SUMMARY OF CHANGES

Protocol Amendment #2

LCCC2033: A phase II trial evaluating the efficacy of polatuzumab vedotin with rituximab, gemcitabine, dexamethasone, and cisplatin (PV-RGDP) chemotherapy for relapsed or refractory diffuse large B-cell lymphoma

AMENDMENT INCORPORATES:
__ Editorial, administrative changes
_X_ Scientific changes
__ Therapy changes
_X_ Eligibility Changes

Rationale for amendment: The purpose of this amendment is to clarify that subjects who are enrolled on this study do not have to be in their first relapse. Therefore, inclusion criteria and study plan language have been updated accordingly.

Administrative changes:

Section	8.1	T&E table footnotes corrected for consistency.

Scientific changes:

Section 5.1.1	Study design language updated to clarify that subjects who have had at least one prior treatment regimen are eligible for study participation.

Eligibility changes:

Section 4.1.2	Language that mandated subjects must be in first relapse was removed.

THE ATTACHED VERSION DATED November 27, 2023 INCORPORATES THE ABOVE REVISIONS

SUMMARY OF CHANGES

Protocol Amendment #1

LCCC2033: A phase II trial evaluating the efficacy of polatuzumab vedotin with rituximab, gemcitabine, dexamethasone, and cisplatin (PV-RGDP) chemotherapy for relapsed or refractory diffuse large B-cell lymphoma

AMENDMENT INCORPORATES:
_X_ Editorial, administrative changes
_X_ Scientific changes
__ Therapy changes
__ Eligibility Changes

Rationale for amendment: The purpose of this amendment is to rectify inconsistencies that were observed between the protocol and the time and events table.

Editorial, administrative changes:
Grammer and mechanical edits throughout

Scientific changes:

Section 7.1.5	Audiometry language updated to specify that audiometric monitoring will be performed during physical examination prior to initiation of therapy, and then if clinically indicated by formal assessment per physician's discretion.
Section 7.1.7 and T&E Footnote 4	Timing updated so that PET/CT imaging should be obtained within 28 days of initiating study treatment. Language also added to Section 7.1.7 to specify the exact time response assessment will be measured.
Section 7.2.2 and Section 8.0	Time and events table and Blood Chemistry Profile updated to ensure that both sections are consistent with the testing that will be completed.
Section 8.0	Coagulation profile added to T&E table to correspond with Section 7.2.3 of the protocol.
Section 8.3	Language corrected to specify that a CT scan (and not a PET scan) will be conducted during the follow up period.

THE ATTACHED VERSION DATED June 22, 2023 INCORPORATES THE ABOVE REVISIONS

LCCC2033: A phase II trial evaluating the efficacy of polatuzumab vedotin with rituximab, gemcitabine, dexamethasone, and cisplatin (PV-RGDP) chemotherapy for relapsed or refractory diffuse large B-cell lymphoma

Short Title: Polatuzumab vedotin with R-GDP in relapsed/refractory diffuse large B-cell lymphoma

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IND: 161215
Funding Source: Genentech
Version #: Amendment 2
Version Date: November 27, 2023, Version 2.1

LCCC2033: A phase II trial evaluating the efficacy of polatuzumab vedotin with rituximab, gemcitabine, dexamethasone, and cisplatin (PV-RGDP) chemotherapy for relapsed or refractory diffuse large B-cell lymphoma

Principal Investigator
Christopher Dittus, DO, MPH
[redacted]

Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

Version #: Amendment 2
Version Date: November 27, 2023, Version 2.1

LIST OF ABBREVIATIONS

ADC	Antibody-drug conjugate
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	*Bis in die* (twice daily)
BSA	Body surface area
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CBCD	Complete blood count with differential
CBR	Clinical benefit rate
cfDNA	Circulating free deoxyribonucleic acid
CL	Clearance
CLL	Chronic Lymphocytic Leukemia
Cmax	Maximum plasma drug concentration
CMP	Comprehensive metabolic panel
CPO	Clinical Protocol Office
CR	Complete response
CrCl	Creatinine Clearance
CT	Computer tomography
DEL	Double-expressor lymphomas
DHL	Double hit lymphoma
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data safety monitoring committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
GC	Germinal Center
GCP	Good Clinical Practice
GPA	Granulomatosis with Polyangiitis
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
IDS	Investigational drug service
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMIDs	Immunomodulators
INR	International normalized ratio
IV	Intravenous
LCCC	Lineberger Comprehensive Cancer Center
LDH	Lactate dehydrogenase
MRI	Magnetic resonance Imaging
MPA	Microscopic Polyangiitis
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
OAT	Organic anion transporter

OATP	Organic anion transporter polypeptide
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PE	Polyethylene
PET	Positron Emission Tomography
PFS	Progression free survival
PFT	Pulmonary function test
Pgp	P-glycoprotein
PI	Principal investigator
PK	Pharmacokinetic(s)
PR	Partial response
PRC	Protocol review committee
PT	Prothrombin time
PTT	Partial thromboplastin time
PV	Polatuzumab vedotin or Pemphigus Vulgaris
PVC	Polyvinylchloride
PV-RGDP	Rituximab, gemcitabine, dexamethasone, and cisplatin
RA	Rheumatoid arthritis
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
rrDLBCL	Relapse-refractory diffuse large B-cell lymphoma
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Stable disease
SAR	Serious adverse reaction
t½	Half-life
TBNK	T or B-cell natural killer
THL	Triple hit lymphoma
ULN	Upper limit of normal
UNC	University of North Carolina
USP	United States Pharmacopeia

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

LCCC 2033 is a multicenter, open-label, single arm, phase 2 study to evaluate the efficacy of a novel regimen consisting of polatuzumab vedotin in combination with rituximab, gemcitabine, dexamethasone, and cisplatin (PV-RGDP) for the treatment of relapsed/refractory diffuse large B-cell lymphoma (rrDLBCL). RGDP is a standard regimen for rrDLBCL and PV is a novel antibody-drug conjugate targeting CD79b. PV has shown efficacy in the setting of rrDLBCL and we feel it can improve the response rates of standard salvage therapy. This is particularly important because, although there is a cure rate with salvage treatment of rrDLBCL, there is significant room for improvement. This study will focus on subjects in relapse (who have had at least one prior regimen) and will include both subjects who are transplant eligible and those who are transplant ineligible. Subjects who are transplant eligible may proceed to autologous stem cell transplant after a minimum of 2 cycles as long as they achieve a complete or partial remission.

The primary endpoint will be the overall response rate (ORR), with complete response (CR) rate, progression free survival (PFS), and overall survival (OS) being secondary endpoints. The study will use a Simon two-stage design. In the first stage, 27 evaluable subjects will be recruited. If there are at least 13 (≥ 13) subjects with a partial or complete response after at least 2 cycles, another 17 evaluable subjects will be enrolled and treated in the second stage of the trial, for a total of 44 evaluable subjects. We will reject the null hypothesis if and only if there are ≥ 13 subjects with an ORR from the first stage and ≥ 23 subjects with an ORR out of the 44 subjects. We hypothesize that this regimen will be more effective than the historical standard of care, salvage regimens which includes RGDP.

1.2 Disease Background

DLBCL is the most common type of non-Hodgkin lymphoma (NHL) in the United States and is the prototype for aggressive B-cell lymphomas. Based on 2013-2017 SEER data, the estimated number of new cases of DLBCL in the United States is around 18,000 per year [1]. Standard frontline therapy leads to a cure in approximately 60% of patients [2]. Cure rates are highly variable based on multiple factors, including the international prognostic index (IPI), stage, immunohistochemical findings, and chromosomal abnormalities. Of the 40% who will relapse, the standard approach is to proceed with salvage chemotherapy followed by an autologous stem cell transplant (autoSCT) in eligible patients who have chemosensitive disease. This approach was initially described in the seminal PARMA study comparing salvage chemotherapy alone to salvage chemotherapy consolidated with autoSCT [3]. The group that received consolidation autoSCT had an overall survival benefit (53% vs. 32%; $p = 0.038$), setting the new standard of care for relapsed aggressive B-cell lymphoma. The salvage regimen used in the PARMA study was high-dose cytarabine, dexamethasone, and cisplatin (DHAP), which had a response rate of 64% in those who relapsed after frontline chemotherapy and 21% in those who relapsed during frontline chemotherapy.

Despite an improvement in the approach to salvage therapy, significant room for improvement remains.

1.3 Current Standard of Care

Since the PARMA study, the standard of care for relapsed DLBCL has been salvage chemoimmunotherapy followed by autoSCT. Multiple studies have compared standard salvage regimens for DLBCL, including the CORAL study, which compared R-ICE to R-DHAP, and the LY.12 study, which compared (R)-DHAP to (R)-GDP [4, 5]. Each of these studies failed to show a superior regimen, but they did report unique toxicity profiles. The CORAL study had response rates for R-ICE of 63% (ORR) and 36% (CR), while the responses for the R-DHAP arm were 64% (ORR) and 40% (CR). The LY.12 study found that R-DHAP and R-GDP were similar in terms of responses, but with less toxicity in the R-GDP arm. This study described a CR rate of 13.8% and an ORR of 46.1% in the R-GDP arm, and 14.6% and 44.7% in the R-DHAP arm. Although these studies clearly show an effective approach for a proportion of subjects, approximately half of subjects will not achieve a suitable remission for transplant. A follow-up of the CORAL study evaluated subjects who could not proceed to autoSCT, and found that they had an ORR of 39% to third-line chemotherapy (OS of 4.4 months) [2, 6]. Thus, improvements in second-line salvage therapies are tantamount to improved DLBCL survival rates.

One study has evaluated the use of a newer CD20 monoclonal antibody, ofatumumab, in the hope that this would improve the response rate in subjects who had received prior rituximab [7]. Unfortunately, this study showed low response rates in general, including an ORR of 38% in the O-DHAP group and 42% in the R-DHAP group. Other novel agents have been successfully combined with standard salvage regimens in pilot studies, including lenalidomide with R-ICE and ibrutinib with R-ICE [8, 9]. Although response rates seem promising, these studies require further evaluation.

1.4 Polatuzumab

Polatuzumab vedotin (PV) is a novel antibody-drug conjugate (ADC) that contains a humanized monoclonal antibody portion combined with monomethyl auristatin E (MMAE). The monoclonal antibody targets the B-cell antigen receptor complex-associated protein beta chain (CD79b), while the MMAE component is an antimitotic agent that blocks the polymerization of tubulin. PV has been studied in relapsed and frontline DLBCL. This agent was first studied as monotherapy in relapsed B-cell NHL in a phase 1 study and found to have significant activity in subjects with NHL [10]. Specifically, this study showed an ORR of 56% in DLBCL. This study established the recommended phase 2 dose for NHL as 2.4 mg/kg every 21 days. At this dose, investigators found the most common adverse events to be grade 3-4 neutropenia (40%) and grade 1-2 neuropathy (27%).

PV has also been evaluated in the relapsed DLBCL setting in combination with bendamustine and rituximab (PV-BR) [11]. This study found a CR rate of 40% in a heavily pretreated population and compared very well to the CR rate of 15% seen

with bendamustine rituximab alone. Median PFS and OS were also appreciably higher in the PV-BR arm, leading to FDA accelerated approval in 2019. The dose of PV used in this study was 1.8 mg/kg every 21 days, with common adverse reactions including neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia [11].

