration to maintain a 21-day interval between doses.

14.6.6 Incompatibilities

Polatuzumab-vedotin catabolism has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. MMAE is a substrate for CYP3A4. Concomitant use of polatuzumab and strong inducers or inhibitors of CYP3A is contraindicated (see **APPENDIX C**, Section **4.2.1** and **4.3**). MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. MMAE does not induce major CYP enzymes. MMAE does not inhibit P-gp. MMAE is a P-gp substrate. Please refer to the package insert and PDR for full drug interactions and toxicities.

14.7 ADDITIONAL INFORMATION

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section **3.3**. Treatment will continue for up to 6 cycles of treatment until disease progression or other reason for treatment discontinuation as outlined in Section **3.9**.

Investigators are prohibited from supplying study drug to any subjects 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 subjects 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 subject. 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. Subjects 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.

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16 APPENDICES

16.1 APPENDIX A: STUDY CALENDAR – SCHEDULE OF ASSESSMENTS

Procedure	**Screening**[1]	**Baseline**[2]	**Treatment Cycle**								**Disease Progression/ End of Treatment**	**Post-Treatment Follow-Up**[3]		
			Cycles 1, 3, and 5				Cycles 2, 4, and 6					Safety	Follow-Up (Pre-PD)	Survival (Post-PD)
Study Cycle/Day/Time point: *(1 cycle = 21 days)*			1	2	8	15	1	2	8	15		30 days	Q3, 4, 6 and 12-months years 1, 2, 3, and 4-5, respectively[4]	Q6 months
Scheduling Window (Days):	-28/+0		-7	0	±1	±1	-3	0	±1	±1	-7/+7	-2/+7		±28
Tissue/Pathologic Review	X													
Medical History	X													
Physical Exam and ECOG PS	X	X	X				X				X	X	X	
VTE Risk Assessment[5]	X													
Vital Signs	X	X	X	X			X	X			X	X	X	
EKG	X													
Bone Marrow Aspiration/Biopsy[6]		X	(in follow-up as clinically indicated; see footnote)											
Symptoms/Adverse Events	X	X	X X								X	X	X	
Concomitant Medications	X	X	X 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	
Hepatic Panel	X	X	X				X				X	X	X	
LDH and Uric acid	X	X	X		X	X	X		X	X	X	X	X	
Total protein		X	X				X				X	X	X	
TSH	X		X				X				X	X	X	
Hepatitis and HIV testing[7]	X		prior to each treatment cycle if positive for Hep B and with each scheduled follow-up visit through 12 months EoT; see footnote)											
Beta-2 Microglobulin		X												
Coagulation Panel (PT/INR, PTT)	X		X				X				X	X	X	
T/B/NK Cell Subsets, EBV, CMV		X	X				X				X	X	X	
Urinalysis	X											X		
Pregnancy Test[8]	X	X	X			X	X			X		X		
Radiologic Imaging (CT/MRI/PET)[9]	X		X *(Pre-Cycle 3&5)*								X		X	
PET Imaging[10]	X										X			
Study Drug Diary[11]			X				X							
Revlimid REMS® Registration		X												
Biomarker Blood Samples[12]		X	X				X				X		X	
Tumor Tissue/Biopsy[13]		X									X (PD)		X (PD)	
Survival Status[14]														X
PG Samples/Germline DNA		X												

Procedure	**Screening**[1]	**Baseline**[2]	**Treatment Cycle**								**Disease Progression/ End of Treatment**	**Post-Treatment Follow-Up**[3]		
			Cycles 1, 3, and 5				Cycles 2, 4, and 6					Safety	Follow-Up (Pre-PD)	Survival (Post-PD)
Study Cycle/Day/Time point: *(1 cycle = 21 days)*			1	2	8	15	1	2	8	15		30 days	Q3, 4, 6 and 12-months years 1, 2, 3, and 4-5, respectively[4]	Q6 months
Scheduling Window (Days):	-28/+0		-7	0	±1	±1	-3	0	±1	±1	-7/+7	-2/+7		±28
PK Samples[15]				X	X									

