CITY OF HOPE
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A Phase 2 Study of Polatuzumab Vedotin with Rituximab, Ifosfamide, Carboplatin, and Etoposide (PolaR-ICE) as Initial Salvage Therapy for Relapsed/Refractory Diffuse Large B-cell Lymphoma

CITY OF HOPE PROTOCOL NUMBER: IRB #20148 PROTOCOL DATE: 12/20/2021

Initial Submission	Protocol dated 09/17/2020	Packet: 00
COH Amendment 01	Protocol dated 09/17/2020 (TP)	Packet: 01
COH Amendment 02	Protocol dated 09/17/2020 (TP)	Packet: 02
COH Amendment 03	Protocol dated 09/17/2020 (TP)	Packet: 03
COH Amendment 04	Protocol dated 06/23/2021	Packet: 04
COH Amendment 05	Protocol dated 06/23/2021 (TP)	Packet: 05
COH Amendment 06	Protocol dated 06/23/2021 (TP)	Packet: 06
COH Amendment 07	Protocol dated 12/20/2021	Packet: 07
COH Amendment 08	Protocol dated 12/20/2021 (TP)	Packet: 08
COH Amendment 09 at Continuation	Protocol dated 12/20/2021 (TP)	Packet: 09

SITE:

STAGE (If applicable):

MODALITY:

TYPE: Phase II

PRINCIPAL INVESTIGATOR: Alex Herrera, M.D.

PARTICIPATING CLINICIANS:
Elizabeth Budde, M.D., Ph.D., Alexey Danilov, M.D., Ph.D.
Stephen Forman, M.D.
Paul Koller, M.D.
Larry Kwak, M.D., Ph.D.
Matthew Mei, M.D.
Liana Nikolaenko, M.D.
Leslie Popplewell, M.D.
Geoffrey Shouse, D.O.
Tanya Siddiqi, M.D.
Jasmine Zain, M.D.
Ricardo Spielberger, M.D.
Leonardo Farol, M.D.
Joshua Mansour, M.D.
Firoozeh Sahebi, M.D.
James Godfrey. M.D.
Nicole Karras, M.D.
Swetha Kambhampati, M.D.
John Baird, M.D.

	Steven Rosen, M.D.
BIOSTATISTICIAN:	Lu Chen, PhD
PROTOCOL DEVELOPMENT SCIENTIST:	Sandrine Puverel, PhD
PARTICIPATING SITES:	City of Hope, Duarte Stanford University Dana-Farber Cancer Institute Emory University Memorial Sloan Kettering Cancer Center

City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

Clinical Trial Protocol

A Phase 2 Study of Polatuzumab Vedotin with Rituximab, Ifosfamide, Carboplatin, and Etoposide (PolaR-ICE) as Initial Salvage Therapy for Relapsed/Refractory Diffuse Large B-cell Lymphoma

Version Date:	12/20/2021
Protocol Version:	02
City of Hope #:	20148
Agents:	Polatuzumab vedotin, Rituximab, Ifosfamide, Carboplatin, Etoposide
IND Number:	152633
Sponsor/ IND Holder:	City of Hope
Funding Support/ Industry Partner:	Genentech
Industry Partner Protocol ID:	ML41673
NCT Number:	NCT04665765
Participating Sites:	City of Hope (Duarte), Stanford University, Dana-Farber Cancer Institute, Emory University, Memorial Sloan Kettering Cancer Center
Short Title	PolaR-ICE as initial salvage for R/R DLBCL

Principal Investigator
Alex Herrera, MD
City of Hope National Medical Center
Dept. of Hematology
T: 626-256-4673 x 82405
Email: aherrera@coh.org

Coordinating Center
Data Coordinating Center
City of Hope National Medical Center
Email: DCC@coh.org

PROTOCOL TEAM

Biostatistician

Lu Chen, PhD
City of Hope National Medical Center
Dept. of Computational and Quantitative Medicine
T: 626-256-4673 x 86626
Email: lchen@coh.org

Protocol Development Scientist

Sandrine Puverel, PhD
City of Hope National Medical Center
Dept. of Hematology
T: 626-256-4673 x 84220
Email: spuverel@coh.org

Participating non-COH sites

Site Lead Investigator

Ranjana Advani, MD
Stanford University
Dept. of Medicine
Email: radvani@stanford.edu

Site Lead Investigator

Jennifer Crombie, MD
Dana-Farber Cancer Institute
Dept. of Medical Oncology
Email: jlcrombie@partners.org

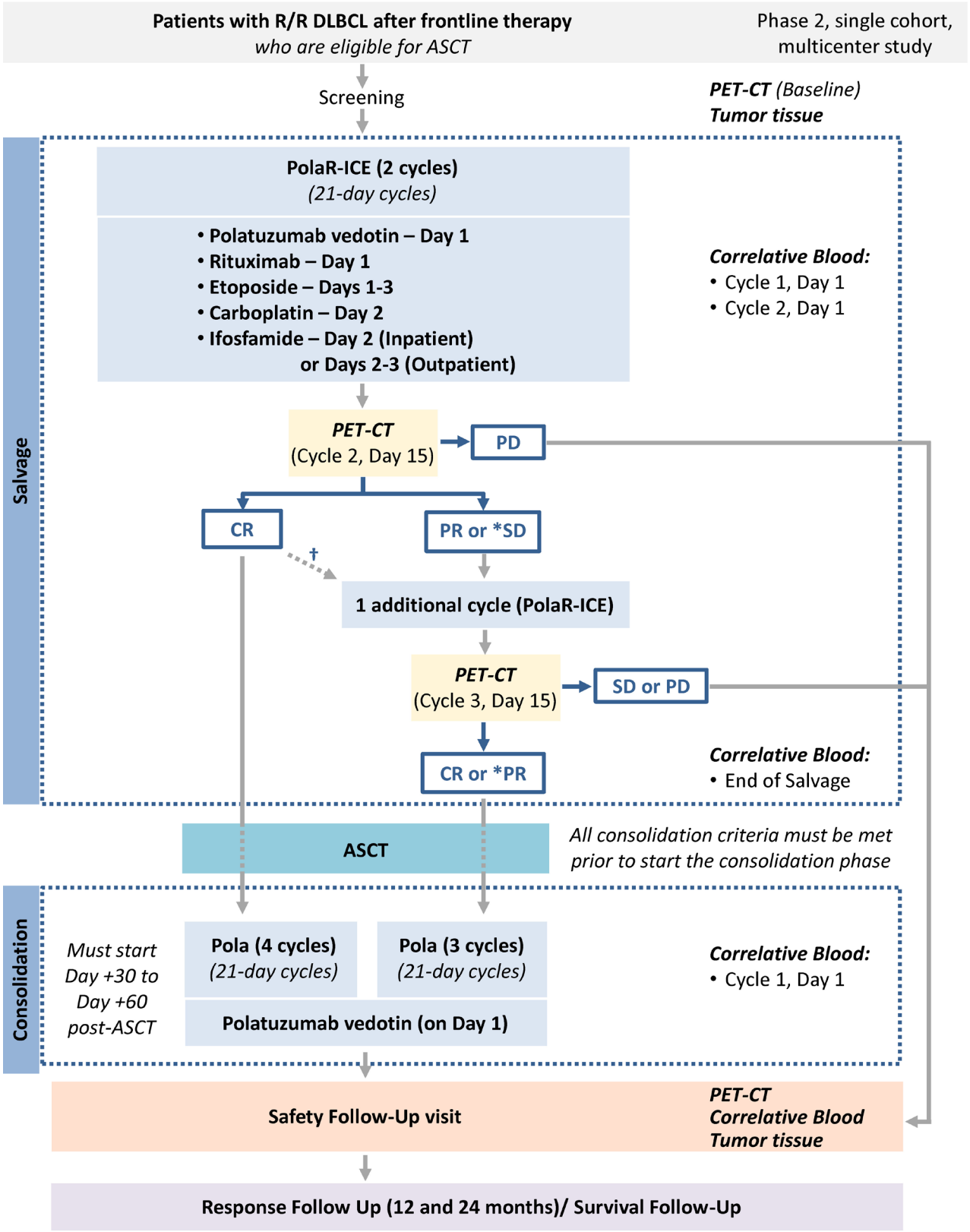
Site Lead Investigator

Jonathon Cohen, MD
Emory University
Dept. of Hematology and Medical Oncology
Email: jonathon.cohen@emory.edu

Site Lead Investigator

Matthew Matasar, MD
Memorial Sloan Kettering Cancer Center
Dept. of Medicine
T: 212-639-8889
Email: matasarm@mskcc.org

STUDY SCHEMA



* *At the treating physician's discretion*

† *Patients in CR may receive a 3rd cycle of PolaR-ICE at the treating physician's discretion*

PROTOCOL SYNOPSIS

Protocol Title

A Phase 2 Study of Polatuzumab Vedotin with Rituximab, Ifosfamide, Carboplatin, and Etoposide (PolaR-ICE) as Initial Salvage Therapy for Relapsed/Refractory Diffuse Large B-cell Lymphoma

Study Detail

Population/Indication(s):	Relapsed/Refractory Diffuse Large B-cell Lymphoma
Phase:	2
Sample Size:	Expected: 40 evaluable patients; Maximum: 53 patients
Estimated Accrual Duration:	24 months
Estimated Study Duration	~ 4 years
Participant Duration:	~ 24 months
Participating Sites:	• City of Hope Duarte, CA • Stanford University • Dana-Farber Cancer Institute • Emory University • Memorial Sloan Kettering Cancer Center
Study Agents:	Polatuzumab vedotin, Rituximab, Ifosfamide, Carboplatin, Etoposide
Sponsor:	City of Hope
Industry Partner:	Genentech

Rationale for this Study

Novel treatment strategies are needed to improve outcomes for relapsed/refractory (R/R), transplant-eligible DLBCL patients, where the goal is to achieve a high-quality remission that enables subsequent ASCT. The primary unmet need is the failure to achieve a high rate of CR, as achievement of a PET-negative CR following second-line salvage therapy has been associated with improvement in outcome in relapsed DLBCL patients who proceed to ASCT.[1-3] Pola is a potent anti-CD79b ADC with demonstrated anti-tumor efficacy in R/R DLBCL and has been combined safely with chemotherapy resulting in higher response rates compared to chemotherapy alone.[4] Notably, Pola combined with BR in a population of heavily treated patients also resulted in improved PFS and OS compared to BR alone. Therefore, it has been demonstrated that Pola combined with chemotherapy can improve outcomes in patients with DLBCL. An important observation about the clinical use of Pola is that peripheral neuropathy has limited the therapeutic index of the drug, with the ultimate dose of the drug being 1.8 mg/kg as opposed to the 2.4 mg/kg dose initially chosen as the recommended phase 2 dose. In addition, the duration of Pola dosing has been limited to 6 doses, prior to the onset of dose-limiting neuropathy. Therefore, the ideal dosing of Pola may be as a short course to improve upon the efficacy of combination chemotherapy, as demonstrated with bendamustine and CHOP in other studies. With the need for more effective bridging therapy prior to ASCT in R-R DLBCL, there is an ideal opportunity to utilize Pola as part of salvage therapy to increase the CR rate prior to ASCT. The CR rate prior to transplant is an important prognostic factor for ASCT outcome; therefore, our hypothesis is that improving salvage therapy with Pola may increase the durable response rate with a salvage/ASCT approach.