1.4.1.1 Clinical Studies [12]

Polatuzumab vedotin is currently being investigated in ongoing clinical trials in subjects with B-cell hematological malignancies.

1.4.1.2 Pharmacokinetics

Distribution

The antibody conjugated (acMMAE) central volume of distribution estimated based on population pharmacokinetic analysis is 3.15 L. For human, MMAE plasma protein binding is 71% to 77% and the blood to plasma ratio is 0.79 to 0.98, in vitro.

Elimination

After the first 1.8 mg/kg polatuzumab vedotin dose, the acMMAE mean (± standard deviation) Cmax was 803 (± 233) ng/mL and AUCinf was 1860 (± 966) day*ng/mL; the terminal half-life is 5.05 (± 1.60) days for acMMAE and 6.59 (± 2.08) days for total antibody.

Metabolism

PV 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.

Specific Populations

No clinically significant differences in the pharmacokinetics of PV were observed based on age (20 to 89 years), sex, or race/ethnicity (Asian and non-Asian). Mild renal impairment did not result in clinically significant differences in the pharmacokinetics of acMMAE or unconjugated MMAE. There was a 40% increase in MMAE exposure with mild hepatic impairment that was not clinically significant. The effect of severe renal or hepatic impairment are unknown.

Drug Interaction Studies

No dedicated clinical drug–drug interaction studies with PV in humans have been conducted. In vitro studies indicate MMAE is a substrate for CYP3A4/5. MMAE is a weak time-dependent inhibitor of CYP3A4/5 but does not competitively inhibit CYP3A4/5 at clinically relevant concentrations. MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. MMAE is not an inducer of major CYP enzymes.

1.4.1.3 Clinical Safety [12]

In addition to the study mentioned above, GO29044 is an ongoing Phase Ib/II study investigating polatuzumab vedotin in combination with rituximab (375 mg/m^2 IV), cyclophosphamide (750 mg/m^2 IV), doxorubicin (50 mg/m2 IV) and prednisone/prednisolone (100 mg/day PO on Days 1 – 5 of each cycle) (R-CHP), or in combination with obinutuzumab (1000 mg IV) plus CHP (G-CHP), for 6-8 treatment cycles in B-cell lymphoma subjects.

The most common AEs (occurring in ≥ 10% of subjects) included fatigue (50%), nausea (50%), diarrhea (48%), neutropenia (40%), anemia (27%), alopecia and constipation (24% each), and thrombocytopenia (20%).

Grade 3-4 AEs regardless of relationship to study drugs were reported in 33/53 subjects (62%) receiving polatuzumab vedotin plus R-CHP. Grade 3-4 AEs reported in more than two subjects in this group (all doses) included neutropenia (14/53 [26%]), febrile neutropenia (6/53 [11%]), leukocytosis and leukopenia (5/53 [9%] each), thrombocytopenia (4/53 [8%]), and hyperglycemia (3/53 [6%]).

In the polatuzumab vedotin plus G-CHP group (all doses), Grade 3-4 AEs reported in more than two patients included neutropenia (12/29 [41%]), febrile neutropenia (8/29 [28%]), anemia (4/29 [14%]), thrombocytopenia (4/29 [14%]), and leukocytosis (3/29 [10%]).

Grade 5 AEs were reported in two subjects (1 septic shock event in the polatuzumab vedotin 1.8 mg/kg plus G-CHP group and 1 atrial fibrillation event in the polatuzumab vedotin 1.8 mg/kg plus R-CHP group).

Additional information on adverse events can be found in Section 6.1.

1.5 Rationale for Clinical Study

Although the majority of patients will be cured in the frontline setting, 40% will still require salvage therapy [2]. These patients do poorly, with a 2-year survival rate estimated to be 20% [13]. As described above, the standard of care for relapsed DLBCL is an autoSCT. Once a patient is deemed eligible for a transplant in terms of underlying medical problems and performance status, the patient must meet two criteria: 1) they need a complete or good partial remission with salvage chemotherapy and 2) they need an adequate collection of stem cells. Given there are many salvage regimens, the overarching goal of treatment is to provide high response rates with low toxicities, specifically those related to myelosuppression. Recommended second-line regimens include R-ICE, R-DHAP (R-DHAX), and R-GDP. These regimens have ORRs that range from 38 to 64% and transplant rates that range from 33 to 55% [14]. As described above, based on current evidence, these regimens are all equal in efficacy, but R-GDP is better tolerated than R-DHAP [5].

Several new agents have been developed to improve the response and survival rates of relapsed DLBCL. As described in Section 1.4, PV has been studied both as monotherapy and in combination with bendamustine-rituximab in relapsed DLBCL [10,11]. The combination of PV-BR found a CR rate of 40% in a heavily pretreated population compared very well to the CR rate of 15% seen with BR alone [15]. This CR rate also compares favorably to our current standard salvage regimens. Although the PV-BR data are very exciting, BR is not a regimen typically used in the first relapse setting. Based on these encouraging data, we propose a single-arm study evaluating PV in combination with a safe and effective standard salvage regimen consisting of rituximab, gemcitabine, cisplatin, and dexamethasone (R-GDP). Because only half of patients are able to proceed to transplant, our study will include both transplant eligible and ineligible subjects. If successful, this regimen could define a new standard for relapsed/refractory DLBCL.

1.5.1 Dose Rationale

The phase 1 study on PV established that the recommended phase 2 dose for NHL was 2.4 mg/kg every 21 days, with grade 3-4 neutropenia and grade 1-2 neuropathy as the most common adverse effects at rates of 40% and 27% respectively for this particular dose [10]. The dose of polatuzumab vedotin used in the GO29365 study, which led to FDA approval, was 1.8 mg/kg, given day 2 of cycle 1 and on day 1 of subsequent cycles every 21 days [11]. Additionally, the frontline randomized trial evaluating PV with CHP, used a dose of 1.8 mg/kg once every 21 days ClinicalTrials.gov NCT01992653. We plan to use PV dosed at 1.8 mg/kg once every 21 days.

1.6 Correlative Studies

Genomic alterations and protein expression in DLBCL have also been found to be prognostically significant. Double-expressor lymphomas (DEL) have co-expression of MYC and BCL2 and have had worse responses to frontline chemotherapy [17]. Additionally, DLBCL that has *MYC* with *BCL2* and/or *BCL6* rearrangements (i.e. double hit and triple hit lymphomas [DHL and THL, respectively]) have been found to have a worse prognosis and poorer outcomes with standard frontline regimens such as R-CHOP. We will compare response rates, progression free survival and overall survival between these more aggressive variants and standard DLBCL [18, 19].

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the overall response rate (ORR) rate for polatuzumab vedotin in combination with R-GDP in rrDBLCL.

2.2 Secondary Objectives

2.2.1 To determine the complete response rate (CR) for polatuzumab vedotin in combination with R-GDP in rrDBLCL.

2.2.2 To determine median progression free survival (PFS) for polatuzumab vedotin in combination with R-GDP in rrDBLCL.

2.2.3 To determine median progression free survival (PFS) for polatuzumab vedotin in combination with R-GDP in rrDBLCL who receive autologous stem cell transplant (AutoSCT).

2.2.4 To determine median progression free survival (PFS) for polatuzumab vedotin in combination with R-GDP in rrDBLCL who do not receive autologous stem cell transplant (AutoSCT).

2.2.5 To determine the median overall survival (OS) for polatuzumab vedotin in combination with R-GDP in rrDBLCL.

2.2.6 To determine the safety of polatuzumab vedotin in combination with R-GDP in subjects with rrDBLCL.

2.3 Exploratory Objectives

2.3.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.0 Criteria for Evaluation / Study Endpoints

3.1 Primary Endpoint

3.1.1 Overall response rate (ORR) defined as the proportion of subjects who achieve CR and PR responses by Lugano classification (Appendix A) in subjects with rrDLBCL after receiving at least 2 cycles of PV-RGDP.

3.2 Secondary Endpoints

3.2.1 Complete response rate (CR) as defined by the Lugano classification (Appendix A) in subjects with rrDLBCL receiving at least 2 cycles of PV-RGDP.

3.2.2 Progression free survival (PFS) defined as the time from the start of study treatment until progression or death in subjects with rrDLBCL receiving PV-RGDP who received autologous stem cell transplant (AutoSCT).

3.2.3 Progression free survival (PFS) defined as the time from the start of study treatment until progression or death in subjects with rrDLBCL receiving at least 2 cycles of PV-RGDP who did not receive AutoSCT.

3.2.4 Overall survival (OS) defined as the time from the start of treatment until death from any cause in subjects with rrDLBCL receiving at least 2 cycles of PV-RGDP.

3.2.5 Toxicity/safety as defined in the CTCAE v5.0 in subjects with rrDLBCL receiving at least one treatment with PV-RGDP.

3.3 Exploratory Endpoints

3.3.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3.5.2 [redacted],

4.0 SUBJECT ELIGIBILITY

In order to participate in this study a subject must meet ALL of the eligibility criteria outlined below.

4.1 Inclusion Criteria

4.1.1 Written informed consent obtained to participate in the study and HIPAA authorization for release of personal health information.

4.1.2 Biopsy proven diffuse large B-cell lymphoma (DLBCL) who have had at least one prior treatment regimen (biopsy can be from initial diagnosis). The study will allow high-grade B cell lymphoma, but not including Burkitt's lymphoma. Per the 2016 WHO criteria, the following histologies are eligible to participate in this study:

- Diffuse large B-cell lymphoma (DLBCL), NOS
- Germinal center B-cell type
- Activated B-cell type
- T-cell/histiocyte-rich large B-cell lymphoma
- EBV+ DLBCL, NOS
- DLBCL associated with chronic inflammation
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK+ large B-cell lymphoma
- HHV8+DLBCL, NOS
- High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
- High-grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

4.1.3 Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 (Appendix B).

4.1.4 Age ≥ 18 at the time of consent.

4.1.5 Radiologic evidence of active disease per Lugano criteria (Appendix A) within 42 days of starting trial therapy.

4.1.6 Subject must have at least one prior line of therapy.

4.1.7 Prior cancer treatment or other investigational treatment must be completed at least 21 days or 5 half-lives (whichever is longer) prior to start of treatment and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to ≤ Grade 1 at **start of treatment.**

4.1.8 Subjects with a history of prior or concurrent second primary malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the study drugs are eligible for enrollment in the trial. This includes localized prostate cancer, bladder cancer, *in situ* breast cancer and

non-melanoma skin cancers.

4.1.9 Subjects may be eligible or ineligible for autologous stem cell transplant.
NOTE: The reason for transplant ineligibility should be recorded on the eCRF

4.1.10 Subjects with HIV will be allowed to participate in the trial if they have controlled HIV (CD4+ counts >200 cells/uL). Subjects must be tested within 28 days of starting trial therapy.

4.1.11 If positive for HBV core antibody or surface antigen, subjects will be allowed to participate in the trial with HBV prophylaxis. If positive for HCV exposure or active infection, the subject will be allowed to participate in the trial with pharmacotherapy and monitoring for liver function abnormalities. Tests for HBV and HCV within 1 year of starting study treatment are acceptable.

4.1.12 Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation > 91% on room air.

4.1.13 Prior therapy with polatuzumab is allowed [21].

4.1.14 Demonstrate adequate hematologic and organ function as defined in the table below; all screening labs to be obtained within 7 days prior to initiating study treatment.