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 antibody, Hepatitis B surface antigen and Hepatitis C antibody (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] All post-treatment visit(s) may be completed by remote visit with a member of the study team (e.g., if the patient is not able to return to the NIH CC). Required labs/scans can be obtained by a local provider, with results sent in. A patient may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the investigator.
[4] The windows for assessments post-treatment and prior to progression: ±14 days for years 1 and 2, ±21 days for year 3, and ±28 days for years 4 and 5; after 5 years, contact should occur about every 6 months for survival only. Any ongoing follow-up visits, assessments, or other procedures after 5 years are at the discretion of the investigator.
[5] Venous Thromboembolism Risk Assessment must be assessed at Screening for eligibility; repeat as clinically indicated. See Section **2.2.2.4**
[6] Repeat bone marrow aspiration/biopsy in follow-up if required to confirm suspected CR (if positive at baseline); otherwise, repeat only if clinically indicated.
[7] Ongoing HBV levels should be checked prior to each treatment cycle and at each scheduled follow-up visit through 12 months after EoT in participants in patients with positive antibody testing at baseline. See Section **4.1.7**.
[8] Urine and/or serum HCG in individuals of childbearing potential (within 10-14 days prior to initiation of Revlimid and again within 24 hours prior to initiation of Revlimid). See additional pregnancy testing requirements in Sections **2.1.1.8**, **2.2.2**, and **3.5.1**.
[9] CT neck, chest, abdomen and pelvis preferred (with IV and PO contrast unless contraindicated); MRI and/or PET 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 patients 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 **3.5.3**and **3.5.4**, 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
[10] Repeat PET Imaging (i.e., whole body ^{18}F-FDG PET/CT or as clinically indicated) to confirm suspected CR (if positive at baseline) at end-of-treatment; otherwise, repeat only if clinically indicated.
[11] Subjects will be given a Study Drug Diary with each cycle to document administration of oral study drugs. See **APPENDIX D**.
[12] Correlative blood samples (e.g., Streck, red top, and CPT tubes) will be collected at Baseline/pre-Cycle 1, at every cycle on treatment, at each disease re-assessment and at disease progression/recurrence. See Section **5**.

[13] Archival tissue will be accessed for research correlates, if available. Subjects may also have an optional fresh tumor biopsy at baseline and at disease progression/recurrence if accessible tumor and acceptable risk. See Section **5**.
[14] After 5 years of follow-up without disease progression, or upon progression or initiation of alternative antineoplastic therapy, subjects 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. **NOTE:** Investigators should continue to report serious adverse events that are attributed to the study treatment in follow-up; including occurrences of secondary malignancies; see also Section **8.1.6**.
[15] Only select patients will undergo PK testing. Samples on Cycle 1 day 2 will be drawn pre-dose, 0.5 (+/-15min), 1 (+/-15min), 2 (+/-15min), 4 (+/-15min), 6 (+/-15min), and 24 (+/-15min) hours post study drug dosing. Samples drawn on Cycle 1 day 8 will be drawn pre-dose (just before C1D8 dose is taken) and 2 (+/-15min) hours post study drug dosing. See section **5**.

16.2 APPENDIX B: 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.

16.3 APPENDIX C: INHIBITORS AND INDUCERS OF CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: https://drug-interactions.medicine.iu.edu/main-table.

The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section **4.2.1** and **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: https://drug-interactions.medicine.iu.edu/main-table

16.4 APPENDIX D: STUDY DRUG DIARY

Patient Name: _____ 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
i = Ibrutinib	Ibrutinib capsules should be taken with a glass of water with or without food
P = Prednisone	Prednisone tablets should be taken with a glass of water with or without food
O = Obinutuzumab	Obinutuzumab is given by IV, in the clinic
R = REVLIMID® (Lenalidomide)	Lenalidomide capsules should be taken with a glass of water with or without food
Pola = Polatuzumab	Polatuzumab is given by IV, in the clinic
	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: In clinic, take the ibrutinib, prednisone, and lenalidomide with water when instructed, with or without food. About 30-60 minutes later, receive the obinutuzumab infusion.
- Day 2: In clinic, take the venetoclax, ibrutinib, prednisone, and lenalidomide with water and food when instructed. About 30-60 minutes later, receive the obinutuzumab infusion followed by the polatuzumab infusion.
- Days 3 through 7: Take the venetoclax, ibrutinib, prednisone, and lenalidomide with water and food (e.g., with breakfast).
- Days 8 through 14: Take the venetoclax, ibrutinib and lenalidomide with water and food (e.g., with breakfast).
- Days 15-21: 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	**Ibrutinib**	**Prednisone**	**Obinutuzumab**	**Lenalidomide (Revlimid®)**	**Polatuzumab**	
		V	**i**	**P**	**O**	**R**	**Pola**	
-1		NO DRUG						Fluid Intake
1		NONE			IV, in clinic		NONE	
2							IV, in clinic	
3					NONE		NONE	
4					NONE		NONE	
5					NONE		NONE	
6					NONE		NONE	
7					NONE		NONE	
8				NONE	NONE		NONE	
9				NONE	NONE		NONE	
10				NONE	NONE		NONE	
11				NONE	NONE		NONE	
12				NONE	NONE		NONE	
13				NONE	NONE		NONE	
14				NONE	NONE		NONE	
15-21		NO DRUG						