In addition, it has been demonstrated in Hodgkin lymphoma that the use of an effective ADC (brentuximab vedotin) after ASCT can improve progression-free survival. The AETHERA trial demonstrated that brentuximab vedotin consolidation treatment following ASCT prolongs PFS in patients with high risk relapsed or refractory classical Hodgkin lymphoma compared to placebo.[5] Like brentuximab vedotin in R/R Hodgkin lymphoma, Pola is an ADC that has potent anti-tumor activity in patients with R/R DLBCL. Pola has already been associated with improved survival in patients with R/R DLBCL receiving chemotherapy as compared to chemotherapy alone.[6] Therefore, we propose to use Pola as consolidation therapy after ASCT with the goal of increasing the proportion of patients with durable remission after ASCT.

Objectives

Primary Objectives

- Safety Lead-in: Evaluate the safety and tolerability of polatuzumab vedotin (Pola) added to rituximab, ifosfamide, carboplatin, and etoposide (PolaR-ICE) as first salvage therapy for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).
- Phase 2: Evaluate the anti-tumor activity of PolaR-ICE as first salvage therapy for R/R DLBCL as assessed by the complete response rate after 2 cycles.

Secondary Objectives

- Evaluate the overall response rate to PolaR-ICE as first salvage therapy for R/R DLBCL.
- Evaluate the progression-free and overall survival of patients who received PolaR-ICE as first salvage therapy for R/R DLBCL followed by autologous stem cell transplantation (ASCT) and single-agent Pola consolidation after ASCT.
- Evaluate the CR rate after Pola consolidation among those who were PR at ASCT.
- Evaluate the toxicity of PolaR-ICE salvage therapy and that of Pola consolidation after ASCT.
- Assess the rate of stem cell mobilization and collection failure in patients with R/R DLBCL who receive PolaR-ICE as first salvage therapy.

Exploratory Objectives

- Assess the kinetics of circulating tumor DNA after PolaR-ICE as first salvage therapy for R/R DLBCL followed by ASCT and single-agent Pola consolidation after ASCT.
- Assess possible biomarkers of response to PolaR-ICE in patients with R/R DLBCL.
- Examine the association between clinical outcomes (response, PFS) and pathological tumor characteristics.
- Examine the association between clinical outcomes (response, PFS) and ctDNA characteristics (mutation profile, kinetics of clearance).

Study Design

This is a phase 2 study of PolaR-ICE followed by ASCT and Pola consolidation in patients with relapsed or refractory (R/R) DLBCL. Adult patients with pathologically documented relapsed or refractory DLBCL after induction therapy will be enrolled. Patients with subsets of DLBCL, including mediastinal large B-cell lymphoma, transformed DLBCL, and aggressive B-cell lymphoma unclassified will not be excluded. Patients must have received anthracycline- or anthracenedione-containing induction chemotherapy. The Safety Lead-In will use a design that is slightly modified from the IQ rolling 6 design.[7] Dose level 1 will use the standard doses of R-ICE (rituximab 375 mg/m2, ifosfamide 5000 mg/m2 or 3 x 1670 mg/m2, carboplatin area under the curve 5 mg/mL x min; maximum dose, 750 mg, and etoposide 100 mg/m2 per day for 3 days) with the approved dose of Pola (1.8 mg/kg). There will be a dose de-escalation dose level (dose level -1), only if necessary. Dose level -1 will use the standard doses of R-ICE with a reduced dose of Pola (1.4 mg/kg). The maximum number of PolaR-ICE cycles is 3. Patients who proceed to ASCT directly after PolaR-ICE and have achieved an objective response to PolaR-ICE will receive single-agent Pola consolidation after ASCT at the standard dose of Pola (1.8 mg/kg) every 21 days. The maximum number of Pola-containing cycles of therapy is 6.

After the tolerable dose is confirmed the study will progress to the phase 2 portion of the study, which will employ a two-stage design to evaluate the CR rate after 2 cycles of PolaR-ICE. Patients who were enrolled during the safety lead-in portion at the final dose level deemed tolerable for Phase 2 will also be included in the Phase 2 response evaluation if they are evaluable for response.

Evaluation Criteria and Endpoints

Toxicities will be will be graded using the NCI CTCAE v 5.0.

Response/progression will be assessed per 2014 Lugano classification.

Primary Endpoint(s):

- Safety Lead-in: Unacceptable toxicity (defined in Section 11.2) during the first 2 cycles of PolaR-ICE therapy.
- Phase 2: Complete response (CR) rate after 2 cycles of PolaR-ICE therapy.

Secondary Endpoint(s):

- Overall response rate (ORR) at the end of PolaR-ICE therapy.
- Progression-free survival (PFS) and Overall survival (OS).
- CR rate after Pola consolidation among patients who were PR at ASCT.
- Toxicity of PolaR-ICE salvage therapy and toxicity of Pola consolidation after ASCT.
- Stem cell mobilization rate and collection failure.

Statistical Considerations

Safety Lead-in:

During the safety lead-in portion of the study, a design that is slightly modified from the IQ rolling 6 design will be used.[7] In this design, up to 8 evaluable patients may be treated at each dose level, and the highest dose level with <33% evaluable patients having unacceptable toxicities will be considered tolerable with respect to unacceptable toxicities. If DL 1 is not tolerable, DL -1 will be explored.

Phase 2:

The Phase 2 portion of the study adopts a two-stage design. Patients who were enrolled during the safety lead-in portion at the final dose level deemed tolerable for Phase 2 will also be included in the Phase 2 response evaluation if they are evaluable for response.

At the first stage, 20 patients will be enrolled. If <8 complete responses are seen, the accrual will be terminated. If at least 8 patients achieve a complete response, the trial will continue to the second stage. At the second stage, 20 additional patients will be entered. At the end of stage 2, if 21 or more patients out of the total 40 patients experience a complete response, the combination will be considered worthy of further study. If <21 patients experience a complete response then no further investigation of the combination is warranted.

The 2-stage design aims to differentiate between the null hypothesis (disappointing rate) of 40% CR rate and an alternative hypothesis (promising rate) of 60% CR rate. The null hypothesis of 40% CR rate is based on a large randomized study comparing R-ICE with R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) as salvage regimen followed by ASCT for relapsed/refractory DLBCL [8]. Similar complete response rates were observed after 3 cycles of R-ICE (37%, n=197) vs. 3 cycles R-DHAP (40%, n=191). Therefore, we would consider a 40% CR rate a discouraging rate and 60% a promising CR rate for this regimen to merit further study. The design has a 1-sided type I error of 7.3% and a power of 87%. The expected sample size under the null hypothesis is 31.7, and the design has a 42% chance of early termination after Stage I if the true CR rate is 40%.

Abbreviated Eligibility Criteria

Main Inclusion Criteria

- Age: ≥ 18 years
- ECOG ≤ 2
- Histologically confirmed diagnosis of diffuse large B-cell lymphoma according to the WHO classification, with hematopathology review at the participating institution. Subtypes of DLBCL including transformed indolent lymphomas (TIL), primary mediastinal large B-cell lymphoma (PMBCL), and high-grade B-cell lymphoma not otherwise specified (HGBCL-NOS) are eligible.
- Biopsy-proven relapsed or refractory disease after 1 line of frontline CD20-directed immunotherapy with anthracycline- or anthracenedione-based multi-agent chemotherapy. Monotherapy with rituximab or other CD20-directed

immunotherapy prior to frontline chemotherapy or as maintenance therapy, and radiation therapy in a limited field or as a part of the frontline treatment plan are permitted.

- Prior lymphoma therapy should be completed at least 2 weeks before start of protocol therapy.
- Measurable disease by CT or PET/CT scan with one or more sites of disease ≥ 1.5 cm in longest dimension.
- Considered eligible for high-dose chemotherapy followed by ASCT.
- Fully recovered from the acute toxic effects (except alopecia) to ≤ Grade 1 to prior anti-cancer therapy.
- Be willing to provide archival tissue of a biopsy that was performed after the frontline systemic therapy (if unavailable, exceptions may be granted with Study PI approval).
- Adequate hematological, renal, and hepatic function.
- Women of childbearing potential: negative urine or serum pregnancy test.
- Agreement to use an effective method of contraception for both women of childbearing potential and male patients during the study and through at least 12 months post-last dose of pola or rituximab for women, 5 months post-last dose of pola or 3 months post-last dose of rituximab for men, and 6 months post-last dose of ifosfamide, carboplatin, or etoposide for both women and men.

Main Exclusion Criteria

- Patients who are not hematopoietic stem cell transplant candidates.
- Prior solid organ transplantation.
- Systemic steroid therapy or any other form of immunosuppressive therapy for lymphoma symptom control must be tapered down to ≤ 10 mg/day prednisone or equivalent. See exceptions in Section 3.2.
- Peripheral neuropathy ≥ grade 2 or demyelinating form of Charcot-Marie-Tooth disease.
- Known active central nervous system (CNS) involvement by lymphoma, including leptomeningeal involvement.
- Active infection requiring systemic therapy.
- Other active malignancy requiring therapy. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- History of severe allergic reactions attributed to compounds of similar chemical or biologic composition to study agents.
- Recent major surgery (within 4 weeks) prior to start of protocol therapy, other than for diagnosis.
- Symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), cerebrovascular event/stroke or myocardial infarction within the past 6 months.
- Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (See Section 3.2).
- Known active human immunodeficiency virus (HIV) infection (Section 3.2).
- History of or current progressive multifocal leukoencephalopathy (PML).
- *Females only*: Pregnant or breastfeeding.

Investigational Product Dosage and Administration

The treatment plan for the Safety Lead-in and Phase 2 cohorts is as follows.

Treatment may be given on an inpatient or outpatient basis.

The maximum number of Pola-containing cycles of therapy is 6 (See Sections 5.6 and 5.7).

Note: For the drugs that are given as standard of care (i.e. R-ICE), the schedule (e.g. day of drug administration), and order of drug administration may be modified for any component of R-ICE at the investigator's discretion/ per institutional standards. In addition, dose modifications/ discontinuation of ifosfamide, carboplatin, and etoposide, whether or not they are due to toxicity are permitted at the investigator's discretion/ per institutional standards.

	SALVAGE - PolaR-ICE ‡ (Section 5.6)				
	Agent	**Dose**	**Route**	**Schedule (Days within each 21-day cycle)**	**Maximum # Cycles**
R-ICE **(Inpatient Schedule)****	Rituximab	375 mg/m²	IV	Day 1	2-3
	Etoposide	100 mg/m²	IV	Days 1-3	
	Carboplatin	AUC 5 (750 mg max)	IV	Day 2	
	Ifosfamide **	5000 mg/m²	IV	Day 2	
	Polatuzumab Vedotin (Pola)	**Safety Lead-in:** • ***Dose Level 1: 1.8 mg/kg** • Dose Level -1: 1.4 mg/kg (Section 5.4) **Phase 2:** Tolerable dose from Safety Lead-in (Section 5.5)	IV	Day 1	2-3

	CONSOLIDATION - Pola ‡‡ (Section 5.7)				
	Agent	**Dose**	**Route**	**Schedule (Days within each 21-day cycle)**	**Maximum # Cycles**
	Polatuzumab Vedotin (Pola)	**1.8 mg/kg**	IV	Day 1	3-4

* ***Starting dose is Dose Level 1.***

** ***Outpatient treatment is allowed*** and schedule is similar to Inpatient schedule, except for ifosfamide which will be given at a dose of 1670 mg/m² on Days 1-3 (instead of 5000 mg/m² on Day 2). Ifosfamide is always given with Mesna, according to institutional standards (Section 5.14).

‡ ***G-CSF prophylaxis*** should be administered with each PolaR-ICE Salvage cycle. The schedule and G-CSF formulation are at the investigator's discretion.

‡‡ For participants with ***objective response*** (CR or PR).