Table 1. Screening Labs

System	Laboratory Value
Hematological*	
Absolute Neutrophil Count (ANC)	$\geq 1 \times 10^9$/L
Platelets	$\geq 75 \times 10^9$/L
Renal*	
Calculated creatinine clearance	≥ 60 mL/min using the Cockcroft-Gault formula
Hepatic*	
Bilirubin	≤ 1.5 × upper limit of normal (ULN). Subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >1.5 mg/dL if their conjugated bilirubin is <1.5× ULN)
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN

*Note: Hematology and other lab parameters that are ≥ grade 1 BUT still meet criteria for study entry are allowed. Furthermore, changes in laboratory parameters during the study should not be considered adverse events unless they meet criteria for dose modification(s) of study medication outlined by the protocol and/or worsen from baseline during therapy.

4.1.15 Females of childbearing potential must have a negative serum pregnancy test within 72 hours prior to initiation of study treatment. NOTE: Females are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months. Documentation of postmenopausal status must be provided.

4.1.16 Females of childbearing potential must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 12 months after rituximab discontinuation and 9 months after last dose of polatuzumab vedotin. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method or an intrauterine device that meets < 1% failure rate for protection from pregnancy in the product label.

4.1.17 Male subjects with female partners of childbearing potential must have had a prior vasectomy or agree to use an adequate method of contraception (i.e., double barrier method: condom plus spermicidal agent) starting with the first dose of study therapy and 6 months after the last dose of polatuzumab vedotin.

4.1.18 Subjects are willing and able to comply with study procedures based on the judgement of the investigator.

4.2 Exclusion Criteria

4.2.1 Known severe, active bacterial, viral, fungal, mycobacterial, parasitic, or other infections at study enrollment that may put the subject at undue risk as determined by the investigator.

4.2.2 Subjective hearing loss interfering with daily activities or born with impaired or loss of hearing.

4.2.3 Women who are pregnant or breastfeeding or who intend to become pregnant within a year of the last dose of study treatment (NOTE: breast milk cannot be stored for future use while the mother is being treated on study).

4.2.4 History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine.

4.2.5 Contraindication to gemcitabine or cisplatin, or dexamethasone or similar corticosteroid.

4.2.6 Symptomatic cardiac disease including ventricular dysfunction, left ventricular ejection fraction < 40%, symptomatic coronary artery disease or symptomatic arrhythmias.

4.2.7 Subjects with severe hepatic insufficiency Child-Pugh Score > 6 (see Appendix C).

4.2.8 Pre-existing ≥ grade 2 neuropathy.

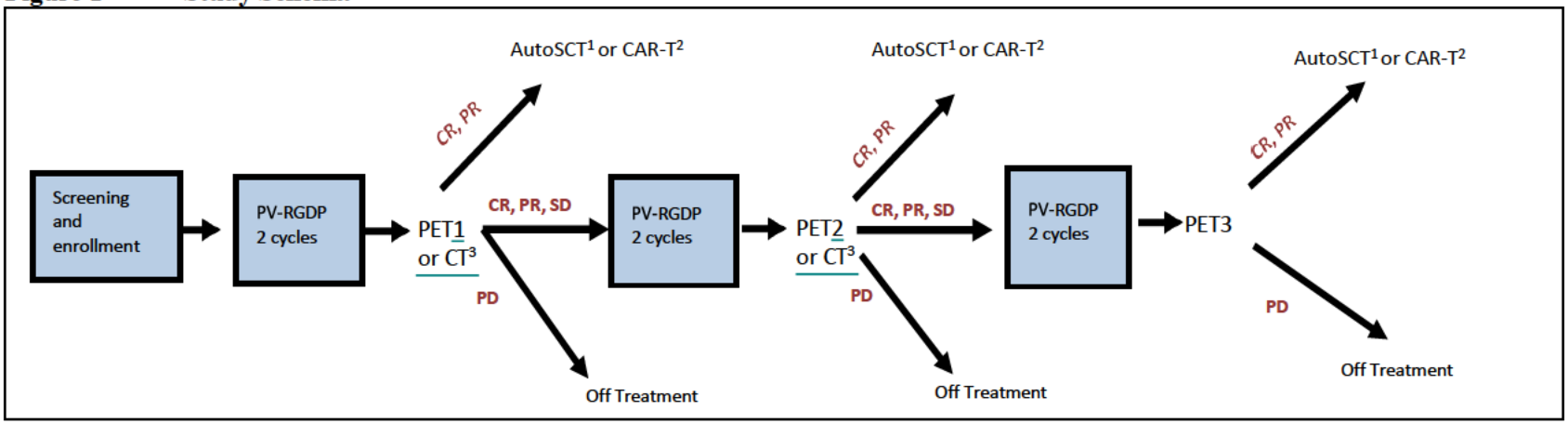
4.2.9 Active CNS disease.

4.2.10 Subject is receiving prohibited medications or treatments, such as strong CYP3A inhibitors and inducers, as listed in Section 5.5 of the protocol that cannot be discontinued/replaced by an alternative therapy.

5.0 TREATMENT PLAN

5.1 Schema

Figure 1 Study Schema



[1] Transplant eligible subjects will proceed to AutoSCT Therapy

[2] Transplant ineligible subjects may be eligible for CAR-T therapy

[3] Subjects who are not eligible for transplant may have a CT scan instead of a PET after cycles 2 and 4.

Figure 2 Simon Two-Stage

STAGE 1	***STAGE 2***
(n= 27 evaluable Subjects)	**(n= 17 evaluable Subjects)** If 13 or more subjects achieve a CR or PR, the second stage of the study will recruit 17 additional subjects. If less than 13 individuals achieve a CR or PR the study will close at stage 1

5.1.1 Study Design

This will be an open-label, single-arm phase II study meant to examine the efficacy of polatuzumab vedotin with rituximab, gemcitabine, cisplatin, and dexamethasone (PV-RGDP) in subjects with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). We will enroll subjects with biopsy-proven diffuse large B-cell lymphoma (DLBCL) who have had at least one prior treatment regimen. Using a Simon two-stage design, we will plan to enroll 27 eligible and evaluable subjects to receive treatment in the first stage. If there are at least 13 (≥ 13) subjects with an overall response (PR or CR), another 17 evaluable subjects will be enrolled and treated in the second stage of the trial, for a total of 44 evaluable subjects. We will reject the null hypothesis if and only if there are ≥ 13 subjects with an ORR from the first stage and ≥ 23 subjects with an ORR out of the 44 subjects.

Subjects enrolled in the study will be treated with PV-RGDP. Transplant eligible patients will be assessed for response every two cycles of PV-RGDP with a PET-CT (PET1, PET2 and PET3). If the subject has a complete response (CR) they may go to transplant or CAR-T at any time after 2 cycles have been completed (per investigator discretion). If the subject has a partial response (PR), they may go to transplant or CAR-T at any time after 4 cycles have been completed. If the subject is not transplant eligible, and has CR, PR, or SD on imaging, the subject will continue for six total cycles of therapy.

Safety data on adverse events will be recorded. Specifically, Grade 3 + toxicities as described in Section 5.3.2, unacceptable toxicities will be monitored, and the study will be halted if per the stopping rules in **Toxicities and Dosing Delays/Dose Modifications**.

5.2 Treatment Dosage and Administration

Table 2 Regimen Description

REGIMEN DESCRIPTION[5]					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule[3]**	**Cycle Length**
Polatuzumab vedotin (PV)	Administer an antihistamine and antipyretic at least 30 to 60 minutes prior to PV for potential infusion-related reactions	1.8 mg/kg	IV	Day 1	3 weeks (21 days)
Rituximab[1]		375 mg/m^2	IV	Day 1 or Day 2	
		1,400 mg/23,400 units hyaluronidase	SC[4]	SC administration may start at cycle 2.	
Gemcitabine		1,000 mg/m^2	IV	Days 1 and 8	
Cisplatin		75 mg/m^2	IV	Day 1	
Dexamethasone[2]		40 mg	IV, PO	Day 1: IV Days 2-4: PO	
GCSF (e.g. neupogen, Neulasta, biosimilar or Onpro)	Required for all subjects. Agent choice per institutional standard				

1. Biosimilars is allowed in this study.
2. Other corticosteroids may be used at equivalent dose
3. Treatment visits may have a window of +/- 2 days.
4. SC dosing may start after cycle 1. All subjects must receive at least 1 full dose of rituximab by IV prior to starting SC treatment.
5. If a subject is clinically high-risk they may receive PJP prophylaxis per institutional standards.

5.2.1 Order of Dosing

On treatment cycles where PV and rituximab are scheduled on the same day, PV will be administered first, followed by rituximab. On Cycle 1 Day1, the initial dose of PV will be administered over 90 minutes (+/- 30 minutes). Monitor subject for infusion-related reaction during the infusion and for a minimum of 90 minutes (+/- 30 minutes) following completion of the initial dose and prior to administration of rituximab. If the previous treatments were well tolerated, the subsequent dose of PV will be administered as a 30 (+/- 15 min) infusion and subject should be monitored during the infusion and for at least 30 minutes after completion of the infusion and prior to administration of rituximab.

Subjects must receive a full dose of rituximab by IV prior to starting Rituxan Hycela or a biosimilar by SC (see section 6.4). Previous research has demonstrated that IV and SC rituximab have equivalent safety and efficacy, with a patient preference for SC administration. After initial IV treatment of rituximab, subjects can receive SC rituximab for all subsequent doses. Subjects will not be allowed to resume IV administration once they have transitioned to SC administration. Cisplatin and gemcitabine will be administered via IV on Day1, and gemcitabine will be administered again on Day 8. Dexamethasone will be administered via IV on Day 1 and PO on days 2-4.

5.3 Toxicities and Dosing Delays/Dose Modifications

5.3.1 General Considerations

5.3.1.1 Subjects may have one agent (with the exception of polatuzumab) discontinued and remain on the study and be evaluable for efficacy. However, if polatuzumab or more than one drug is discontinued, then the subject should be removed from the study treatment but will still be followed for disease progression (Section 5.10). If subjects are otherwise responding to therapy and given that R-GDP is a standard salvage regimen, patients will be given the opportunity to continue to receive R-GDP off study per SOC.

5.3.1.2 If there is a delay for D1, then all drugs will be delayed. This delay can be extended for a maximum of 3 weeks or the subject should be permanently discontinued. If the subject doesn't meet treatment parameters for D8 gemcitabine, then the dose of gemcitabine should be skipped.

5.3.1.3 Tumor lysis prophylaxis (administer aggressive intravenous hydration, anti-hyperuricemic agents, and monitor renal function, Section 6.3.8) will be administered prior to cycles 1 per institutional standards. Prophylaxis is not needed after cycle 1 since the bulk of disease would be controlled at cycle 1.

5.3.2 Definition of a Treatment Related Unacceptable Toxicity

≥ Grade 3 myelosuppression resulting in study discontinuation and ≥ Grade 3 peripheral neuropathy or any Grade 4 toxicity, except for electrolyte abnormalities, resulting in discontinuation of polatuzumab by CTCAE v5.0.