16.5 APPENDIX E: 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 patient 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.
- 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 18: 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.

Abnormality	Management Recommendations
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.
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 Patient 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 patient is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient 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 18**).

- 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 18**).

16.6 APPENDIX F: THE LUGANO CLASSIFICATION RESPONSE CRITERIA FOR NHL

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.

16.7 APPENDIX G: RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS FOR LENALIDOMIDE

Risks Associated with Pregnancy

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

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

Criteria for females of childbearing potential (FCBP)

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

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential or pregnant female, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential or pregnant female.

Contraception

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

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

- Highly effective methods:
    - Intrauterine device (IUD)

  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

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

Pregnancy Testing

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

Before starting lenalidomide

Female Patients:

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

Male Patients:

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

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.

- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

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

Additional Precautions:

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

16.8 APPENDIX H: SAFETY REPORTING GUIDELINES - GENENTECH

Methods and Timing for Assessing and Recording Safety Variables

A. Adverse Event Reporting Period

The study period during which all adverse events and serious adverse events must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report serious adverse events that are attributed to prior study treatment.

B. Assessment of Adverse Events

All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported adverse event or serious adverse event will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of adverse event and serious adverse event causality assessments, investigators should apply the following general guideline:

- Yes: There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
- No: Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the USPI or current IB.

Unexpected adverse events are those not listed in the USPI or current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the USPI or IB. For example, under this definition, hepatic necrosis would be unexpected if the USPI or IB only referred to elevated hepatic enzymes or hepatitis.

Procedures for Eliciting, Recording and Reporting Adverse Events

A. Eliciting Adverse Event Information

A consistent methodology for eliciting adverse events at all subject evaluation time points should be adopted using non-directive questions. Examples of non-directive questions include:

"How have you felt since your last clinical visit?"

"Have you had any new or changed health problems since you were last here?"

B. Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting adverse events or serious adverse events. Avoid colloquialisms and abbreviations.

- *Infusion-Related Reactions:* Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction." If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately, with signs and symptoms also recorded separately.
- *Diagnosis versus Signs and Symptoms:* If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.
- *Deaths:* All deaths that occur during the protocol-specified adverse event reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.
- *Preexisting Medical Conditions:* A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an adverse event or serious adverse event only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).
- *Hospitalizations for Medical or Surgical Procedures:* Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an adverse event, the event responsible for the procedure, not the procedure itself, should be reported as the serious adverse event. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the serious adverse event.
- Hospitalizations for the reasons/exceptions noted in Section **6.1.1** do not require reporting.
- *Congenital Anomalies/Birth Defects and Abortions:* Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as a serious adverse event. Similarly, any congenital anomaly/birth defect in a

child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event.

- *Post-Study Adverse Events:* The investigator should expeditiously report any serious adverse event occurring after a subject has completed or discontinued study participation if attributed to prior study drug exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as a serious adverse event.
- *Reconciliation:* The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format but agree at minimum to exchange quarterly line listings of cases received by the other party, unless otherwise stated in the collaborative agreement(s).