Clinical Observations and Tests to be Performed

- Safety assessments (CBCs with differential, comprehensive chemistry panel)
- Response assessments
- CT/PET/MRI scans
- Bone marrow biopsy/aspirate
- Correlative tumor tissue
- Correlative blood collection

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Meaning
ADC	Antibody-drug conjugate
AE	Adverse Event
ASCT	Autologous Stem Cell Transplantation
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Coordinator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose Limiting Toxicity
DSMC	Data & Safety Monitoring Committee
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
MMAE	Monomethyl auristatin E
NCI	National Cancer Institute
OIDRA	Office of IND Development and Regulatory Affairs
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PI	Principal Investigator
PMT	Protocol Management Team
Pola	Polatuzumab Vedotin
PR	Partial Response
R-ICE	Rituximab, ifosfamide, carboplatin, etoposide
SAE	Serious Adverse Event
SD	Stable disease

1.0 OBJECTIVES

1.1 Primary Objectives

Safety Lead-In

- Evaluate the safety and tolerability of polatuzumab vedotin (Pola) added to rituximab, ifosfamide, carboplatin, and etoposide (PolaR-ICE) as first salvage therapy for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

Phase 2

- Evaluate the anti-tumor activity of PolaR-ICE as first salvage therapy for R/R DLBCL as assessed by the complete response rate after 2 cycles.

1.2 Secondary Objectives

- Evaluate the overall response rate to PolaR-ICE as first salvage therapy for R/R DLBCL.
- Evaluate the progression-free and overall survival of patients who received PolaR-ICE as first salvage therapy for R/R DLBCL followed by autologous stem cell transplantation (ASCT) and single-agent Pola consolidation after ASCT.
- Evaluate the CR rate after Pola consolidation among those who were PR at ASCT.
- Evaluate the toxicity of PolaR-ICE salvage therapy and that of Pola consolidation after ASCT.
- Assess the rate of stem cell mobilization and collection failure in patients with R/R DLBCL who receive PolaR-ICE as first salvage therapy.

1.3 Exploratory Objectives

- Assess the kinetics of circulating tumor DNA after PolaR-ICE as first salvage therapy for R/R DLBCL followed by ASCT and single-agent Pola consolidation after ASCT.
- Assess possible biomarkers of response to PolaR-ICE in patients with R/R DLBCL.
- Examine the association between clinical outcomes (response, PFS) and pathological tumor characteristics.
- Examine the association between clinical outcomes (response, PFS) and ctDNA characteristics (mutation profile, kinetics of clearance).

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma and accounts for 30-40% of newly diagnosed patients with non-Hodgkin lymphoma (NHL), representing the most common lymphoid neoplasm in adults.[9] DLBCL is considered as one of the aggressive type of NHL, with median age 70 years at diagnosis. Although the majority of patients with newly diagnosed DLBCL achieve long-term remissions with rituximab and multi-agent chemotherapy, approximately 30% of patients will experience relapse or progression. At the time of relapsed disease, the treatment approach is based on whether the patient is a candidate for autologous stem cell transplant (ASCT). In patients considered to be transplant eligible, the decision to proceed to ASCT is determined by the response to salvage treatment.[10, 11] The goals of salvage therapy are typically to minimize disease burden and induce remission, providing the best opportunity to benefit from consolidative ASCT.

Various multi-agent salvage regimens incorporating rituximab have been explored in DLBCL patients. A large randomized comparison of the most commonly used salvage regimens demonstrated the equivalence of rituximab combined with either ICE (ifosfamide, carboplatin, etoposide) or DHAP (dexamethasone, cytarabine, cisplatin).[8]

There were no significant differences overall between these regimens, and the combined results supported an overall response rate (ORR) of 63%, with 37% of patients achieving a complete remission (CR of 25%, unconfirmed CR of 12%). The median progression-free survival (PFS) was found to be approximately 1 year, with a 3-year event-free survival of 31% and 3-year overall survival (OS) of 50%. Patients with chemo-sensitive disease who achieved a CR or partial remission (PR) and had adequate stem cell collection were candidates to proceed to ASCT; only 50% of patients were able to undergo ASCT following salvage therapy. The most common reason to not proceed to ASCT was treatment failure to induce remission.

In general, treatment guidelines support ASCT as the treatment of choice for patients with chemo-sensitive relapsed or refractory DLBCL.[10, 11] Patients who are candidates for ASCT should be treated with multi-agent chemotherapy regimens combined with rituximab, such as DHAP, ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin), GDP (gemcitabine, dexamethasone, and cisplatin), GCD (gemcitabine, carboplatin, dexamethasone), GemOx (gemcitabine and oxaliplatin), ICE or MINE (mesna, ifosfamide, mitoxantrone, etoposide); there is no clear advantage of one regimen over another. Patients achieving remission should then proceed to consolidative ASCT.[10, 11]

Obtaining a positive emission tomography (PET)-negative CR following second-line salvage therapy has been associated with improvement in outcome in relapsed DLBCL patients who proceed to ASCT.[1-3] A meta-analysis, including 300 patients with DLBCL, demonstrated that a positive PET scan pre-ASCT was associated with a significantly shorter PFS interval (random effects hazard ratio 4.3; 95% CI 3.1, 6; $p<0.0001$).[3] A PET-positive status pre-ASCT resulted in a 4 to 5-fold higher risk for treatment failure versus a PET-negative status. A smaller study evaluating the prognostic value of pre-ASCT PET scanning in relapsed DLBCL patients found a striking difference in long term outcome, with a 3-year PFS of 81% for patients with a negative scan versus 35% for those with a positive scan. This translated into similar 3-year OS findings, with 81% of patients alive with a negative scan versus 39% with a positive scan.[1]

Novel treatment strategies are needed to improve outcomes for relapsed, transplant-eligible DLBCL patients. The goal of treatment in this population is to achieve a high-quality remission that enables subsequent ASCT. The primary unmet need is the failure to achieve a high rate of CR. Achieving a CR with salvage therapy prior to ASCT has been associated with improved long-term outcomes. Chemo-immunotherapy regimens such as RICE or RDHAP result in less than half of patients achieving CR; adding a novel agent with demonstrated activity in relapsed DLBCL to these regimens has the potential to improve outcomes.

2.1.2 Polatuzumab vedotin

Polatuzumab vedotin (Pola) is an ADC with a monomethyl auristatin E (MMAE) payload directed against CD79b, a part of the B-cell receptor complex that is ubiquitously expressed on B cells. Pola has been studied in B-cell NHL (B-NHL) and CLL as a single agent, and in multiple Pola-based combination studies in patients with B-NHL. The initial phase I dose-escalation study enrolled 95 patients with R/R NHL or CLL, with 86 receiving Pola as a single agent and 9 patients receiving Pola combined with rituximab. Pola was well-tolerated as a single agent and in combination with rituximab, with most treatment-emergent AEs being mild, and the most common grade 3-4 AEs being neutropenia (40%), anemia (11%), or peripheral neuropathy (9%) in heavily treated patients (80% with ≥ 3 prior lines of therapy). At the recommended phase 2 dose of Pola, the ORR to monotherapy among patients with NHL (indolent B-NHL, n=16; DLBCL, n=27; MCL, n=2) was 55%, including an ORR of 56% and CR rate of 15% in patients with DLBCL.[12] In the randomized phase II ROMULUS study, patients with R/R FL or DLBCL were randomized to receive either Pola or the anti-CD22 ADC pinatuzumab vedotin (PiV) plus rituximab. Patients with R/R DLBCL who received Pola plus rituximab (n=39) had an ORR of 56% with a CR rate of 15% while patients with R/R FL had an ORR of 70% and a CR rate of 40% (n=20). Similarly, in a separate phase Ib/II study of Pola plus obinutuzumab, patients with R/R DLBCL had a best ORR of 52% and CR rate of 29% and patients with R/R FL had an ORR of 78% and CR rate of 30%. Pola has also been combined with 6 cycles of bendamustine and either rituximab or obinutuzumab in patients with R/R DLBCL or FL as part of a phase I/II study that had dose expansion and randomized cohorts (rituximab-bendamustine, BR vs Pola+rituximab-bendamustine, Pola-BR). In patients

with R/R DLBCL, the best ORR and CR rate to Pola+BR in the randomized phase II portion of the study (n=40) were 70% and 57.5% as compared to 32.5% and 20%, respectively, in patients who received BR alone (n=40). The best ORR and CR rate to Pola with bendamustine and obinutuzumab were 59% and 41%, respectively. PFS and OS were significantly longer in patients who received Pola-BR, with a median OS of 12.4 months compared to 4.7 months in patients who received BR (HR 0.42; 95% CI, 0.24 to 0.75). In patients with R/R FL, the CR rate at the end of 6 cycles of Pola+BR (n=39, 69%) was similar to BR (n=41, 63%) and PFS was also similar (17 versus 17.3 months) with OS not reached in both arms.[13] Based on these findings, the FDA approved Pola plus BR for use in patients with relapsed/refractory DLBCL who have received at least two prior therapies. Pola has also been evaluated as part of initial therapy (cyclophosphamide, doxorubicin, and prednisone with either rituximab, R-CHP, or obinutuzumab, G-CHP) in a phase I study of patients with newly diagnosed DLBCL. The end of treatment ORR and CR rate after R-CHP (n=45) were 91% and 78%, respectively, and the ORR and CR rate after G-CHP (n=21) were 91% and 81%, respectively. [14] There is currently a randomized, double-blinded, placebo-controlled, phase III trial evaluating the addition of Pola to R-CHP compared to R-CHOP as initial therapy for DLBCL (POLARIX, clinicaltrials.gov: NCT03274492).

2.1.3 Rituximab with ifosfamide, carboplatin, and etoposide (R-ICE)

RICE is a standard chemo-immunotherapy regimen consisting of rituximab, etoposide, ifosfamide, and carboplatin. Rituximab is a CD20-directed cytolytic antibody. Etoposide is a topoisomerase inhibitor. Ifosfamide is a nitrogen mustard alkylating agent. Carboplatin is a platinum-based antineoplastic agent that intercalates with DNA to interfere with DNA repair. RICE is a commonly used regimen for salvage therapy before ASCT in DLBCL patients.

The dose of rituximab (375 mg/m2) is the standard approved dose for patients with previously untreated DLBCL when given in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or other anthracycline-based chemotherapy regimens. There is no standard dose or schedule for rituximab in the relapsed or refractory setting; however, the dose (375 mg/m2) and schedule (every 3 weeks) selected in the current study have been safely and effectively employed in combination with various single- and multi-agent chemotherapy regimens for this patient population.[8, 11] The doses of ifosfamide (5000 mg/m2), carboplatin (area under the curve 5 mg/mL x min; maximum dose, 750 mg), and etoposide (100 mg/m2 per day for 3 days) are based on the original publication from Memorial Sloan Kettering Cancer Center and are the standard doses when given in a combination setting.[15]

Ifosfamide is extensively metabolized (70-86% of the dose) by CYP3A4 and CYP2B6 (Ifosfamide Prescribing Information, APP Pharmaceuticals, January 2008). Carboplatin is mainly eliminated by renal glomerular filtration (Paraplatin Prescribing Information, Bristol-Myers Squibb, July 2010). Etoposide is eliminated by multiple mechanisms, including renal and biliary excretion and several metabolic pathways (sulfation, glucuronidation, and oxidation by CYP3A4) (Etoposide Prescribing Information, Bristol-Myers Squibb, March 2011).