5.3.3 Considerations for Peripheral Neuropathy

Table 3. Modifications for Peripheral Neuropathy (Cisplatin, Gemcitabine and PV)

Peripheral Neuropathy			
NCI CTC Grade	**Cisplatin**	**Gemcitabine**	**Polatuzumab***
0-1	No reduction	No reduction	No reduction

2-3	Hold until resolved to ≤ Grade 1, then reduce to **50 mg/m^2**	No reduction	Hold polatuzumab dosing until improvement to Grade 1 or lower. If recovered to Grade 1 or lower on or before Day 14, restart polatuzumab with the next cycle at a permanently reduced dose of 1.4 mg/kg. If a prior dose reduction to 1.4 mg/kg has occurred, discontinue polatuzumab. If not recovered to Grade 1 or lower on or before Day 14, discontinue polatuzumab.
Grade 4	Discontinue	No reduction	Discontinue

* For polatuzumab there should be no dose reduction to a dose below 1.4 mg/kg.
Note: Grade 2-3 Neuropathy**:** consider providing gabapentin (or similar agent) as supportive care per institutional standards.

5.3.4 Considerations for Hematological Toxicity (neutropenia and thrombocytopenia)

Table 4. Modifications for Cisplatin, Gemcitabine and Polatuzumab vedotin

Hematological toxicity (Neutropenia and Thrombocytopenia)			
NCI CTC Grade	**Cisplatin**	**Gemcitabine**	**PV**
0	No reduction	No reduction	No reduction
1	No reduction	No reduction	No reduction
2	Thrombocytopenia: • Hold until PLT are at least 75,000/mm^3 • Reduce cisplatin dose by 25% • For second occurrence of grade 2 or higher thrombocytopenia: o Reduce cisplatin dose by 50% • For third occurrence of grade 2 or higher thrombocytopenia o Reduce cisplatin by 75% • Discontinue for any subsequent occurrences of grade 2 or higher thrombocytopenia	Thrombocytopenia: • Hold until platelets recover to at least 75,000/mm^3 • Reduce subsequent cycles gemcitabine 800 mg/m2 on day 1 and day 8 • For second occurrence of grade 2 or higher thrombocytopenia: o Reduce gemcitabine to 800 mg/m2 and administer on day 1 only o Day 8 should be discontinued. • For third occurrence of grade 2 or higher thrombocytopenia o Reduce gemcitabine to 400 mg/m2 day 1 only • Discontinue for any subsequent occurrences of grade 2 or higher	Thrombocytopenia: • Hold until platelets recover to greater than 75.0×10^9/L. • If platelets recover to greater than 75.0×10^9/L on or before Day 14, resume all treatment without any additional dose reductions. • If platelets recover to greater than 75.0×10^9/L after Day 14: o restart all treatment dose reduction of polatuzumab to 1.4

		thrombocytopenia	
3[a,b]	Neutropenia: • Hold until ANC recovers to greater than 1.0 × 10^9/L, and • Reduce cisplatin dose by 25% • For second occurrence of grade 3 or higher neutropenia: o Reduce cisplatin dose by 50% • For third occurrence of grade 3 or higher neutropenia: o Reduce cisplatin dose by 75% • Discontinue for any subsequent occurrences of grade 3 or higher neutropenia Thrombocytopenia: • Hold until PLT are at least 75,000/mm^3 • Reduce cisplatin dose by 25% • For second occurrence of grade 3 or higher thrombocytopenia: o Reduce cisplatin dose by 50% • For third occurrence of grade 3 or higher thrombocytopenia: o Reduce cisplatin dose by 75% Discontinue for any subsequent occurrences of grade 3 or higher thrombocytopenia	Neutropenia: • Hold until ANC recovers to greater than 1.0 × 10^9/L, and • Reduce subsequent cycles day 1 and day 8 to gemcitabine 800 mg/m2 • For second occurrence of grade 3 or higher neutropenia: o Reduce gemcitabine to 800 mg/m2 and administer on day 1 only • For third occurrence of grade 3 or higher neutropenia: o Reduce gemcitabine to 400 mg/m2 on day 1 only • Discontinue for any subsequent occurrences of grade 3 or higher neutropenia Thrombocytopenia: • Hold until PLT are at least 75,000/mm^3 • Reduce subsequent cycles gemcitabine 800 mg/m2 on day 1 and day 8 • For second occurrence of grade 3 or higher thrombocytopenia: Reduce gemcitabine to 800 mg/m2 and administer on day 1 only; Day 8 should be discontinued. • For third occurrence of grade 3 or higher thrombocytopenia: • Reduce gemcitabine to 400 mg/m2 on day 1 only • Discontinue for any subsequent occurrences of grade 3 or higher neutropenia	Neutropenia: • Hold all treatment until ANC recovers to greater than 1.0 × 10^9/L. • If ANC recovers to greater than 1.0 × 10^9/L on or before Day 14, resume all treatment without any additional dose reductions. Consider granulocyte colony stimulating factor prophylaxis for subsequent cycles, if not previously given. • If ANC recovers to greater than 1.0 × 10^9/L after Day 14: o restart all treatment dose reduction of polatuzumab to 1.4 mg/kg. Thrombocytopenia: • Hold until platelets recover to greater than 75.0 × 10^9/L. • If platelets recover to greater than 75.0 × 10^9/L on or before Day 14, resume all treatment without any additional dose reductions. • If platelets recover to greater than 75.0 × 10^9/L after Day 14: o restart all treatment dose reduction of polatuzumab to 1.4 mg/kg
4[a,b]	Neutropenia: • Hold until ANC recovers to greater than 1.0 × 109/L, and • Reduce cisplatin dose by 25%	Neutropenia: • Hold until ANC recovers to greater than 1.0 × 109/L, and • Reduce subsequent cycles day 1 and day 8 to	Neutropenia: • Hold all treatment until ANC recovers to greater than 1.0 × 10^9/L. • If ANC recovers to greater than 1.0 × 10^9/L

	• For second occurrence of grade 3 or higher neutropenia: o Reduce cisplatin dose by 50% • For third occurrence of grade 3 or higher neutropenia: o Reduce cisplatin dose by 75% • Discontinue for any subsequent occurrences of grade 3 or higher neutropenia	gemcitabine 800 mg/m2 • For second occurrence of grade 3 or higher neutropenia: o Reduce gemcitabine to 800 mg/m2 and administer on day 1 only; Day 8 should be discontinued. • For third occurrence of grade 3 or higher neutropenia: o Reduce gem dose by to 400 mg/m2 on day 1 only • Discontinue for any subsequent occurrences of grade 3 or higher neutropenia	on or before Day 14, resume all treatment without any additional dose reductions. Consider granulocyte colony stimulating factor prophylaxis for subsequent cycles, if not previously given. • If ANC recovers to greater than 1.0×10^9/L after Day 14: o restart all treatment dose reduction of polatuzumab to 1.4 mg/kg.
	Thrombocytopenia: • Hold until PLT are at least 75,000/mm^3 • Reduce cisplatin dose by 25% • For second occurrence of grade 3 or higher thrombocytopenia: o Reduce cisplatin dose by 50% • For third occurrence of grade 3 or higher thrombocytopenia: Reduce cisplatin dose by 75% • Discontinue for any subsequent occurrences of grade 3 or higher thrombocytopenia	Thrombocytopenia: • Hold until PLT are at least 75,000/mm^3 • Reduce subsequent cycles gemcitabine 800 mg/m2 on day 1 and day 8 • For second occurrence of grade 3 or higher thrombocytopenia: o Reduce gemcitabine to 800 mg/m2 and administer on day 1 only; Day 8 should be discontinued. • For third occurrence of grade 3 or higher thrombocytopenia: o Reduce gemcitabine to 400 mg/m2 day 1 only • Discontinue for any subsequent occurrences of grade 3 or higher thrombocytopenia	Thrombocytopenia: • Hold all treatment until platelets recover to greater than 75.0×10^9/L. • If platelets recover to greater than 75.0×10^9/L on or before Day 14, resume all treatment without any additional dose reductions. • If platelets recover to greater than 75.0×10^9/L after Day 14: o restart all treatment dose reduction of polatuzumab to 1.4 mg/kg

[a] Severity on Day 1 of any cycle.
[b] If primary cause is due to lymphoma, dose delay or reduction may not be needed at discretion of investigator

5.3.5 Considerations for Non-Hematological Toxicities

Table 5. Considerations for Non-Hematological Toxicities

Non-Hematological Toxicities			
NCI CTC Grade	**Cisplatin[2,3]**	**Gemcitabine[2]**	**Polatuzumab[4]**

0-1	No reduction	No reduction	No reduction
2	No reduction except for renal toxicity: CrCl 46 to 50 mL/min: Reduce dose by 25%. CrCl 31 to 45 mL/min: reduce dose by 50%.	No Reduction	No reduction
Grade 3-4	Reduce dose of Cisplatin by 50% for other Grade 3 or 4 non-hematological adverse reactions until resolved to ≤ Grade 2. For grade 3-4 Renal toxicity: (CrCl<30mL/min): Discontinue cisplatin Permanently discontinue for any recurrent Grade 3 or 4 non-hematological adverse reaction possibly related to cisplatin.	Reduce dose of gemcitabine by 50% for Grade 3 or 4 non-hematological adverse reactions at least possibly related to gemcitabine until resolved to ≤ Grade 2. • If resolved – return to full dose. Permanently discontinue for any recurrent Grade 3 or 4 non-hematological adverse reaction possibly related to gemcitabine[1].	Discontinue

1. Permanently discontinue gemcitabine for any of the following:
   - Unexplained dyspnea or evidence of severe pulmonary toxicity
   - Hemolytic uremic syndrome (HUS) or severe renal impairment
   - Severe hepatic toxicity
   - Capillary leak syndrome (CLS)
   - Posterior reversible encephalopathy syndrome (PRES)
   - Recurrent grade 3 or 4 non-hematologic adverse reactions possibly related to gemcitabine
2. No dose modifications are recommended for alopecia, nausea, or vomiting.
3. Permanently discontinue Cisplatin for any of the following:
   - Severe hypersensitivity reactions
4. For polatuzumab: New-onset symptoms suggestive of progressive multifocal leukoencephalopathy (PML) and permanently discontinue if diagnosis is confirmed.

5.3.6 Dose Modifications for Rituximab

Dosage adjustments for rituximab are not recommended.

Table 6. Dose Modifications for IRR

Event	Dose Modification
Grade 1–3 Infusion-Related Reaction	Interrupt polatuzumab infusion and give supportive treatment. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue polatuzumab. For recurrent Grade 2 wheezing or urticaria permanently discontinue polatuzumab. For any other recurrent grade 3 symptoms, permanently 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	Stop polatuzumab infusion immediately. Give supportive treatment. Permanently discontinue polatuzumab

5.4 Concomitant Medications/Treatments/Supportive Care Allowed

The following concomitant medications/treatment and supportive cares are allowed:

- G-CSF (all formulations, including long and short acting and biosimilars) is mandatory for all subjects.

Subjects on the trial are allowed to receive all supportive care therapy needed to alleviate symptoms related to their cancer diagnosis or other medical problems at the investigator's discretion. No treatments should be withheld due to a subject's participation in this study. Prophylaxis for infusion-related reactions should be employed per institutional guidelines.