  If discrepancies are identified, the parties will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

16.9 APPENDIX I: PREGNANT PARTNER MEDICAL INFORMATION RELEASE FORM

Parent Study Title: Phase 1 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Revlimid in Combination with Polatuzumab (ViPOR-P) in Relapsed/Refractory B-cell Lymphoma

Study Doctor: Christopher Melani, M.D.
Study Center: National Cancer Institute
10 Center Drive Bethesda, MD 20892
Phone: 240-760-6092

Participant's Name: _____

Introduction

You are being asked to let information be collected about your pregnancy and the birth and health of your child because you became pregnant while the biological father of your child was participating in a study called a Phase 1 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Revlimid in Combination with Polatuzumab (ViPOR-P) in Relapsed/Refractory B-cell Lymphoma.

The purpose of this Release Form is to inform you about the nature of this follow-up information so that you may make an informed decision as to whether you would allow Genentech to collect information regarding the outcome of your pregnancy. If you have any questions, please ask the Study Doctor or Study Nurse to explain any words or information that you do not understand.

Why is this pregnancy follow-up information required?

The purpose of this Pregnant Partner Medical Information Release is to gather medical information about your pregnancy and the birth and health of your child for safety monitoring purposes. We want to assess if the study drugs have any effects on your pregnancy and the health of your child.

What will happen if you agree to share your medical information?

If you agree to share your medical information, we will ask you for your permission to review you and your child's medical records relating to:

- your pregnancy
- the delivery of your child
- the health of your child up to **6-8 weeks** of age.

Information from your baby's medical record that will be collected will include any medical concerns, and the baby's height and weight.

If you agree, you will be asked to give the ML42527 Study Doctor the names and telephone numbers of the doctor who is taking care of you during your pregnancy and the doctor who is taking care of your child. If your doctor's or the child's doctor's contact information changes, please tell your Study Doctor.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address, date of birth
- Medical information about your pregnancy, the birth and health of your child and how the investigational drug may have affected either of them.

If you do not sign this form, you and your child's health information will not be collected. In addition, it will not affect your right to receive healthcare or other benefits you are entitled to. You can change your mind and withdraw this permission for pregnancy follow-up information at any time. However, before you decide to withdraw these permissions, we encourage you to talk to your Study Doctor and your regular doctor first.

To withdraw these permissions, please send a letter to the Study Doctor listed on this form. Your Study Doctor will still use information about you that was collected before you withdrew permission. The National Cancer Institute and Genentech will do everything possible to protect your privacy.

You are not expected to receive any direct medical benefits from releasing your medical information.

You will not incur any costs for releasing this medical information nor will it cover any costs related to your pregnancy, delivery or care of your child. You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

You will not be paid for releasing your pregnancy follow up medical information.

Confidentiality

The information in you and your child's medical records, and the information you give to us, will be kept confidential (private) to the extent allowed by law. Your data will be coded to hide your identity and the identity of your baby. The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy.

There is a small risk that information from your health records and of your child's health records will be released to an unauthorized party. However, the chance that this information will be given to someone else is very small.

Your information may be shared with:

- The researchers to make sure they observe the effects of the study and understand its results.
- People or committees that oversee the ViPOR-P study
- Genentech, the Sponsor's representatives, and any collaborator or partner of the Sponsor who participates in any of the Sponsor's research and development programs researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA).

A description of the main clinical trial (ViPOR-P) that your partner is participating in is available on *http://www.ClinicalTrials.gov,* as required by U.S. Law.

Who to contact if you have any questions about this release?

Dr. Christopher Melani or one of the other study doctors has explained this release to you and answered your questions. You may contact the Study Doctor at the phone listed on page one of this form.

What does your signature mean?

If you sign this document, you are giving permission for the use and disclosure of you and your child's health information for the purposes of the safety monitoring activities described above.

Before you sign this form, please ask questions about any part of this release that is not clear to you. Your signature below means that you understand the information given to you about this release of medical information.

Consent From Adult

To be completed by participant if 18 years of age or older.

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

By signing below you confirm that you have fully explained this release to the potential subject, allowed them time to read the release or have the release read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Only include if the pregnant partner is a minor (<18 years of age)

Parental/Guardian Permission
By signing below you confirm you have the legal authority to sign for this child.

_____	_____	_____
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

Person Obtaining Parental Permission
By signing below you confirm that you have fully explained this release to the parent/guardian, allowed them time to read the release or have the release read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING PARENTAL PERMISSION (SIGNATURE)	PERSON OBTAINING PARENTAL PERMISSION (PRINT NAME)	DATE