2.1.4 Rationale for combination of PolaR-ICE followed by Pola consolidation after ASCT in R/R DLBCL

As described above, novel treatment strategies are needed to improve outcomes for relapsed/refractory (R/R), transplant-eligible DLBCL patients, where the goal is to achieve a high-quality remission that enables subsequent ASCT. The primary unmet need is the failure to achieve a high rate of CR, as achievement of a PET-negative CR following second-line salvage therapy has been associated with improvement in outcome in relapsed DLBCL patients who proceed to ASCT.[1-3] Pola is a potent anti-CD79b ADC with demonstrated anti-tumor efficacy in R/R DLBCL and has been combined safely with chemotherapy resulting in higher response rates compared to chemotherapy alone.[16] Notably, Pola combined with BR in a population of heavily treated patients also resulted in improved PFS and OS compared to BR alone. Therefore, it has been demonstrated that Pola combined with chemotherapy can improve outcomes in patients with DLBCL. An important observation about the clinical use of Pola is that peripheral neuropathy has limited the therapeutic index of the drug, with the ultimate dose of the drug being 1.8 mg/kg as opposed to the 2.4 mg/kg dose initially chosen as the recommended phase 2 dose. In addition, the duration of Pola dosing has been limited to 6 doses, prior to the onset of dose-limiting neuropathy.

Therefore, the ideal dosing of Pola may be as a short course to improve upon the efficacy of combination chemotherapy, as demonstrated with bendamustine and CHOP in other studies. With the need for more effective bridging therapy prior to ASCT in R-R DLBCL, there is an ideal opportunity to utilize Pola as part of salvage therapy to increase the CR rate prior to ASCT. The CR rate prior to transplant is an important prognostic factor for ASCT outcome; therefore, our hypothesis is that improving salvage therapy with Pola may increase the durable response rate with a salvage/ASCT approach.

In addition, it has been demonstrated in Hodgkin lymphoma that the use of an effective ADC (brentuximab vedotin) after ASCT can improve progression-free survival. The AETHERA trial demonstrated that brentuximab vedotin consolidation treatment following ASCT prolongs PFS in patients with high risk relapsed or refractory classical Hodgkin lymphoma compared to placebo.[5] Like brentuximab vedotin in R/R Hodgkin lymphoma, Pola is an ADC that has potent anti-tumor activity in patients with R/R DLBCL. Pola has already been associated with improved survival in patients with R/R DLBCL receiving chemotherapy as compared to chemotherapy alone. [17] Therefore, we propose to use Pola as consolidation therapy after ASCT with the goal of increasing the proportion of patients with durable remission after ASCT.

2.2 Rationale for Correlative Studies

The correlative analyses that will be performed as part of this clinical trial are exploratory and intended to generate hypotheses that can be validated in a larger study. The assays described are still under development and refinement, so the exact analyses may change during the course of this study.

2.2.1 Circulating tumor DNA

The detection of circulating tumor DNA (ctDNA) has been studied in lymphoma. Next-generation sequencing (NGS)-based ctDNA detection performed by NGS of the immunoglobulin (Ig) or T-cell receptor genes can identify ctDNA in the peripheral blood mononuclear cells (PBMC) and plasma (cell-free DNA) at diagnosis in a range of lymphomas, including diffuse large B-cell lymphoma (DLBCL).[18-21] In addition, ctDNA levels correlate with treatment response in DLBCL, and the persistence or recurrence of ctDNA during and after upfront therapy is associated with subsequent DLBCL relapse.[20, 21] While the Ig-NGS method is powerful, the investigation of only Ig genes limits its sensitivity, resulting in a sizable minority of patients in whom the assay is not applicable. Meanwhile, ctDNA assessment using capture-based NGS for recurrent mutations and rearrangements has been explored in DLBCL, and the method appears feasible and highly sensitive.[22, 23] Like IgNGS, capture-based NGS MRD detection exploits the genetic features of a lymphoma to identify tumor-specific DNA in the peripheral blood of patients with lymphoma. Utilizing bioinformatics pipelines optimized for low input DNA, hybridization capture-based NGS is performed on a patient sample (i.e. peripheral blood, tumor tissue) that evaluates a panel of single-nucleotide variants (SNVs), insertions/deletions (indels), and chromosomal translocations known to be recurrently mutated in a specific lymphoma subtype (to date, primarily DLBCL). CtDNA can be quantitated by calculating the proportion of tumor-specific cfDNA molecules within a sample (the variant allele fraction). Thus far, studies have demonstrated that genetic alterations detected in ctDNA using capture-based NGS analysis of the peripheral blood are highly concordant with genetic alterations determined by NGS of a primary DLBCL tumor sample.[24-26] Similar to IgNGS, capture-based NGS based MRD detection can identify ctDNA in patients with DLBCL prior to treatment, can quantify ctDNA levels that track with treatment response and resistance, and can detect relapse prior to and at the time of clinically apparent relapse.[23-25, 27] In a study examining DLBCL patients receiving frontline or salvage therapy at several independent centers, ctDNA was detectable in 98% of patients, and pretreatment ctDNA levels and molecular responses were independently prognostic of outcomes.[28]

2.2.2 Gene expression profiling

Gene expression profiles define distinct subsets of DLBCL and are associated with outcome after standard therapy in patients with DLBCL.[29, 30] Both the cell of origin and a newer double-hit signature identify subsets of patients who have poorer outcomes with standard therapy.[31] We will study both COO and the double-hit signature in patients treated with PolaR-ICE and evaluate associations with response to therapy and PFS.

2.2.3 Mutation profiling

Recent work from multiple laboratories have studied the mutational landscape in DLBCL and identified biological clusters of mutation profiles that have prognostic significance. We will perform next-generation sequencing to evaluate the mutational landscape in patients treated with PolaR-ICE and associations with response to study treatment and PFS.[32-34]

2.2.4 Multispectral immunofluorescence

We will use the Vectra spatial multispectral immunofluorescence (mIF) system to evaluate pre-treatment and on-treatment changes in immune cell subset density and relative proximities in the tumor microenvironment.

Proof of concept that mIF is a valuable tool in studying the tumor microenvironment in lymphomas was demonstrated in Hodgkin lymphoma by the Shipp lab, where unique microenvironmental features of the HL microenvironment were elucidated.[35]

2.3 Overview and Rationale for Study Design

This is a phase 2 study of PolaR-ICE followed by ASCT and Pola consolidation in patients with relapsed or refractory (R/R) DLBCL. Adult patients with pathologically documented relapsed or refractory DLBCL after induction therapy will be enrolled. Patients with subsets of DLBCL, including mediastinal large B-cell lymphoma, transformed DLBCL, and aggressive B-cell lymphoma unclassified will not be excluded. Patients must have received anthracycline- or anthracenedione-containing induction chemotherapy. The Safety Lead-In will use a design that is slightly modified from the IQ rolling 6 design.[7] Dose level 1 will use the standard doses of R-ICE (rituximab 375 mg/m2, ifosfamide 5000 mg/m2 or 3 x 1670 mg/m2, carboplatin area under the curve 5 mg/mL x min; maximum dose, 750 mg, and etoposide 100 mg/m2 per day for 3 days) with the approved dose of Pola (1.8 mg/kg). There will be a dose de-escalation dose level (dose level -1), only if necessary. Dose level -1 will use the standard doses of R-ICE with a reduced dose of Pola (1.4 mg/kg). The maximum number of PolaR-ICE cycles is 3. ASCT will be performed according to institutional standards. Patients who proceed to ASCT directly after PolaR-ICE and have achieved an objective response to PolaR-ICE will receive single-agent Pola consolidation after ASCT at the standard dose of Pola (1.8 mg/kg) every 21 days. The maximum number of Pola-containing cycles of therapy is 6.

After the tolerable dose is confirmed the study will progress to the phase 2 portion of the study, which will employ a two-stage design to evaluate the CR rate of PolaR-ICE after 2 cycles. Patients who were enrolled during the safety lead-in portion at the final dose level deemed tolerable for Phase 2 will also be included in the Phase 2 response evaluation if they are evaluable for response. At the first stage, 20 patients will be enrolled. If <8 complete responses are seen, the accrual will be terminated. If at least 8 patients achieve a complete response, the trial will continue to the second stage. At the second stage, 20 additional patients will be entered. At the end of stage 2, if 21 or more patients out of the total 40 patients experience a complete response, the combination will be considered worthy of further study.

3.0 ELIGIBILITY CRITERIA

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent of the participant and/or legally authorized representative.

- Assent, when appropriate, will be obtained per institutional guidelines

__2. Be willing to provide archival tissue of a biopsy that was performed after the frontline systemic therapy.

- If unavailable, exceptions may be granted with Study PI approval.

Age Criteria, Performance status

__3. Age: ≥ 18 years

__4. ECOG ≤ 2

Nature of Illness and Illness Related Criteria

__5. Histologically confirmed diagnosis of diffuse large B-cell lymphoma according to the WHO classification, with hematopathology review at the participating institution. Subtypes of DLBCL including transformed indolent lymphomas (TIL), primary mediastinal large B-cell lymphoma (PMBCL), and high-grade B-cell lymphoma not otherwise specified (HGBCL-NOS) are eligible.

__6. Biopsy-proven relapsed or refractory disease after 1 line of frontline CD20-directed immunotherapy with anthracycline- or anthracenedione-based multi-agent chemotherapy. Monotherapy with rituximab or other CD20-directed immunotherapy prior to frontline chemotherapy or as maintenance therapy, and radiation therapy in a limited field or as a part of the frontline treatment plan are permitted.

__7. Prior lymphoma therapy should be completed at least 2 weeks before start of protocol therapy.

__8. Measurable disease by CT or PET/CT scan with one or more sites of disease ≥ 1.5 cm in longest dimension.

__9. Considered eligible for high-dose chemotherapy followed by ASCT.

__10. Fully recovered from the acute toxic effects (except alopecia) to ≤ Grade 1 to prior anti-cancer therapy.

Clinical Laboratory and Organ Function Criteria

__11. **Without bone marrow involvement**: ANC ≥ 1,000/mm^3 **With bone marrow involvement**: ANC ≥ 750/mm^3 **NOTE:** Growth factor is not permitted within 7 days of ANC assessment unless cytopenia is secondary to disease involvement.	ANC:	Date:
__12. **Without bone marrow involvement**: Platelets ≥ 100,000/mm^3 **With bone marrow involvement**: Platelets ≥ 75,000/mm^3 **NOTE:** Platelet transfusions are not permitted within 7 days of platelet assessment unless cytopenia is secondary to disease involvement.	Plts:	Date:

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__13. Hemoglobin ≥ 8 g/dL (no erythropoietin and/or pRBC transfusion allowed within 7 days prior to screening) Exception: unless cytopenia is secondary to disease involvement.	Hgb:		Date:
__14. Total bilirubin ≤ 1.5 X ULN If hepatic involvement by lymphoma, or Gilbert's disease: ≤ 3X ULN	ULN: Bil: Liver involvement: Y/N Gilbert's disease: Y/N		Date:
__15. AST ≤ 2.5 x ULN If hepatic involvement by lymphoma: AST ≤ 5 x ULN	ULN: AST: Liver involvement: Y/N		Date:
__16. ALT ≤ 2.5 x ULN If hepatic involvement by lymphoma: ALT ≤ 5 x ULN	ULN: ALT: Liver involvement: Y/N		Date:
__17. Creatinine clearance of ≥ 50 mL/min per 24 hour urine test or the Cockcroft-Gault formula or $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ (x 0.85 for females) **Or** $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}}$ (x 0.85 for females)	Serum Cr: Cr Clearance:		Date:
__18. **If not receiving anticoagulants**: International Normalized Ratio (INR) OR Prothrombin (PT) ≤ 1.5 x ULN **If on anticoagulant therapy**: PT must be within therapeutic range of intended use of anticoagulants	ULN: INR: PT: On anticoagulant therapy: Yes/No		Date:
__19. **If not receiving anticoagulants**: Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 x ULN **If on anticoagulant therapy**: aPTT must be within therapeutic range of intended use of anticoagulants	ULN: aPTT: On anticoagulant therapy: Yes/No		Date:
__20. **Women of childbearing potential (WOCBP)**: negative urine or serum pregnancy test If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	Urine:	Serum:	Date:

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

Contraception

Agreement by females **and** males of childbearing potential* to use an effective method of birth control or abstain from heterosexual activity for the course of the study through at least 12 months after the last dose of polatuzumab vedotin or rituximab for women, at least 5 months following the last dose of polatuzumab vedotin or 3 months following the last dose of rituximab for men, and at least 6 months following the last dose of ifosfamide, carboplatin, or etoposide for both women and men.

* Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 1 year (women only).

3.2 Exclusion Criteria

Prior and concomitant therapies

__1. Patients who are not hematopoietic stem cell transplant candidates are excluded.

__2. Prior solid organ transplantation.

__3. Systemic steroid therapy or any other form of immunosuppressive therapy for lymphoma symptom control must be tapered down to ≤ 10 mg/day prednisone or equivalent. Exceptions are:

- Inhaled or topical steroids
- Adrenal replacement doses > 10 mg daily prednisone equivalents in the absence of active autoimmune disease.

Other illnesses or conditions

__4. Peripheral neuropathy ≥ grade 2 or demyelinating form of Charcot-Marie-Tooth disease.

__5. Known active central nervous system (CNS) involvement by lymphoma, including leptomeningeal involvement.

__6. Active infection requiring systemic therapy.

__7. Other active malignancy requiring therapy. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

__8. History of severe allergic reactions attributed to compounds of similar chemical or biologic composition to study agents.

__9. Recent major surgery (within 4 weeks) prior to start of protocol therapy, other than for diagnosis.

__10. Symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), cerebrovascular event/stroke or myocardial infarction within the past 6 months. See Appendix C.

__11. Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Patients with past HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) are eligible if HBV DNA is undetectable. Patients who are positive for HCV antibody are eligible if PCR is negative for HCV RNA.
Testing to be done only in patients suspected of having infections or exposures.

__12. Known active human immunodeficiency virus (HIV) infection. Subjects who have an undetectable or unquantifiable HIV viral load with CD4 ≥ 200 and are on HAART medication are allowed. Testing to be done only in patients suspected of having infections or exposures.

__13. History of or current progressive multifocal leukoencephalopathy (PML).

__14. *Females only*: Pregnant or breastfeeding.

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__15. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__16. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT

NOTE: Sites must meet activation requirements prior to enrolling participants.

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained.

The informed consent process is to be fully documented (see Section 17.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0 (Study Calendar).

4.2 Participant Enrollment

4.2.1 COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

- E-mail: DCC@coh.org

4.2.2 Slot verification and reservation

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.3 Registration Process

Allow up to 24 hours for the DCC to review. To register a participant the subsequent procedure is to be followed:

1. The study team should contact the DCC via email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The study team will email a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:
    - Registration Cover Sheet (Appendix D)
    - Completed eligibility checklist (printed from Section 3.0 of the protocol) with required signature(s)
    - Signed Informed Consent
    - Signed HIPAA authorization form (if separate from informed consent)
    - Signed subject's bill of Rights (California only)
3. In some cases, the DCC may request additional documentation prior to registration. Please refer to the Work Instruction – Reviewing Packets and Registering Subjects for more information. A copy of this work instruction can be provided by the DCC, upon request.
4. When all documents are received, the DCC will review and work with the study team to resolve any missing elements. Any missing documents may delay registration. A participant failing to meet all requirements will not be registered and the study team will be immediately notified.
5. The DCC will send a Confirmation of Registration Form, including the Subject Study Number and cohort assignment to:
    - The study team: Site Lead Investigator, treating physician/ sub-investigator, protocol nurse, CRC and pharmacy (as needed).
    - The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
6. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore. The DCC will register non-COH patients in OnCore.

4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment.

For non-COH sites, the reason for screen failure will be documented in the registration coversheet (Appendix D) and submitted to the DCC.

Issues that would cause treatment delays should be discussed with the Study Principal Investigator.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a multicenter, open-label, phase 2 clinical trial of polatuzumab vedotin plus rituximab, ifosfamide, carboplatin, and etoposide (PolaR-ICE), followed by single agent polatuzumab vedotin (Pola) consolidation post-ASCT, for patients with DLBCL who are refractory or relapsed after frontline therapy.

The trial consists of a:

- **Safety Lead-in stage** to evaluate safety/tolerability of PolaR-ICE (Section 5.4.) and
- **Phase 2 stage** to evaluate anti-tumor activity of the regimen in the study population (Section 5.5).

For both Salvage and Consolidation, each cycle will be 21 days. During Salvage, patients will receive 2-3 cycles of PolaR-ICE. Participants with objective response (CR or PR) following Salvage will be eligible to proceed to autologous stem cell transplantation (ASCT), prior to continuing with 3-4 cycles of single-agent Pola Consolidation. ASCT will be performed according to institutional standards. See Section 5.6 and Section 5.7 for details.

Participants who end protocol therapy will undergo follow-up (Section 5.11). Windows for all assessments and treatments are detailed in Section 10.

5.2 Salvage and Consolidation: Treatment Cycle Definition

In the absence of a delay due to toxicity, each treatment cycle lasts 21 days with a ± 3 day window during both Salvage and Consolidation.

- **Salvage PolaR-ICE** (Section 5.6):
  - Day 1 of each cycle will be defined as the first day of administration of Pola.
  - If Pola is not administered, then Day 1 will be defined as the day of administration of rituximab.
- **Consolidation Pola** (Section 5.7):
  - Day 1 of each treatment cycle is defined by the day of administration of Pola.

5.3 Treatment Plan

The treatment plan for the Safety Lead-in and Phase 2 cohorts is as follows (Table 5.3).

Treatment may be given on an inpatient or outpatient basis.

The maximum number of Pola-containing cycles of therapy is 6 (See Sections 5.6 and 5.7).

Table 5.3 Treatment Regimen and Schedule

Notes:

- For rituximab and G-CSF, the use of biosimilars is allowed.
- For the drugs that are given as standard of care (i.e. R-ICE), the schedule (e.g. day of drug administration), and order of drug administration may be modified for any component of R-ICE at the investigator's discretion/ per institutional standards. In addition, dose modifications/ discontinuation of ifosfamide, carboplatin, and etoposide, whether or not they are due to toxicity are permitted at the investigator's discretion/ per institutional standards.

	SALVAGE - PolaR-ICE ‡ (Section 5.6)				
	Agent	**Dose**	**Route**	**Schedule (Days within each 21-day cycle)**	**Maximum # Cycles**
R-ICE **(Inpatient Schedule)****	Rituximab	375 mg/m²	IV	Day 1	2-3
	Etoposide	100 mg/m²	IV	Days 1-3	
	Carboplatin	AUC 5 (750 mg max)	IV	Day 2	
	Ifosfamide **	5000 mg/m²	IV	Day 2	
	Polatuzumab Vedotin (Pola)	**Safety Lead-in:** • ***Dose Level 1: 1.8 mg/kg** • Dose Level -1: 1.4 mg/kg (Section 5.4) **Phase 2:** Tolerable dose from Safety Lead-in (Section 5.5)	IV	Day 1	2-3

	CONSOLIDATION - Pola ‡‡ (Section 5.7)				
	Agent	**Dose**	**Route**	**Schedule (Days within each 21-day cycle)**	**Maximum # Cycles**
	Polatuzumab Vedotin (Pola)	**1.8 mg/kg**	IV	Day 1	3-4

* ***Starting dose is Dose Level 1.***

** ***Outpatient treatment is allowed*** and schedule is similar to Inpatient schedule, except for ifosfamide which will be given at a dose of 1670 mg/m² on Days 1-3 (instead of 5000 mg/m² on Day 2). Ifosfamide is always given with Mesna, according to institutional standards (Section 5.14).

‡ ***G-CSF prophylaxis*** should be administered with each PolaR-ICE Salvage cycle. The schedule and G-CSF formulation are at the investigator's discretion.

‡‡ For participants with ***objective response*** (CR or PR).

5.4 Safety Lead-In Cohort

During the Safety Lead-in, up to 5-16 evaluable participants will be enrolled using a design that is slightly modified from the IQ rolling 6 design.[7] (see Section 12 for details). The starting dose for polatuzumab vedotin will be 1.8 mg/kg in combination with R-ICE (Table 5.3). Unacceptable toxicities (defined in Section 11.2) will be evaluated during the first 2 cycles of PolaR-ICE Salvage therapy.

In the event the initial starting polatuzumab vedotin dose is not tolerated (2+ patients with unacceptable toxicity out of ≤6, 3+/7, or 3+/8 evaluable participants), a polatuzumab vedotin dose of 1.4 mg/kg (Dose Level -1) will be explored in an additional up to 8 evaluable participants. If Dose Level -1 is not tolerated, the study will be stopped.

5.5 Phase 2 Cohort

The tolerable dose of polatuzumab vedotin established during the Safety Lead-in will be used for the Phase 2 portion (Table 5.3). Participants treated at the final dose level deemed tolerable for Phase 2 during the Safety Lead-in will be included in the Phase 2 portion of the study if they are evaluable for response. Between 20-40 patients will be enrolled using a two-stage design (see Section 12 for details).

5.6 Salvage (PolaR-ICE)

- See Section 5.14 regarding G-CSF administration as supportive care.
- 2-3 cycles of PolaR-ICE:
  - All patients are planned to receive 2 cycles of PolaR-ICE.
  - Patients with PR after 2 cycles will receive an additional cycle of PolaR-ICE (3 cycles total). Patients with CR or SD after 2 cycles may receive an additional cycle of PolaR-ICE (3 cycles total) at the treating physician's discretion.
- If one agent is discontinued due to toxicity, then the participant may continue to receive the other protocol therapy agents. Note: if an agent is discontinued, administration of R-ICE should be prioritized since it is the standard of care and as the use of polatuzumab vedotin as part of salvage therapy remains investigational.

Timing and windows for imaging are detailed in Section 10.0.

5.7 Consolidation (Polatuzumab Vedotin Single-Agent)

NOTE: Participants **must meet criteria** in Section 5.7.1 to initiate Consolidation.

- See Section 5.14 regarding G-CSF administration as supportive care.
- 3-4 cycles of Pola:
  - Patients who received 2 cycles of PolaR-ICE during Salvage will receive 4 cycles of Pola Consolidation.
  - Patients who received 3 cycles of PolaR-ICE during Salvage will receive 3 cycles of Pola Consolidation.

  The maximum number of Pola-containing cycles of therapy is 6.
- Initiate after autologous stem cell transplantation (ASCT). Stem cell mobilization and collection and ASCT will be performed per institutional standards.
- Initiate Consolidation between Day + 30 and Day + 60 post-ASCT. A delay of up to Day + 75 is permitted following consultation with the Study PI for certain criteria (see Section 5.7.1 below). Screening may initiate 21 days after ASCT.

Timing and windows for imaging are detailed in Section 10.0.

5.7.1 Criteria to Receive Consolidation Polatuzumab Vedotin

Participants must meet the below criteria to receive Consolidation therapy with single-agent Pola after completing PolaR-ICE Salvage. Criteria must be met within 28 days of starting Consolidation therapy, except where otherwise specified (labs).