Transfusion of blood products allowable for subjects with symptomatic or at risk for symptomatic anemia and/or thrombocytopenia per Investigator's discretion and per institution guidelines.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

5.5 Medications/Treatment Precautions

The following medications/treatments are required precautions or are prohibited

- Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid, if possible, consider switching subject to a low molecular weight heparin or DOAC during treatment or if the subject continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
- Concomitant use of strong CYP3A inhibitors or inducers has the potential to affect the exposure to unconjugated monomethyl auristatin E (MMAE) (Appendix D).
- Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin.
- Diuretics: increased risk of nephrotoxicity and ototoxicity, monitor fluid status and creatine closely if given
- Nephrotoxic drugs
- Ototoxic drugs
- Phenytoin: cisplatin reduces absorption and efficacy of phenytoin, monitor levels and adjust dose as necessary
- Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricemia and gout.

- Lithium: cisplatin may affect lithium plasma levels – monitor

5.6 Other Modalities or Procedures

AutoSCT may be performed for eligible subjects as early as Cycle 2 in subjects that demonstrate CR and 4 cycles in subjects that demonstrate PR or CAR-T at any time after 2 cycles have been completed (per investigator discretion). If the subject has a partial response (PR), they may go to transplant or CAR-T at any time after 4 cycles have been completed. Transplant ineligible subjects may be eligible for CAR-T therapy

5.7 Duration of Therapy

Treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Pregnancy
- Subject decides to withdraw from study treatment.
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.
- Subject completes maximum number (6 cycles) of treatment cycles allowed per protocol.
- Subject is lost to follow-up.
- If polatuzumab or more than one drug is discontinued for treatment. Note: subjects may continue to receive the remaining regimen off study.

5.7.6 Off-treatment Status:

- Survival and progression follow- up.
  - If subject achieves a CR at completion of therapy (after transplant in transplant eligible group, or after 6 cycles of PV-RGDP in transplant ineligible group).
  - If subject achieves a PR or stable disease at the completion of therapy (but have not started a new treatment).

- Survival follow-up only
  - Subject develops PD at any point in the study.
  - If the subject starts a new treatment.
  - If polatuzumab or more than one drug is discontinued for treatment.

5.8 Duration of Follow Up

All subjects will be followed for up to 5 years, or until death, whichever occurs first after removal from study treatment for determination of study endpoints. Follow-up for progression and survival is at least every 6 months (more frequently if needed per Investigator discretion) with CT imaging for 2 years and every 6 months with survival assessment for 5 years. Subjects removed from study treatment for unacceptable AEs will be followed for resolution or stabilization of the adverse event(s). All subjects (including those withdrawn for AEs and non-evaluable subjects) should be followed after removal from study treatment for survival as stipulated in the protocol.

5.9 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The subject should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the subject's study withdrawal should be obtained with an explanation of why the subject is withdrawing from the study.
- If the subject is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

5.10 Off-Study Criteria

- Subject has completed all study activities including any needed follow-up activities and no further data collection from the subject is needed (Section 5.8).
- Subject withdraws consent to be in the study (Section 5.9)
- Death
- Lost to follow-up.
- Situations in which the treating physician feels it is in the best interest for the subject to not continue on the study.

6.0 DRUG INFORMATION

6.1 Polatuzumab

The information in this section is from the polatuzumab Investigator's Brochure (IB), version 13. For additional information, please refer to the IB.

6.1.1 Description

Polatuzumab vedotin-piiq is a CD79b-directed antibody-drug conjugate (ADC) consisting of three components: 1) the humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for human CD79b; 2) the small molecule anti-mitotic agent MMAE; and 3) a protease-cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB) that covalently attaches MMAE to the polatuzumab antibody.

Polatuzumab vedotin-piiq exhibits activity against dividing B cells. The small molecule, MMAE is an anti-mitotic agent covalently attached to the antibody via a cleavable linker. The antibody binds to a B-cell specific surface protein CD79b, a component of the B-cell receptor. Polatuzumab vedotin-piiq is then internalized, and lysosomal proteases cleave the linker enabling intracellular delivery of MMAE. MMAE inhibits cell division and induces apoptosis in dividing cells by binding to microtubules.

6.1.2 How Supplied

Polatuzumab vedotin-piiq (PV) is an investigation product provided by Genentech. PV for injection is a preservative-free, white to grayish-white lyophilized powder, which has a cake-like appearance, supplied in a single-dose vial.

6.1.3 Preparation

Reconstitute and further dilute PV prior to intravenous infusion.

PV 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.

6.1.3.1 Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose, the total volume of reconstituted PV solution required, and the number of PV vials needed.
- Reconstitute each 140 mg PV 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 PV 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.

6.1.3.2 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 PV 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 PV solution as specified in Table 7. Discard if storage time exceeds these limits. Do not freeze or expose to direct sunlight.

6.1.4 Storage and Handling

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.

6.1.5 Stability

Table 7 Diluted Polatuzumab Vedotin Solution Storage Conditions

Diluent Used to Prepare Solution for Infusion	Diluted Polatuzumab Vedotin 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
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
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 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 **Table 7**.

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 PV and intravenous infusion bags with product contacting materials of polyvinyl chloride (PVC) or polyolefins such as polyethylene (PE) and polypropylene. No incompatibilities have been observed with infusion sets or infusion aids with product-contacting materials of PVC, PE, polyurethane, polybutadiene (PBD), acrylonitrile butadiene styrene, polycarbonate, polyetherurethane, fluorinated ethylene propylene, or polytetrafluorethylene, or with filter membranes composed of polyether sulfone or polysulfone.

6.1.6 Route of Administration

See Section 5.2. Administer only as an intravenous infusion. Do not administer as an intravenous push or bolus.

6.1.7 Method of Administration

IV

Reconstitute and further dilute PV prior to intravenous infusion.

PV 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.

On treatment cycles where PV and rituximab are scheduled on the same day, PV will be administered first, followed by rituximab. On Cycle 1 Day1, the initial dose of PV will be administered over 90 minutes (+/- 30 minutes). Monitor subject for infusion-related reaction during the infusion and for a minimum of 90 minutes (+/- 30 minutes) following completion of the initial dose and prior to administration of rituximab. If the previous treatments were well tolerated, the subsequent dose of PV will be administered as a 30 (+/- 15 min) infusion and subject should be monitored during the infusion and for at least 30 minutes after completion of the infusion and prior to administration of rituximab.

Do not mix PV with or administer as an infusion with other drugs.

6.1.8 Drug Ordering and Accountability

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from the company sponsor or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial. An accurate and current accounting of the dispensing and return of investigational study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The amount of study drug dispensed and returned by the subject will be recorded in the Investigational Drug Accountability Record.

6.1.9 Return and Retention of Study Drug

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy (e.g., UNC IDS drug destruction policy). It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.1.10 Adverse Events Associated with Polatuzumab Vedotin-piiq

The most common adverse reactions (≥20%) included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

6.1.11 Contraindications

None

6.1.12 There are no other known contraindications for polatuzumab vedotin. Other Significant AEs and Precautions

Other significant adverse reactions include the following:

- Peripheral neuropathy
- Infusion-related reactions
- Myelosuppression
- Serious and opportunistic infections
- Progressive multifocal leukoencephalopathy (PML)
- Tumor lysis syndrome
- Hepatotoxicity
- Embryo-fetal toxicity

6.1.13 Drug Interactions

Strong CYP3A Inhibitors and Strong CYP3A Inducers are prohibited (Appendix D). MMAE is a substrate for CYP3A4/5.

6.2 Dexamethasone

The following is a summary of dexamethasone information. Refer to package insert for complete dispensing instructions available at:

http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Roxane/Dexamethasone/Dexamethasone%20Tablets%20Solution%20and%20Intensol.pdf

6.2.1 Brief Description:

Dexamethasone is a practically white or white, odorless, crystalline powder that is a synthetic glucocorticoid. Glucocorticoids produce varied metabolic effects.

6.2.2 Dosage and Administration:

See Section 5.2

6.2.3 Storage and Stability:

Store dexamethasone at 20°C-25°C (68°F-77°F).

6.2.4 Handling and Disposal:

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

6.2.5 Adverse Events Associated with Dexamethasone

Gastrointestinal: Nausea, vomiting, anorexia, increased appetite, weight gain; aggravation of peptic ulcers.

Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).

Neurologic: Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, muscle weakness.

Cardiovascular: Fluid retention and edema, hypertension; rarely, thrombophlebitis. Ocular: Cataracts, increased intraocular pressure, exophthalmos.

Metabolic: Hyperglycemia, decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia.

Hematologic: Leukocytosis.

Other: Osteoporosis (and resulting back pain), appearance of serious infections including herpes zoster, varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

6.2.6 Contraindications

Contraindicated in systemic fungal infections.

6.2.6.1 Use in Pregnancy

Pregnancy Category C: Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose.

6.2.6.2 Use in Nursing Women

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other adverse effects on the nursing infant.

6.2.6.3 Overdose

Treatment of overdosage is by supportive and symptomatic therapy. In the case of acute overdosage, according to the subject's condition, supportive therapy may include gastric lavage or emesis.

6.3 Rituximab

The following is a summary of rituximab details. For more information, please refer to the full prescribing package insert information. Importantly, biosimilars and subcutaneous dosing is allowed in this study (see Section 6.4 Rituxan Hycela).

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b172773b-3905-4a1c-ad95-bab4b6126563

6.3.1 Supplier/How Supplied

Rituximab is commercially available.

Rituximab injection is a sterile, preservative-free, clear, colorless solution for intravenous infusion).

6.3.2 Brief Description:

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD.

Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium that may contain the antibiotic gentamicin. Gentamicin is not detectable in the final product.

6.3.3 Dosage and Administration:

See Section 5.2. Administer only as an intravenous infusion. Do not administer as an intravenous push or bolus.

On days when PV and rituximab infusion are scheduled, rituximab would be administered following PV infusion (see section 6.1.7).

6.3.4 Storage and Stability:

Store rituximab vials refrigerated at 2°C to 8°C (36°F to 46°F). Rituximab vials should be protected from direct sunlight. Do not freeze or shake.

6.3.5 Handling and Disposal:

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

6.3.6 Adverse Events Associated with Rituximab

Most common adverse reactions in clinical trials were:

- Non-Hodgkin's Lymphoma (NHL) (≥ 25%): infusion-related reactions, fever, lymphopenia, chills, infection, and asthenia
- Chronic Lymphocytic Leukemia (CLL) (≥ 25%): infusion-related reactions and neutropenia
- Rheumatoid arthritis (RA) (≥ 10%): upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (other important adverse reactions include infusion-related reactions, serious infections, and cardiovascular events).
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) (≥15 %): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, infusion-related reactions.
- Pemphigus Vulgaris (PV) (≥15%): infusion-related reactions, depression (other important adverse reactions include infections).

6.3.7 Contraindications

None

6.3.8 Precautions

Renal toxicity when used in combination with cisplatin.

- Tumor lysis syndrome: Administer aggressive intravenous hydration, anti-hyperuricemic agents, monitor renal function.
- Infections: Withhold rituximab and institute appropriate anti-infective therapy
- Cardiac adverse reactions: Discontinue infusions in case of serious or life-threatening events.
- Renal toxicity: Discontinue in subjects with rising serum creatinine or oliguria.
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms.
- Immunizations: Live virus vaccinations prior to or during rituximab treatment not recommended
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.

6.4 Rituxan Hycela

The following is a summary of Rituxan Hycela details. For more information, please refer to the full prescribing information.