Criteria to be met in order to initiate Consolidation with polatuzumab vedotin	Action if criterion to the left is NOT met
1. Achieved objective response per 2014 Lugano Classification at end of Salvage	Discontinue protocol therapy.
2. No ≥ Grade 2 peripheral neuropathy	<u>For Grade 2 or 3:</u> · Wait until toxicity improves to ≤ Grade 1. · Administer Pola consolidation at the permanently reduced dose of **1.4 mg/kg**. If patient was already at 1.4 mg/kg during salvage, discontinue protocol therapy. Following consultation with Study PI delay initiation of Consolidation up to Day +75 post-ASCT may be permitted. <u>For Grade 4:</u> Discontinue protocol therapy.
3. Absence of unrelated toxicity not present at baseline that might adversely affect participation/ administration of polatuzumab vedotin	Discontinue protocol therapy.
4. Recovered from ASCT toxicities Including: outpatient status, able to drink and eat normally, and do not need intravenous hydration prior to Cycle 1 Day 1 of Consolidation therapy	Following consultation with Study PI delay initiation of Consolidation up to Day +75 post-ASCT may be permitted.
5. Will initiate treatment between Day +30 and Day +60 post-ASCT	
6. ECOG ≤ 2 within the screening period	
7. ANC ≥ 1,000/mm^3 within 14 days prior to Day 1 of Consolidation	
8. Platelets ≥ 75,000/mm^3 within 14 days prior to Day 1 of Consolidation	
9. Total serum bilirubin ≤ 1.5X upper limit of normal (ULN), **OR** if Gilbert's disease: ≤ 3X ULN, within 14 days prior to Day 1 of Consolidation	
10. AST ≤ 2.5 x ULN, **OR** if hepatic involvement by lymphoma: AST ≤ 5 x ULN, within 14 days prior to Day 1 of Consolidation	
11. ALT ≤ 2.5 x ULN, **OR** If hepatic involvement by lymphoma: ALT ≤ 5 x ULN, within 14 days prior to Day 1 of Consolidation	
12. Creatinine clearance of ≥ 40 mL/min within 14 days prior to Day 1 of Consolidation	
13. No active ≥ Grade 3 infection within 14 days prior to Day 1 of Consolidation	

Criteria to be met in order to initiate Consolidation with polatuzumab vedotin	Action if criterion to the left is NOT met
14. No other active malignancy requiring therapy. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer.	Discontinue protocol therapy.
15. No symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), cerebrovascular event/stroke or myocardial infarction within the last 6 months	Discontinue protocol therapy.
16. No central nervous system involvement by lymphoma, including leptomeningeal involvement	Discontinue protocol therapy.
17. No history of or current progressive multifocal leukoencephalopathy (PML)	Discontinue protocol therapy.

5.8 Agent Administration

Refer to **Section 5.14** for **supportive care**, including **mandatory prophylaxis for infusion-related reactions** and **growth factor support.**

Note: For the drugs that are given as standard of care (i.e. R-ICE), the schedule (e.g. day of drug administration), and order of drug administration may be modified for any component of R-ICE at the investigator's discretion/ per institutional standards. In addition, dose modifications/ discontinuation of ifosfamide, carboplatin, and etoposide, whether or not they are due to toxicity are permitted at the investigator's discretion/ per institutional standards.

5.8.1 Order of drug administration on Days 1 during Salvage

Rituximab will be administered first. Once the rituximab infusion is completed, patients are to be observed for 30 min before the start of the next infusion. Pola will be administered next (follow guidelines in Section 5.8.2). ICE will be administered as per institutional standards.

5.8.2 Polatuzumab vedotin

Administer the initial dose of polatuzumab vedotin over 90 min (+/- 10 min). Monitor patients for infusion-related reactions during the infusion and for a minimum of 90 min following completion of the initial dose. **If the initial infusion was well tolerated**, the subsequent doses may be administered over 30 min (+/- 10 min) and patients should be monitored during the infusion and for at least 30 min after completion of the infusion.

Dosing should be based on the patient's baseline weight (C1D1, pre-dose). Doses will be adjusted for patients who experience a ≥10% change in weight during the study. Rounding is permissible according to institutional standards.

5.8.3 Rituximab, Ifosfamide, Carboplatin, Etoposide (R-ICE)

Administer R-ICE per institutional standards. Inpatient or outpatient administration is allowed. Dosing should be based on the patient's baseline height and weight (C1D1, pre-dose) or per institutional standards. Doses will be adjusted for patients who experience a ≥10% change in weight during the study. Rounding is permissible according to institutional standards.

Mesna will be given with ifosfamide according to institutional standards.

5.9 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see Section 10.

Note: Initiate a new cycle after all procedures/safety assessments have been completed.

5.9.1 Infusion-related reactions

- Infusion or hypersensitivity reactions may occur to polatuzumab vedotin or R-ICE.
- If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions.
- Refer to Section 5.14 for infusion-related reaction/hypersensitivity guidelines.

5.9.2 Peripheral neuropathy

- Patients receiving polatuzumab vedotin may develop peripheral neuropathy (sensory and/or motor).
- Patients receiving study treatment should be monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, or neuropathic pain.
- Refer to Section 7.1 for dose modification guidelines.

5.10 Duration of Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy (Salvage and Consolidation) until one of the below criteria are met:

- Confirmed Disease progression per 2014 Lugano Classification
- Participant unable to proceed with Consolidation
- Completed protocol therapy (Salvage and Consolidation)
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
  - **Note:** If one agent is discontinued due to toxicity, then the participant may continue to receive the other study agents
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy (See Section 17.5)

Once a participant meets criteria for removal from protocol therapy, the participant should then proceed to follow-up assessments (Section 5.11).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.11 Follow-Up

All participants who end protocol therapy will enter follow-up for 2 years.

NOTE: Assessments may be combined if the windows for the two visits overlap.

Follow-up is comprised of:

- **Safety Follow-up**- 30 days post-last dose of protocol therapy.

- **Note** the period for safety follow-up will be extended until stabilization or resolution for all reportable AEs (per the agreement of the Study PI) and accompanying follow-up safety report.
- **Response Follow-up**- for those who have yet to have disease progression.
- **Survival Follow-up**- for all participants who have progressed OR completed Active Response Follow-Up OR initiated a new anti-lymphoma therapy. This follow-up will be performed typically via medical record review. It will entail (a) Disease status (for those who have yet to progress) (b) Vital status (all participants).

Assessment time points and windows are detailed in Section 10.

5.12 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and follow-up after protocol treatment)
- Withdrawal of consent (See Section 17.5)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.13 Prohibited and Concomitant Therapies/Medications

5.13.1 Allowed concomitant medications

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded in the eCRF and documented in the Electronic Health Record/medical record.

5.13.2 Prohibited medications/ therapies

- Prohibited from **Day 1 of protocol therapy until end of protocol therapy** (last day of study agent or decision to end study agent(s) whichever occurs later).

- Herbal and natural remedies
- Other investigational therapy
- Other concurrent systemic anti-cancer therapy: chemotherapy, biological response modifiers, hormone therapy, surgery, palliative radiation therapy, or immunotherapy.

- Prohibited during Salvage:

- Strong CYP3A4 inducer or inhibitor. A washout period of 10 days is required before start of Salvage therapy.

- Exception post- Salvage but prior to Consolidation with polatuzumab vedotin:

- Consolidation ASCT**.**

5.14 Supportive care

With the exception of prohibited therapies (Section 5.13), participants should receive prophylactic or supportive as clinically indicated per institutional policies.

Prophylaxis for infusion-related reactions

- Patients should be pre-medicated with at least an anti-histamine and antipyretic (e.g. 50-100 mg diphenhydramine, 500-1000 mg oral acetaminophen) prior to all rituximab and polatuzumab vedotin infusions, per institutional standards.
- If not already pre-medicated for rituximab administration, administer an antihistamine and antipyretic at least 30 to 60 minutes prior to Pola infusion for potential infusion-related reactions.

Blood products and growth factors

- *Platelet and/or red blood cell supportive growth factors or transfusions*
  - Permitted when applicable. For growth factors, the use of biosimilars is allowed.
- *Colony stimulating factors (CSFs)* (The use of biosimilars is allowed).
  - **Salvage:** All patients should receive G-CSF with each PolaR-ICE cycle. The schedule and G-CSF formulation are per investigator discretion.
  - **Consolidation**: Per investigator's discretion and institutional practice.

Anti-emetic prophylaxis

- Routine anti-emetic prophylaxis regimen should be administered per institutional standards.

Prophylaxis for hemorrhagic cystitis

- Mesna is to be administered with ifosfamide according to institutional standards (e.g. 5000 mg/m^2 on Day 2 (inpatient schedule) or 1670 mg/m^2 on Days 1-3 (outpatient schedule)).

Corticosteroids

- *Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption)*
  - Permitted
- *Systemic corticosteroids*
  - Physiologic replacement doses permitted even if > 10 mg/day prednisone or equivalent.
- *Brief course of corticosteroids (< 3 weeks)*
  - Permitted for prophylaxis (e.g. contrast dye allergy)
  - Permitted for treatment of non-autoimmune conditions (e.g, delayed-type hypersensitivity reaction caused by contact allergen)

Management of infusion related reactions

- Grade 1-2:
  - Slow or hold infusion
  - Give supportive treatment*****
  - Upon symptom resolution, may resume infusion (rate escalation at the investigator's discretion******)
    Note: for Grade 2 wheezing or urticaria, patient must be premedicated for any subsequent doses. If symptoms recur, the infusion must be stopped immediately and study drug permanently discontinued.
- Grade 3:
  - Discontinue infusion
  - Give supportive treatment*****
  - Upon symptom resolution, may resume infusion (rate escalation at the investigator's discretion****)**
    Note: if the same adverse event recurs with same severity, treatment must be permanently discontinued.
    Note: for Grade 3 hypotension or fever, patient must be premedicated before re-treatment. If symptoms recur, then study drug must be permanently discontinued.
    Note: if patient has Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence, study drug must be permanently discontinued.

- Grade 4:
  - Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue study drug.

***** Supportive treatment: patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the previous 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g. 100 mg IV prednisolone or equivalent), and/or bronchodilators. Patients with hypotension who require vasopressor support must be permanently discontinued from study drug.
****** Infusion rate escalation after re-initiation: upon complete resolution of symptoms, the 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 50mg/hour every 30 minutes.

P-gp inhibitors

- Closely monitor for AEs when administered concomitantly with polatuzumab vedotin.

Anti-viral and anti-pneumocystis prophylaxis

- Routine anti-viral (coverage for HSV and VZV) and anti-pneumocystis prophylaxis is required beginning at the initiation of study treatment and continuing for at least 6 months after completion of study treatment, per institutional standards. If clinically indicated, anti-infective prophylaxis for other infectious agents is permitted. For patients who proceed to AHCT, continue prophylaxis for at least 9 months after AHCT. If prophylaxis is held, the reasoning (e.g. renal dysfunction) must be documented.

Intrathecal prophylactic treatment for cerebral/meningeal disease

- Permitted at the discretion of the investigator

Tumor lysis syndrome (TLS) prophylaxis and management

- Permitted at the discretion of the investigator, per institutional standards
  For patients that are considered at risk for TLS [e.g. bulky disease, or high LDH (≥ 1000 IU/L) at baseline, or high uric acid (≥ 7 mg/dL) at baseline], allopurinol (300 mg po daily, dose adjusted per renal function) may be given. If a diagnosis of TLS is established, monitoring and multi-disciplinary management will be per institutional practice.

6.0 ANTICIPATED ADVERSE EVENTS

6.1 Polatuzumab vedotin

The Investigator's Brochure (IB) is the primary source for safety information. Refer to the most recent IB, which is updated periodically, for current information on polatuzumab vedotin.

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

Table 6.1 (polatuzumab vedotin IB V11, October 2019) lists all expected serious adverse drug reactions (SADRs) for polatuzumab vedotin. These SADRs were selected based on individual and aggregate assessment, medical review, and prior reports of the adverse reactions in clinical trials. Frequencies are based on pooled clinical trial data and/or single clinical trial data using only related serious adverse events as noted.

Table 6.1 Serious adverse drug reactions (SADRs) to polatuzumab vedotin in B-cell lymphomas including indolent non-Hodgkin lymphoma and diffuse large B-cell lymphoma considered expected for safety reporting purposes

System Organ Class	SADRs	(Cumulative clinical trial exposure (N=635)		
		All SADRs N* (%)	Fatal SADRs N* (%)	Life-threatening SADRs N* (%)
Blood and lymphatic disorders	Leukopenia	2 (0.3)	n/a	n/a
	Febrile neutropenia	43 (6.7)	n/a	n/a
	Neutropenia	11 (1.7)	n/a	n/a
Nervous system disorders	Peripheral motor neuropathy	3 (0.5)	n/a	n/a
	Peripheral sensory neuropathy	3 (0.5)	n/a	n/a
Infections and infestations	Pneumonia	10 (1.57)	n/a	n/a
Gastro-intestinal disorders	Abdominal pain	2 (0.3)	n/a	n/a
	Diarrhea	9 (1.4)	n/a	n/a
	Vomiting	2 (0.3)	n/a	n/a
General disorders and administration	Pyrexia	8 (1.3)	n/a	n/a

n/a = fatal or life-threatening SADRs are not considered expected.
All fatal or life-threatening SADRs are considered unexpected for regulatory purposes.
N* = number of patients who experienced the SADR.

Table 6.2 summarizes commonly reported reactions in study GO29365 (NCT02257567) where Pola was combined with chemotherapy.

Table 6.2 Adverse reactions occurring in >10% of patients with relapsed or refractory DLBCL and ≥5% more in the polatuzumab vedotin (Pola) plus bendamustine and rituximab (BR) product group.

Adverse Reactions by Body System	Pola + BR (n=45) All Grades (%)	BR (n=39) All Grades (%)
Blood and Lymphatic System Disorders		
Neutropenia	49	44
Thrombocytopenia	49	33
Anemia	47	28
Lymphopenia	13	8
Nervous System Disorders		
Peripheral neuropathy	40	8
Dizziness	13	8
Gastrointestinal Disorders		
Diarrhea	38	28
Vomiting	18	13
General Disorders		
Infusion-related reaction	18	8
Pyrexia	33	23
Decreased appetite	27	21
Infections		

Adverse Reactions by Body System	Pola + BR (n=45) All Grades (%)	BR (n=39) All Grades (%)
Pneumonia	22	15
Upper respiratory tract infection	13	8
Investigations		
Weight decreased	16	8
Metabolism and nutrition disorders		
Hypokalemia	16	10
Hypoalbuminemia	13	8
Hypocalcemia	11	5

Other clinically relevant adverse reactions (<10% or with a <5% difference) in recipients of polatuzumab vedotin plus BR included:

- **Blood and lymphatic system disorders:** pancytopenia (7%)
- **Musculoskeletal disorders:** arthralgia (7%)
- **Investigations:** hypophosphatemia (9%), transaminase elevation (7%), lipase increase (7%)
- **Respiratory disorders:** pneumonitis (4.4%)

6.2 Rituximab

The most common (≥25%) adverse reactions in clinical trials for NHL and CLL were infusion reactions, fever, lymphopenia, chills, infection, asthenia, and neutropenia.

According to the package insert for rituximab, rituximab can cause:

- *Infusion reactions:* Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.
- *Severe mucocutaneous reactions:* These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure.
- *Hepatitis B virus reactivation:* Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab.
- *Progressive Multifocal Leukoencephalopathy (PML):* JC virus infection resulting in PML and death can occur in rituximab-treated patients with hematologic malignancies.
- *Tumor lysis syndrome:* Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12-24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells (≥25,000/mm3) or high tumor burden, confers a greater risk of TLS.
- *Infections:* Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab-based therapy.
- *Cardiac arrhythmias and angina*
- *Renal toxicity*
- *Bowel obstruction and perforation*

- *Cytopenias*

6.3 Ifosfamide

In clinical trials of ifosfamide monotherapy, the most common (≥10%) adverse reactions were alopecia, nausea/vomiting, leukopenia, anemia, CNS toxicity, hematuria, and infection.

According to the package insert for ifosfamide, ifosfamide can cause:

- *Myelosuppression:* Can be severe and lead to fatal infections.
- *Neurotoxicity:* Severe and fatal neurotoxicity can occur. Carefully monitor the patient for CNS toxicity and other neurotoxic effects.
- *Urotoxicity:* Severe nephrotoxicity with renal failure and death can occur. Monitor for nephrotoxicity with serum and urine chemistries. Mesna should be used to reduce hemorrhagic cystitis.
- *Cardiotoxicity:* Arrhythmias, other ECG changes, and cardiomyopathy can occur and result in death. Use with caution in patients with cardiac risk factors and in patients with preexisting cardiac disease. The risk of cardiotoxicity is dose dependent.
- *Pulmonary toxicity:* Interstitial pneumonitis, pulmonary fibrosis, and other forms of pulmonary toxicity with fatal outcomes can occur. Monitor for signs and symptoms of pulmonary toxicity and treat as clinically indicated.
- *Secondary malignancies* as late sequelae have occurred.
- *Veno-occlusive Liver Disease.*
- *Pregnancy:* Can cause fetal harm. Women should not become pregnant and men should not father a child during therapy.
- *Effects on Fertility.* Sterility may be irreversible in some patients.
- *Anaphylactic/anaphylactoid reactions* have been reported.
- *Impairment of wound healing.*
- *Nursing:* Ifosfamide is excreted in breast milk.

6.4 Carboplatin

According to the package insert for carboplatin, carboplatin can cause:

- *Hematologic Toxicity:* Bone marrow suppression is the dose-limiting toxicity of carboplatin. Thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of the patients; neutropenia with granulocyte counts below 1000/mm^3 occurs in 16% of the patients; leukopenia with WBC counts below 2000/mm^3 occurs in 15% of the patients. The nadir usually occurs about day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm^3; 74% have neutrophil counts above 2000/mm^3; 67% have leukocyte counts above 4000/mm^3.

  Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Transfusions have been administered to 26% of the patients treated with carboplatin.

  Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.

- *Gastrointestinal Toxicity:* Vomiting occurs in 65% of the patients and in about one-third of these patients it is severe. Nausea alone occurs in an additional 10 to 15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Emesis was increased when

carboplatin was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6%; and constipation, also in 6%.

- *Neurologic Toxicity:* Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin with mild paresthesias occurring most frequently.

  Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.

- *Nephrotoxicity:* Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about one-half of them were reversible.

- *Hepatic Toxicity:* The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients.

- *Electrolyte Changes:* The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%.

- *Allergic Reactions:* Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum- containing compounds, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

- *Injection Site Reactions:* Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.

- *Other Events:* Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely.

  Malaise, anorexia and hypertension have been reported as part of postmarketing surveillance.

- *Pregnancy:* Carboplatin may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women.

6.5 Etoposide

The most common adverse reaction is neutropenia.

According to the package insert for etoposide, etoposide can cause:

- *Myelosuppression:* Etoposide causes myelosuppression that results in thrombocytopenia and neutropenia. Fatal infections and bleeding have occurred.

- *Secondary Leukemias:* Secondary leukemias have occurred with long term use of etoposide.

- *Hypersensitivity Reactions:* Etoposide can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis.
- *Embryo-Fetal Toxicity:* Based on animal studies and its mechanism of action, etoposide can cause fetal harm when administered to a pregnant woman.
- *Lactation:* There is no information regarding the presence of etoposide in human milk or its effects on breastfed infant milk production. There is a potential for serious adverse reactions in nursing infants from etoposide.
- *Infertility:* Etoposide may result in permanent loss of fertility.
- *Gastrointestinal Toxicity:* Nausea and vomiting are the major gastrointestinal toxicities. The severity of nausea and vomiting is generally mild to moderate, with treatment discontinuation required in 1% of patients.

Other clinically important adverse reactions in clinical trials were:

- *Gastrointestinal:* abdominal pain, constipation, dysphagia.
- *General:* fever.
- *Ocular:* transient cortical blindness, optic neuritis.
- *Respiratory:* interstitial pneumonitis/pulmonary fibrosis.
- *Skin:* pigmentation, radiation recall dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.
- *Neurologic:* seizure, aftertaste.
- *Hepatobiliary disorder:* hepatotoxicity.

7.0 DOSE DELAY / MODIFICATION GUIDELINES

7.1 Dose Delay / Modification

- Toxicities will be graded using the NCI CTCAE v 5.0.
- Baseline values are from the last values obtained prior to treatment.
- When attribution of a toxicity is unclear due to overlapping toxicity profiles of the drugs included in protocol therapy (e.g. hematologic, infections, febrile neutropenia), administration of R-ICE should be prioritized since it is the standard of care and as the use of polatuzumab vedotin as part of salvage therapy remains investigational. Therefore, dose reduction/delay of polatuzumab vedotin should be attempted before dose reduction/delay of agents included in R-ICE.
- If one agent is held due to toxicity for a given cycle, administration of the delayed agent should resume once the toxicity is resolved on the same schedule with the next cycle of combination therapy.
- If one agent is permanently discontinued, then the participant may continue with other agent(s). Refer to Section 5.6.
- If all agents are held together due to toxicity and the delay lasts > 6 weeks, then protocol therapy will be discontinued.
- **Polatuzumab vedotin**
  - Dose delay/modification guidelines for polatuzumab vedotin-related toxicity are described in Table 7.1.
  - If a delay due to toxicity lasts > 6 weeks, permanently discontinue polatuzumab vedotin.
  - Doses reduced for polatuzumab vedotin-related toxicity should not be re-escalated without discussion with the Study PI.

- Dose reductions below 1.4 mg/kg are not permitted, and toxicities should be managed with dose delays or polatuzumab vedotin should be permanently discontinued.

- **R-ICE**
  - Dose modifications for rituximab are not permitted.
  - Dose modifications/ discontinuation of ifosfamide, carboplatin, and etoposide, whether or not they are due to toxicity are permitted at the investigator's discretion/ institutional standards.

Table 7.1 Dose Modifications for Polatuzumab Vedotin

Toxicity	Polatuzumab Vedotin Dose Management Guidelines
Peripheral Neuropathy	
Grade 1 *Asymptomatic; clinical or diagnostic observations only; intervention not indicated*	Continue at same dose level
Grade 2/3 *G2:Moderate symptoms; limiting instrumental ADL* *G3: Severe symptoms; limiting self care ADL; assistive device indicated*	Withhold until toxicity resolves to ≤ Grade 1, then resume treatment at 1.4 mg/kg See above for guidance if the participant dose is already 1.4 mg/kg.
Grade 4 *Life-threatening consequences; urgent intervention indicated*	Discontinue polatuzumab vedotin
Infusion Related Reaction	
Grade 1/2 *G1: Mild transient reaction; infusion interruption not indicated; intervention not indicated* *G2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs*	• Refer to Section 5.14 for supportive care • Maintain same dose level during subsequent cycles
Grade 3 *Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae*	• Refer to Section 5.14 for supportive care • Polatuzumab vedotin may be restarted at the same dose level per Investigator's discretion with prophylaxis premedication (Section 5.14). Otherwise, permanently discontinue polatuzumab vedotin.
Grade 4 *Life-threatening consequences; urgent intervention indicated*	• Refer to Section 5.14 for supportive care • Discontinue polatuzumab vedotin
Other unspecified non-hematologic	
Grade 1/2	Continue at same dose level
Grade 3	Withhold dose until toxicity is ≤ Grade 2, then resume treatment at the same dose level. – **Note:** Patients who develop Grade 3 electrolyte laboratory abnormalities may continue study treatment without interruption.
Grade 4	Discontinue polatuzumab vedotin – **Note:** Patients who develop Grade 4 electrolyte laboratory abnormalities should have correction to Grade 3 prior to treatment resumption at the same dose.
Hematologic	
Grades 1-2	Continue at same dose level
Grade 3-4	• Withhold until toxicity resolves to ≤ Grade 2

Toxicity	Polatuzumab Vedotin Dose Management Guidelines
	– **NOTE:** Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption • Growth factor support (G-CSF or GMCSF) for neutropenia should be considered for subsequent cycles, if not already given. • *First occurrence:* resume at same dose level • *Second occurrence:* - For any toxicity (including neutropenia despite the use of G-CSF), dose reduction to 1.4 mg/kg should be considered - If the participant is already receiving 1.4 mg/kg, dose discontinuation should be considered.