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3e5b7e82-f018-4eaf-ae78-d6145a906b20

6.4.1 Supplier/How Supplied

Rituxan Hycela is commercially available. Rituxan Hycela is a colorless to yellowish, clear to opalescent solution for subcutaneous injection

6.4.2 Brief Description:

Rituxan Hycela is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

6.4.3 Dosage and Administration:

See Section 5.2.

All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with Rituxan Hycela. If patients are not able to receive one full dose by intravenous infusion, they should continue subsequent cycles with a rituximab product by intravenous infusion and not switch to Rituxan Hycela until a full intravenous dose is successfully administered.

6.4.4 Storage and Stability:

Store Rituxan Hycela vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

6.4.5 Handling and Disposal:

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

6.4.6 Adverse Events Associated with Rituximab

Most common adverse reactions in clinical trials were:

- Severe Mucocutaneous Reaction
- Hepatitis B Virus Reactivation
- Progressive Multifocal Leukoencephalopathy
- Hypersensitivity and other Administration Reactions
- Tumor Lysis Syndrome
- Infections
- Cardiovascular Adverse Reactions
- Renal Toxicity
- Bowel Obstruction and Perforation

6.4.7 Contraindications

None

6.4.8 Precautions

Renal toxicity when used in combination with cisplatin.

- Tumor lysis syndrome: Administer aggressive intravenous hydration, anti-hyperuricemic agents, monitor renal function.
- Infections: Withhold rituximab and institute appropriate anti-infective therapy
- Cardiac adverse reactions: Discontinue infusions in case of serious or life-threatening events.
- Renal toxicity: Discontinue in subjects with rising serum creatinine or oliguria.
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms.
- Immunizations: Live virus vaccinations prior to or during rituximab treatment not recommended
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.

6.5 Gemcitabine:

For more information on this drug please refer to the full prescribing information: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9dc35c59-f4f3-43b4-8251-0cf5c06cdc80

6.5.1 Brief Description:

Gemcitabine is a nucleoside metabolic inhibitor. Gemcitabine hydrochloride is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents. Gemcitabine is a sterile white to off-white lyophilized powder and available as 200 mg and 1 g single-dose vials for intravenous use only.

6.5.2 Supplier/How Supplied

Gemcitabine is commercially available.

Gemcitabine is a sterile white to off-white lyophilized powder available in single-dose vials individually packaged in a carton containing 200 mg or 1 g gemcitabine.

6.5.3 Preparation

6.5.3.1 Preparation and Administration Precautions

Exercise caution and wear gloves when preparing gemcitabine solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if gemcitabine contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption.

6.5.3.2 Preparation for Intravenous Infusion Administration

Reconstitute the vials with 0.9% Sodium Chloride Injection without

preservatives. Add 5 mL to the 200-mg vial or 25 mL to the 1-g vial. These dilutions each yield a gemcitabine concentration of 38 mg/mL. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. Inspect visually prior to administration and discard for particulate matter or discoloration.

6.5.4 Dosage and Administration:

See Section 5.2

6.5.5 Storage and Stability:

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

6.5.6 Handling and Disposal:

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

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:

https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

6.5.7 Adverse Events Associated with Gemcitabine

The most common adverse reactions for the single agent (≥20%) are nausea/vomiting, anemia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema.

6.5.8 Contraindications

Gemcitabine is contraindicated in subjects with a known hypersensitivity to gemcitabine. Reactions include anaphylaxis.

6.5.9 Other Significant AEs and Precautions with Gemcitabine

Other significant adverse reactions include the follow (for more information please refer to the package insert or prescribing information):

- Hypersensitivity
- Schedule-Dependent Toxicity
- Myelosuppression
- Pulmonary Toxicity and Respiratory Failure
- Hemolytic Uremic Syndrome
- Hepatic Toxicity
- Exacerbation of Radiation Therapy Toxicity

- Capillary Leak Syndrome
- Posterior Reversible Encephalopathy Syndrome

6.6 Cisplatin

6.6.1 Brief Description:

Cisplatin Injection is a clear, colorless, sterile aqueous solution. Each 50 mL, 100 mL or 200 mL amber vial of Cisplatin Injection contains: 1 mg/mL cisplatin, 9 mg/mL sodium chloride, hydrochloric acid and/or sodium hydroxide to adjust pH, and water for injection to a final volume of 50 mL, 100 mL, or 200 mL, respectively. The pH range of Cisplatin Injection is 3.8 to 5.9.

6.6.2 Supplier/How Supplied

Cisplatin Injection (1 mg/mL)

6.6.3 Preparation

The 50 mg vials should be reconstituted with 50 mL of Sterile Water for Injection, USP.

6.6.3.1 Preparation Precautions

Caution should be exercised in handling the aqueous solution. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing cisplatin.

Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

6.6.3.2 Instructions for Preparation

The aqueous solution should be used intravenously only and should be administered by IV infusion over a 6- to 8-hour period.

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

6.6.4 Dosage and Administration:

See Section 5.2

Cisplatin is administered by slow intravenous infusion. Cisplatin SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION.

6.6.5 Storage and Stability:

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not refrigerate. Protect from light.

6.6.6 Handling and Disposal:

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

6.6.7 Adverse Events Associated with Cisplatin

6.6.7.1 Nephrotoxicity

Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28% to 36% of subjects treated with a single dose of 50 mg/m 2. It is first noted during the second week after a dose and is manifested by elevations in blood urea nitrogen (BUN) and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given. Elderly subjects may be more susceptible to nephrotoxicity.

Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using a 6- to 8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

6.6.7.2 Anti-Emetics and Hydration Prior to and Post Cisplatin

Appropriate pre- and post-hydration for cisplatin chemotherapy will be included according to institutional guidelines. Furosemide, mannitol, and electrolyte supplementation may be included according to local practices as well. Anti- emetic prophylaxis should be administered with cisplatin according to the following table and are recommended to include a corticosteroid and a 5-HT3 antagonist. Corticosteroids should only be used as pre- and post-medication for antiemetic prophylaxis for cisplatin therapy and should be dosed as delineated below.

Chemotherapy	Premed Day	Premeds	Suggested Home Regimen
Cisplatin	Day 1	Dexamethasone 8mg IV or po and 5-HT3 antagonist and/or Lorazepam	Dexamethasone 8mg po days 2,3 9, and 10 AND 5-HT3 antagonist prn and/or Lorazepam prn

6.6.7.3 Ototoxicity

Ototoxicity has been observed in up to 31% of subjects treated with a single dose of cisplatin 50 mg/m 2 and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz). The prevalence of hearing loss in children is particularly high and is estimated to be 40 to 60%. Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Ototoxic effects may be more severe in children

receiving cisplatin.

Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated cisplatin doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Vestibular toxicity has also been reported. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Ototoxicity can occur during treatment or be delayed. Audiometric monitoring will be performed prior to initiation of therapy, and then if clinically indicated by formal assessment.

The risk of ototoxicity may be increased by prior or simultaneous cranial irradiation and may be more severe in subjects less than 5 years of age, subjects being treated with other ototoxic drugs (e.g., aminoglycosides and vancomycin), and in subjects with renal impairment.

Genetic factors (e.g., variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.

6.6.7.4 Hematologic

Myelosuppression occurs in 25% to 30% of subjects treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most subjects recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m 2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in subjects with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly subjects may be more susceptible to myelosuppression.

In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician.

The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

6.6.7.5 Gastrointestinal

Marked nausea and vomiting occur in almost all subjects treated with cisplatin and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment.

Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in subjects attaining complete emetic control on the

day of cisplatin therapy.

Diarrhea has also been reported.

6.6.8 Precautions

6.6.8.1 Drug Interactions

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy.

6.6.8.2 Pregnancy

Pregnancy Category D

6.6.9 Nursing Mothers

Cisplatin has been reported to be found in human milk; subjects receiving cisplatin should not breast-feed.

6.6.10 Geriatric Use

Insufficient data are available from clinical trials of cisplatin in the treatment of metastatic testicular tumors or advanced bladder cancer to determine whether elderly subjects respond differently than younger subjects. In four clinical trials of combination chemotherapy for advanced ovarian carcinoma, 1,484 subjects received cisplatin either in combination with cyclophosphamide or paclitaxel. Of these, 426 (29%) were older than 65 years. In these trials, age was not found to be a prognostic factor for survival. However, in a later secondary analysis for one of these trials, elderly subjects were found to have shorter survival compared with younger subjects. In all four trials, elderly subjects experienced more severe neutropenia than younger subjects. Higher incidences of severe thrombocytopenia and leukopenia were also seen in elderly compared with younger subjects, although not in all cisplatin-containing treatment arms. In the two trials where nonhematologic toxicity was evaluated according to age, elderly subjects had a numerically higher incidence of peripheral neuropathy than younger subjects. Other reported clinical experience suggests that elderly subjects may be more susceptible to myelosuppression, infectious complications, and nephrotoxicity than younger subjects.

Cisplatin is known to be substantially excreted by the kidney and is contraindicated in subjects with pre-existing renal impairment. Because elderly subjects are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

6.6.11 Contraindications

Cisplatin is contraindicated in subjects with pre-existing renal impairment. Cisplatin should not be employed in myelosuppressed subjects, or in subjects with hearing impairment.

Cisplatin is contraindicated in subjects with a history of allergic reactions to cisplatin or other platinum-containing compounds.

7.0 CLINICAL ASSESSMENTS

Clinical assessments outlined in this section will be performed as outlined in the Time and Events Table in Section 8.0.

7.1 List of Assessments

7.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

7.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

7.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be recorded at Screening and a focused medical history on symptoms/toxicity will be performed thereafter.

7.1.4 Physical Examination

A complete physical examination including height (at screening only), weight, Performance status ECOG and vital signs will be performed by either the investigator or a sub-investigator who is a physician at Screening.

Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits.

New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

7.1.5 Audiometry

Audiometric monitoring will be performed during physical examination prior to initiation of therapy, and then if clinically indicated by formal assessment per physician's discretion.

7.1.6 Adverse Events

Events should be assessed per NCI-CTCAE criteria v5.0. Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment, and relation to study drug will be recorded in the case report form (CRF).

7.1.7 Disease Assessment

Baseline disease assessment with PET/CT should be obtained within 28 days of initiating treatment through the study per the time and events calendar. Response assessment (C3D1 (-7 days), C5D1 (-7 days) and day 21 of cycle 6 (+/- 14 days))

will require PET/CT imaging. During follow-up (every 6 months for 2 years), CT imaging will be used to evaluate progression.

7.2 Clinical Laboratory Assessments

7.2.1 Hematology

Blood will be obtained and sent to the clinical site hematology lab a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count).

7.2.2 Blood Chemistry Profile

Blood will be obtained and sent to the clinical site chemistry lab for determination of serum sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, albumin, lactate dehydrogenase (LDH), calcium, magnesium, phosphorus, and total protein.

7.2.3 Coagulation

Coagulation profile: prothrombin time or INR and activated partial thromboplastin time.

7.2.4 Pregnancy Test

A urine or serum pregnancy test will be obtained from female subjects who are of childbearing potential within 72 hours of initiating study therapy.

7.3 Virus Testing

Subjects must have been tested for HBV and HCV within 1 year of starting study therapy. Subjects positive for HBV may continue on the trial using prophylactic entecavir. Subjects positive for HCV may participate in the study with monitoring of liver function abnormalities. Subjects with HIV are allowed on study as long as they have a CD4+ count >200 cells/uL.

7.4 Correlative Studies

PFS and OS of PV-RGDP will be examined in germinal center (GC) and post-germinal center (post-GC) tumor subtypes.

PFS and OS will also be examined relative to double-expressor lymphomas (DEL, DEL vs Non-DEL) that have co-expression of MYC and BCL2, and MYC with BCL2 and/or BCL6 rearrangements (i.e., double hit and triple hit lymphomas [DHL and THL, respectively]).

8.0 EVALUATIONS AND ASSESSMENTS

8.1 Time and Events Table

TIME AND EVENTS TABLE[1]															
Assessments	Screening[2]	C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	End of Treatment[12]	Long-term Follow-up[13]
Informed consent	X														
History	X	X	X	X		X		X		X		X		X	X
Physical exam	X	X		X		X		X		X		X		X	
Audiometry[14]	X	X[14]													
Eligibility verification	X														
HIV Testing[3]	X														
Coagulation Profile	X														
ECOG performance status	X	X		X		X		X		X		X		X	
Radiographic tumor evaluation[4,5]	X					X				X				X	X[5]
Pregnancy test[6]	X														
Hematology[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistries[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis Testing[9]	X														
Toxicity assessment[10]	X	X		X		X		X		X		X		X[12]	X[13]

TIME AND EVENTS TABLE[1]															
Assessments	Screening[2]	C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	End of Treatment[12]	Long-term Follow-up[13]
Concomitant med review	X	X		X		X		X		X		X		X	
Polatuzumab vedotin[11]		X		X		X		X		X		X			
Rituximab[11]		X		X		X		X		X		X			
Gemcitabine[11]		X	X	X	X	X	X	X	X	X	X	X	X		
Cisplatin[11]		X		X		X		X		X		X			
Dexamethasone[11]		X		X		X		X		X		X			
AutoSCT (transplant eligible subjects)						X									
Survival															X[13]

Footnotes to Time and Events Table

1 Unless otherwise noted, a window of +/- 14 days applies to all study visits.

2 Windows for the screening assessments are as follows:

a. Complete history, physical exam and all imaging assessments should be performed within 42 days prior to day 1 of study treatment. Complete history is required at the screening visit only, thereafter focused history on symptoms/toxicity.

b. All other screening evaluations (except for pregnancy test) must be performed within 21 days prior to cycle 1 day 1 unless otherwise stipulated. If screening hematology and chemistry labs are completed within 7 days hours prior to start of treatment on Day 1, Cycle 1 do not need to be repeated.

3 For HIV positive subjects, HIV testing must include CD4 lymphocyte subset panel and HIV viral load. The testing must be completed within 28 days of starting trial therapy.

4 Imaging with PET-CT should be obtained at screening within 28 days of initiating study treatment and at C3D1 (-7 days), C5D1 (-7 days) and day 21 of cycle 6 (+/- 14 days) or as needed, if there are any clinical signs/symptoms of progression. If imaging studies are performed at other times after treatment on this study, the data will be collected, and information gained will be used for this study.

5 Follow-up with CT imaging is every 6 months for 2 years.

6 Pregnancy test is required 72 hours prior to initiating study treatment.

7 Hematology includes a CBC with differential.

8 Serum chemistries include sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, albumin, lactate dehydrogenase (LDH), calcium, magnesium, phosphorus, and total protein (See Section 7.2).

9 HBV and HCV. Tests obtained within 1 year are acceptable. Subjects positive for HBV may continue on the trial using prophylaxis. Subjects positive for HCV may participate in the study if baseline bilirubin and transaminases are within normal limits.

10 Cycles are 21 days. For subjects who are not transplant eligible, a total of 6 cycles should be completed as long as they have a CR, PR or SD.

a. For subjects who are transplant eligible, they may proceed to transplant at any time after cycle 2 as long as they have achieved a CR. Subjects with PR must complete 4 cycles prior to proceeding to transplant.

11 See Section 5.2 Treatment Dosage and Administration

12 The end of treatment visit should only occur when subjects permanently stop study treatment and should be performed within 30 days (+/-7 days), ideally before transplant, after the last dose of study medication. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 12 months of the subject's last dose of study should be recorded as SAEs. Follow-up for progression and survival is at least every 6 months (more frequently if needed per Investigator discretion) with CT imaging for 2 years and every 6 months with survival assessment for 5 years. The following conditions provide follow-up by Response Status:

a. CR, Follow-up:
- Every 6 months for 2 years (imaging for progression)
- Every 6 months for 5 years (survival)

b. PR/ SD Follow- up:
- Relevant workup at investigator's discretion. If a subject begins new treatment at any time, they will only be followed for survival and progression.

13. All subjects will be followed for up to 5 years, or until death, whichever occurs first after removal from study treatment for determination of study endpoints.

14. Audiometric monitoring will be performed during physical examination prior to initiation of therapy, and then if clinically indicated by formal assessment per physician's discretion.

8.2 Assessment of Safety

Any subject who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each subject will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAEv5.0. Additionally, the adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age- appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

8.3 Assessment of Efficacy

All subjects should receive at least 2 cycles of the study therapy with PV-RGDP to be included in the efficacy analysis. However, if subjects proceed with stem cell transplant after 2 -3 cycles, they will still be eligible for the efficacy analysis. Any one drug may be held or discontinued during this time with the exception of polatuzumab and the subject will still be evaluable for efficacy. To assess disease response, a skull base to thigh (unless the subject has clinical suspicion for disease outside this area) PET/CT is used at the beginning of the study and while the subject is on treatment. During follow-up, a CT scan will be performed. Disease will be assessed using the Lugano classification (Appendix A) [20].

9.0 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An 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 product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of a central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

9.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the pharmaceutical product is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a pharmaceutical product.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study pharmaceutical product exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with pharmaceutical product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with pharmaceutical product exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than one occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the pharmaceutical product caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the pharmaceutical product treatment group than in a concurrent or historical control group.

9.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs product or as anticipated from the pharmacological properties of the drug product but are not specifically mentioned as occurring with the particular drug product under investigation.

9.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization; *
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse study treatment-related experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

9.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that subject. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

9.3 SAEs or Serious SARs

9.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30-days follow-up period after treatment is discontinued. After this period, investigators should only report SAEs that are attributed to prior study treatment Subjects who have an ongoing ≥grade 2 or SAE at the EOT visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.

9.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within OnCore® for that subject within 24 hours of learning of its occurrence. Additionally, the Multicenter Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

9.4 Adverse Event Reporting

9.4.1 IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem.

Multicenter sites:

- For multicenter sites using a local IRB of record, please submit adverse events per local IRB policy.
- For multicenter sites relying on the UNC-IRB, any SAEs that qualify as an Unanticipated Problem will be entered into OnCore® by the multicenter site and reported to the UNC IRB by the Multicenter Regulatory Associate using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 12 months of the subject's last dose of study should be recorded as SAEs. The subject is to be discontinued immediately from the study.

For multicenter sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Multicenter Project Manager immediately (within 24

hours) via email (preferred) CPOMulticenter@med.unc.edu. The Multicenter Project Manager will then report the event to the Funding Source (see requirements below). The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the Multicenter Project Manager. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

9.4.2 Funding Source (Genentech) Reporting Requirements:

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports)

9.4.2.1 Adverse Event Reporting Period

The study period during which AEs and SAEs as described in section 9.4.2.7 where the subject has been exposed to Genentech product must be reported Reporting period 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 SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs 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 AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to polatuzumab or rituximab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes [Definite, Probable, Possible, Unlikely]

There is a plausible temporal relationship between the onset of the AE and administration of the polatuzumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the polatuzumab or with similar treatments; and/or the AE abates or resolves upon discontinuation of the polatuzumab or dose reduction and, if applicable, reappears upon re- challenge.

No [Unrelated, etc.]]

Evidence exists that the AE has an etiology other than the polatuzumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to polatuzumab 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 Package Insert (P.I) OR current Investigator Brochure (I.B).

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

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. 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?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. 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.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), 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".

c. 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 AE or SAE 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").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

9.4.2.2 Pregnancy

If a female subject becomes pregnant while receiving polatuzumab or within [3 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 5 months, a report should be completed and expeditiously submitted to Genentech, Inc.

If a female subject becomes pregnant while receiving rituximab or within 12 months after the last dose of the study, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 5 months, a report should be completed and expeditiously submitted to Genentech, Inc.

Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

9.4.2.3 AEs of Special Interest (AESIs)

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.

Adverse events of special interest 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 > 3 × ULN in combination with total bilirubin > 2 × ULN
  - Treatment-emergent ALT or AST > 3 × 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 subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

The Polatuzumab Events of Special Interest are:

- Infusion Associated Reactions, Hypersensitivity
- PML (Progressive Multifocal Leukoencephalopathy)
- Tumor lysis syndrome of any grade (irrespective of causality)
- Second malignancies

9.4.2.4 Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding.
- Data related to overdose, abuse, misuse, or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the subject, in order to be able to identify potential safety signals specific to a particular population.

9.4.2.5 Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

9.4.2.6 Post-Study Adverse Events

For studies involving collection of survival data, the investigator after the end of the adverse event reporting period (defined as 30- days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject -including pregnancy occurring in the partner of a male study subject who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period (yearly) to ensure successful transmission of Single case reports.

9.4.2.7 Exchange of Single Case Reports with Genentech

UNC will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the subject has been exposed to the Product. The completed MedWatch form should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Serious Adverse Drug Reactions (SADRs)	15 calendar days of the awareness date
Other SAEs	30 calendar days of the awareness date.
Special Situation Reports (Pregnancy) Special Situation Reports (Other)	30 calendar days of the awareness date. 30 calendar days of the awareness date.
Product Complaints	15 calendar days of the awareness date.
AESIs	15 calendar days of the awareness date.

- **Serious Adverse Drug Reactions (SADRs)**
  Serious AE reports that are related to the Product or where the causality is assessed as unknown or not provided shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Special Situation Reports**
  - Pregnancy reports
    While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

- **Pregnancies in Female Partners of Male Subjects**
  Male subjects will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of polatuzumab. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.
  - Other Special Situation Reports, as defined above, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Product Complaints**
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **AESIs**
  AESIs requiring expedited reporting (related or possibly related to Roche product or where the causality is assessed as unknown or not provided) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others (non-related to Roche product) shall be sent within thirty (30) calendar days.

9.4.2.8 Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via UNC emailing Genentech a Quarterly line-listing documenting single case reports sent by UNC to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech 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. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by UNC to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

Reporting to Regulatory Authorities, Ethics Committees and Investigators

UNC, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

UNC, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through EudraVigilance Clinical Trial Module (EVCTM), where applicable.

UNC, will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

UNC will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Additional Reporting Requirements for IND Holders:

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Email Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of polatuzumab. An unexpected adverse event is one that is not already described in the polatuzumab Investigator Brochure. Such reports are to be emailed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of polatuzumab. An unexpected adverse event is one that is not already described in the polatuzumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted

to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

All written IND Safety Reports submitted to the FDA by the Investigator must also be emails to
Genentech Drug Safety:

Email: usds_aereporting-d@gene.com

And UNC will be responsible for the distribution of safety information to Site IRB:

CB 7097
720 Martin Luther King Jr. Blvd.
Bldg # 385, Second Floor
Chapel Hill, NC 27599-7097
Phone: 919-966-3113

For questions related to safety reporting, please contact Genentech Drug Safety:
Phone: (888) 835-2555

9.4.2.9 Development Safety Update Report

UNC, as the Sponsor of the Study, will be responsible for the preparation of an annual report for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. UNC, agrees to share a copy of their own annual report with Genentech as soon as reasonably possible after completion.

Genentech agrees to forward to UNC an executive summary of the Genentech annual report upon request. Furthermore, Genentech agrees that UNC may cross-reference the executive summary of the Genentech DSUR, as applicable.

9.4.2.10 Other Reports

UNC will forward a copy of the Publication to Genentech upon completion of the Study.

9.4.2.11 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Study mailbox: polatuzumab-gsur@gene.com

And to Genentech Drug Safety CTV oversight mailbox at:
ctvist_drugsafety@gene.com

9.4.2.12 Queries

Queries related to the Study will be answered by UNC. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. UNC agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

9.4.2.13 Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required. Safety Crisis Management

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. UNC agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

9.4.2.14 Compliance with Pharmacovigilance Agreement/Audit

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

9.4.3 FDA Expedited Reporting requirements for studies conducted under an IND:

A sponsor must report any suspected adverse reaction that is both serious and unexpected to the FDA. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The sponsor must submit each IND safety report on FDA Form 3500A. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division that has the responsibility for review of the IND. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

Timing

FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. For Multicenter trials, Lineberger is the sponsor, therefore, the UNC Multicenter Project Manager must be notified of the SAE within 24 hours of the event. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up

The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report." Additionally, upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Notification of Investigators

The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing investigational product 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, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process

If the sponsor deems that an event is both a serious adverse reaction (SAR) AND unexpected, it must also (in addition to OnCore®) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch form and supporting documents defining the event and causality should be sent to the assigned Multicenter Project Manager and also to CPOMulticenter@med.unc.edu. The UNC Multicenter Project Manager will then send the report to the Funding Source and notify the Multicenter and CTO Regulatory Associate of the event. The MedWatch 3500a form can be accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500A, and not form 3500).

Once the UNC Principal Investigator determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA. If the event is serious, unexpected and considered to be possibly-, probably- or definitely-related to the study treatment, the UNC Project Manager will inform the Regulatory Associate at UNC and IND Specialist. The MedWatch form will be submitted according to LCCC SOP for safety reporting for a multi-site study.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The FDA must be notified of any unexpected or life-threatening suspected adverse reactions as soon as possible, but no later than 7 calendar days of learning of the event.

The UNC Multicenter Project Manager will also be responsible for informing each Affiliate site of all serious and unexpected SARs reported to the FDA via fax as soon as possible.

Additional Reporting Requirements

The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the investigational product.

- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the investigational product, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.
- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance

Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

9.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual. These meetings will include the investigators as well as study coordinators, data coordinators, regulatory associates, clinical data management associates, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight of Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of subjects treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, the UNC IRB and DSMB.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design

In this a multi-center open label, single arm phase II study, we aim to examine the efficacy of PV-RGDP in subjects with relapsed/refractory DLBCL.

10.2 Sample Size, Accrual and Duration of Accrual

The null hypothesis is: H0: ORR $\leq$ 44% (based on historical data of RGDP) vs H1: ORR $\geq$ 60% (i.e., 16% improvement). We will need at most (minimax design) 44 subjects (expected number is 34) to achieve 80% power of detecting this difference, at alpha level 0.10. Accrual duration is expected to be approximately 36 months.

More specifically, a Simon two-stage design will be used with alpha level of 0.10 and 80% power. In the first stage, 27 evaluable subjects will be enrolled and treated. If there are at least 13 ($\geq$13) evaluable subjects with overall response, another 17 evaluable subjects will be enrolled and treated in this second stage, for a total of 44 evaluable subjects. If 12 or fewer subjects (out of 27) in stage 1 show overall response, the study will close at stage 1. We reject the null hypothesis if and only if there are >12 ORs from stage 1 and > 23 ORs in the overall 44 subjects.

Per safety of the novel combinations of PV-RGDP, treatment related Grade 3+ toxicity as defined in Section 5.3.2 will also be monitored. The accrual will be halted if the number of subjects with any treatment-related grade 3+ toxicities is equal to or exceeds b_n out of n subjects with full toxicity follow-up (see table 7 below). This is a Pocock type stopping boundary that assumes that a treatment related Grade 3+ toxicity rate of 0.30 is acceptable. If the true treatment related Grade 3+ rate is equal to 0.30, the probability of crossing the boundary is 0.20. For a few treatment related Grade 3+ toxicity rates below or above 0.30, we found that the probability of crossing/reaching the boundary is approximately 0.14% at toxicity 10%; 2.6% at toxicity 20%; 61.7% at toxicity 40%; 93.1% at toxicity 50%. In addition, we do not expect treatment related mortality in this study, and the trial will be stopped and re-evaluated as soon as treatment related death is observed, until the death is resolved by DSMC to be treatment unrelated.

Table 7. Stopping Boundaries

Number of Subjects, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	5	5	5	6	6	7	7	7	8	8	9	9	9	10	10
Number of Subjects, *n*	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	10	11	11	12	12	12	13	13	13	14	14	14	15	15	16	16	16	17	17	17
Number of Subjects, *n*	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Boundary, b_n	18	18	18	19																

10.3 Data Analysis Plans

Analysis of efficacy will be conducted following pre-specified inference rule on rejecting the null hypothesis: H0: ORR <= 44%. Specifically, we will reject the null hypothesis if and only if there are >12 ORs in the 27 subjects accrued at stage 1, and there are > 23 ORs in 44 subjects (with 17 accrued at stage 2).

For the primary outcome, ORR, there should be no missing data. We will replace non-evaluable cases with new subjects so that the total (maximal) sample size of 44 is guaranteed. There is only one test for the primary endpoint and hence there is no multiplicity issue.

Analyses of secondary endpoints will be descriptive. We will calculate rate of CR by sample proportion of complete response and associated 95% confidence interval using exact binomial method. Kaplan-Meier method will be used to examine PFS, OS of patients accrued. All toxicities and adverse events will be listed and tabulated by grade for all and by subgroups: GC vs post-GC, DEL vs non-DEL, DHL/THL vs non-DHL/THL.

Per exploratory endpoints, we will compare PFS and OS in subjects with GC vs post-GC, DEL vs non-DEL, and DHL/THL vs non-DHL/THL, using log-rank tests, at 2-sided alpha level of 0.05.

Also, among the subjects with rrDLBCL receiving PV-RGDP, the number of patients that complete stem cell harvest, the number of subjects that complete autoSCT, and median time to engraftment in these subjects will be summarized to describe the effect of PV-RGDP on stem cell transplant factors.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office (CTO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federalwide Assurance (FWA) number
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate
- Financial Disclosures
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.3 Registration Procedures

All subjects must be registered with the LCCC CTO Multicenter Office at the University of North Carolina before enrollment to study. To register a subject call the Multicenter office at 919-966-7359 Monday-Friday 8:30 am – 5:00 pm EST. Email the registration form, signed informed consents and all source documents to confirm eligibility to the assigned Project Manager (if unknown, email

CPOMulticenter@med.unc.edu). All subjects must have final eligibility verified by the UNC Multicenter Project Manager on behalf of the UNC PI prior to starting treatment. When sending registration request with eligibility documentation, please allow 24 hours for source to be reviewed.

11.4 Data Management and Monitoring/Auditing

The CTO Multicenter Office of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based electronic data capture system, Advarra EDC. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). Multicenter personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into Advarra by the multicenter study teams at participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into Advarra EDC. The Multicenter Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683 or LCCC_Oncore@unc.med.edu.

All data will be monitored, and source data will be verified on selected subjects. Queries will be issued on an ongoing basis on all subjects. Participating sites should respond to data queries within 14 days of receipt. The LCCC compliance committee or their designee will audit trial sites every twelve months while still enrolling or subjects are still on treatment. Participating sites must send source and regulatory documents to LCCC upon request, for remote monitoring and/or audit review.

11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Emergency Modifications

UNC and multicenter investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

<u>For Institutions Relying on UNC's IRB:</u>
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

<u>For Institutions Relying on Their Own IRB:</u>

For multicenter investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Multicenter institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the Multicenter Regulatory Associate).

11.5.2 Single Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

11.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs, please follow the guidelines below:

<u>For Institutions Relying on UNC's IRB</u>:
Protocol Deviations: UNC or multicenter personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNC Multicenter Project Manager within 5 days. UNC will determine if the violation affects the safety of the subject and integrity of the data. Once your institution's IRB response is received, please forward to the Multicenter Regulatory Associate.

Unanticipated Problems:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study personnel using the IRB's web-based reporting system.

Multicenter Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNC Multicenter Project Manager. The Multicenter Regulatory Associate will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the subject, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the amendment to their institution's IRB for approval. For multicenter studies, any multicenter site must submit their informed consent revisions to the Multicenter Regulatory Associate for review and approval prior to submission to their IRB.

11.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug product seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, auditing and monitoring of trials will be conducted, and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

13.1 Appendix A. Revised response criteria for lymphoma

(Cheson, et al. J Clin Oncol. 2014;32(27):3059-68)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	*Complete metabolic response*	*Complete radiologic response (all of the following)*
Lymph nodes and extra-lymphatic sites	Score 1, 2, or 3* with or without a residual mass 5 PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., 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 interred if uptake at sites f initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured 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 extra-lymphatic sites	Score of 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings indicate responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured 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 w/ baseline (diffuse uptake compatible w.	Not applicable

	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 w/ MRI or biopsy or an interval scan	

Revised Criteria for Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (Lugano Criteria)
Continued from previous page

Response and Site	PET-CT-Based Response	CT-Based Response
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
Non measure 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 (e.g., 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
Non measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than	Regrowth of previously resolved lesions

	another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	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

Revised Response Criteria (Table Key)

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 subjects 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 6 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 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 (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measurable lesions: Any disease not selected as measure, 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 (e.g., 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 (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

†*PET 5 PS*: 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.

Reference: Cheson BD, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32:3059-3067.

13.2 Appendix B. ECOG Performance Status

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

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol* 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

13.3 Appendix C. Child-Pugh Score

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

	Class A	Class B	Class C
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

13.4 Appendix D: Strong Inhibitors and Inducers of CYP3A

Strong inhibitors

Atazanavir
Ceritinib
Clarithromycin
Cobicistat and cobicistat-containing coformulations
Darunavir
Idelalisib
Indinavir
Itraconazole
Ketoconazole
Lonafarnib
Lopinavir
Mifepristone
Nefazodone
Nelfinavir
Ombitasvir-paritaprevir-ritonavir
Ombitasvir-paritaprevir-ritonavir plus dasabuvir
Posaconazole
Ritonavir and ritonavir-containing coformulations
Saquinavir
Telithromycin
Tucatinib
Voriconazole

Strong inducers

Apalutamide
Carbamazepine
Enzalutamide
Fosphenytoin
Lumacaftor
Lumacaftor-ivacaftor
Mitotane
Phenobarbital
Phenytoin
Primidone
Rifampin (rifampicin)