8.0 AGENT INFORMATION

8.1 Polatuzumab vedotin

Polatuzumab vedotin is FDA-approved for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, in combination with bendamustine and a rituximab product, after at least two prior therapies.

8.1.1 Other names

Polivy, DCDS4501A.

8.1.2 Description

Polatuzumab vedotin is an ADC that contains a humanized IgG1 anti-CD79b monoclonal antibody (MCDS4409A) and a potent antimitotic agent (MMAE) linked through a protease-cleavable linker. An average of 3.5 molecules of MMAE are attached to each antibody molecule.

Polatuzumab vedotin is approved by the FDA for the treatment of diffuse large B-cell lymphoma, relapsed or refractory, in combination with bendamustine and a rituximab product, after at least 2 prior therapies.

Please refer to the investigator brochure for a detailed description.

8.1.3 Mechanism of action

Polatuzumab vedotin targets the cell surface antigen CD79b which is expressed on mature B cells, with the exception of plasma cells. Following internalization, the ADC is cleaved by lysosomal enzymes to release MMAE and other potentially active catabolites. Free MMAE binds to the microtubule network and subsequently leads to cell cycle arrest and apoptosis.

8.1.4 Pharmacokinetics and Metabolism

ADC Vd:	3.15 L
MMAE protein binding:	71-77%
MMAE Metabolism:	Substrate of CYP3A4 and P-gp
ADC Total body excretion:	0.9 L/day
ADC Elimination half-life:	12 days
MMAE Elimination half-life	4 days

8.1.5 Toxicology

8.1.5.1 Expected human toxicities

See Section 6.1 for a detailed list of anticipated AEs.

8.1.5.2 Potential effects on fertility, pregnancy and lactation

Adverse effects on human reproduction and fertility are anticipated with the administration of polatuzumab vedotin based on the mechanism of action of the cytotoxic component of polatuzumab vedotin as a microtubule inhibitor. Given that MMAE, the cytotoxic component of polatuzumab vedotin, is a microtubule inhibitor targeting rapidly dividing cells and is a known teratogen, polatuzumab vedotin is expected to be teratogenic and embryotoxic.

It is not known whether polatuzumab vedotin can be found in sperm. Based on findings from animal studies, polatuzumab vedotin may impair male fertility. Individual patients seeking to preserve fertility should discuss the options available to them with their physicians prior to treatment initiation.

No clinical studies assessing the reproductive and developmental toxicity of polatuzumab vedotin have been conducted to date. It is not known whether polatuzumab vedotin can cross the placenta or cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. Therefore, polatuzumab vedotin should not be administered to pregnant women.

It is not known whether polatuzumab vedotin is excreted in human breast milk. Because many drugs are excreted in human milk and because of the potential for harm to nursing infants, polatuzumab vedotin should not be administered to nursing mothers.

8.1.6 Formulation

Polatuzumab vedotin is provided in 140 mg, white to grayish-white lyophilized powder for reconstitution, in single-use vials.

8.1.7 Handling, storage, dispensing and disposal

Store refrigerated at 2°C to 8°C in original carton to protect from light. Do not use beyond the expiration date. Do not freeze. Do not shake.

For polatuzumab vedotin reconstitution, dilution, and storage of diluted solutions, please refer to the USPI.

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

8.1.8 Administration

Administer polatuzumab vedotin as an intravenous infusion only.

Polatuzumab vedotin 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 a catheter.

Compatibility between polatuzumab vedotin and closed system transfer devices (CSTDs) or needle free transfer devices has not been assessed. If CSTDs or needle free transfer devices must be used to comply with site regulations, the site should be aware that their use may lead to the introduction of particles and may not allow the withdrawal of the labeled quantity of drug from the vial. Sites should perform a thorough visual inspection of the IV bag for particulates. In addition, sites must use a 0.2 or 0.22 µm polyethersulfone (PES) filter during infusion. The preparation should be discarded if particulates are observed in the IV bag.

Do not mix polatuzumab vedotin with, or administer as an infusion with, other medicinal products.

See Section 5.8.2 for administration guidelines.

8.1.9 Supplier

Polatuzumab vedotin will be supplied free of charge by Genentech.

8.1.10 Ordering

Sites will place orders for polatuzumab vedotin via the Genentech investigator initiated study drug supply request form.

Sites should place orders at least 2 weeks in advance.

8.1.11 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent using a drug accountability log.

8.1.12 Destruction and Return

The investigator is responsible for keeping accurate records of the clinical supplies received from Genentech or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures.

Destruction will be documented in a drug accountability log.

8.2 Rituximab, Etoposide, Ifosfamide, and Carboplatin (R-ICE)

Agents contained in the R-ICE regimen are approved by the FDA for use in treating patients with multiple types of cancer. Please refer to the package insert for a detailed description.

8.2.1 Other names

Rituximab: Rituxan

Etoposide: VePesid, Etopophos, Toposar (VP-16)

Ifosfamide: Ifex

Carboplatin: Paraplatin

8.2.2 Description and mechanism of action

R-ICE is a standard chemo-immunotherapy regimen consisting of rituximab, etoposide, ifosfamide, and carboplatin. Rituximab is a CD20-directed cytolytic antibody. Etoposide is a topoisomerase inhibitor. Ifosfamide is a nitrogen mustard alkylating agent. Carboplatin is a platinum-based antineoplastic agent with a mechanism of action that interacts with DNA to inferfere with DNA repair.

8.2.3 Pharmacokinetics and Metabolism

Refer to respective package inserts for additional information.

Ifosfamide:

Half-life:	Mean terminal t½ between 7-15 hours with single doses
Distribution:	0.64-0.72 L/kg
Protein binding:	low
Metabolism:	Hepatic

Elimination:	Urine (70-86%)

Ifosfamide is a substrate for both CYP3A4 and CYP2B6.

Carboplatin:

Half-life:	Initial t½ is 1.1-2 hours. Post-distribution t½ is 2.6-5.9 hours
Distribution:	16 L
Protein binding:	None
Elimination:	Urine (65-71%)

Etoposide:

Half-life:	Initial t½ is 1.5 hours. Mean terminal t½ is 4 to 11 hours
Distribution:	7-17 L/m^2
Protein binding:	94-98%
Metabolism:	Hepatic via CYP3A4
Elimination:	Urine (56%) within 120 hours; feces (44%) within 120 hours

8.2.4 Human Toxicity

See Sections 6.2 to 6.5.

8.2.5 Formulation

Refer to respective package inserts.

8.2.6 Storage

Rituximab, etoposide, ifosfamide, and carboplatin should be stored per their respective package insert.

8.2.7 Preparation and Handling

Rituximab, etoposide, ifosfamide, and carboplatin should be prepared and handled per their respective package insert and institutional standard.

8.2.8 Administration

See Section 5.8.3.

8.2.9 Supplier

Agents contained in the R-ICE regimen are commercially available and will be billed to patients and/or their third-party payer.

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Research Sample Collection and Dispensation

9.1.1 Correlative tumor tissue

9.1.1.1 Time points of Collection

Baseline tissue: Archival tissue from diagnostic tumor biopsies will be retrieved and submitted post-enrollment.

NOTE: If unavailable, exceptions may be granted with the lead study PI approval.

If safe and feasible, submission of left-over tissue from a standard of care tumor biopsy (fresh core or excisional biopsy) for participants who progress/relapse during study is encouraged.

9.1.1.2 Guidelines for archival specimens

Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:

- If tissue block is available submit:
  6 paraffin scrolls measuring 10 µm thick placed into a tube and frozen at -80° C
  AND
  10 x 5 µm thick unstained slides
- If tissue block is unavailable submit:
  20 x 5 µm thick unstained slides

9.1.1.3 Labeling of samples

Samples will be labeled with the COH protocol #, subject ID (issued by DCC), institution, date, time point of collection, and if applicable patient initials.

9.1.1.4 Sample shipment and receiving lab

Samples will either be taken to (COH only) or batch-shipped (non-COH sites) to COH Pathology Core. For all sites, please include the **Correlative Tissue form (Appendix E)** with your shipment.

Please note that samples should be **batch-shipped from non-COH sites on Monday to Wednesday** in time for receipt Tuesday to Friday. **Refer to Appendix F for tissue shipping details.**

9.1.2 Correlative blood

9.1.2.1 Overview and Time points

Peripheral blood will be collected prior to study treatment/procedures at the time points indicated in Table 9.1.2.1

Table 9.1.2.1 Overview of correlative blood studies

Time points of collection	Total volume collected	Tube type	Receiving laboratory	Type of analysis
• C1D1 • C2D1 • End of Salvage • C1D1 of Consolidation • End of Consolidation* • At Progression/Relapse	20 ml	Cell-free DNA BCT® (Streck)	APCF	ctDNA/MRD

APCF = COH Analytical Pharmacology Core Facility.

Cell-Free DNA BCT® (glass, 10 mL volume) tubes from Streck. Cat. No, as of April 2020, for a box of 100 tubes is: 218962.

* For this time point, correlative blood will be collected at the safety visit (30 days post-).

9.1.2.2 Labeling of blood samples

Label tubes with COH protocol #, subject ID (issued by DCC), institution, date and actual time point of collection (e.g. C1D1 for Day 1 of Cycle 1), and if applicable patient initials.

9.1.2.3 Collection and post-collection guidelines

Refer to Table 9.1.2.3 for collection and post-collection instructions.

Refer to **Appendix G** and **Appendix H** for blood collection form and blood shipping guidelines, respectively.

Table 9.1.2.3 Blood sample collection and post-collection instructions.

Tube Type	Collection details	Site of collection	Post-collection instructions
Cell-free DNA BCT® (Streck)*	1- Blood samples will be collected from an indwelling venous catheter or by venipuncture. ***Prevention of backflow:*** *(Because cell-free DNA BCT® contain chemical additives)* *a. Keep patient's arm in the downward position during the collection procedure.* *b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection.* *c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.* 2- Fill tube completely. 3- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. 4- **Do not freeze** samples. Store samples at 18-25°C until shipment.	COH Only	**Promptly** deliver the blood samples to the APCF, Shapiro room 1042.
		Non-COH Sites Only	Ship to APCF laboratory. See **Appendix H**. Include with shipment: • Blood sample collection form (**Appendix G**). Copy of latest CBC results (with differential) and date of test.

* Tubes are stable when stored at 2-30^{0}C through expiration date.

9.2 Laboratory Studies Performed

Please refer to Section 2.2.

10.0 STUDY CALENDAR

All assessments may increase in frequency as clinically indicated.

Protocol Activity	Screening [a]	Protocol therapy [b]								Follow-up (~2 years)		
		Salvage PolaR-ICE [c]					End of Salvage [h]	Consolidation Pola [d]				
		C1	C2		(C3)			C1	C2 C3 (C4)	Safety 30-days post [i]	Active 12 months & 24 months [j]	Survival [k]
		D1[e]	D1[e]	D15[g]	D1[e]	D15[g]		D1[e]	D1[e,f]			
Informed Consent	X											
Medical History	X											
Eligibility	X											
Registration	X											
Height	X											
Physical Exam [l] & Vital signs [m]	X	X	X		X		X	X	X	X		
ECOG Status (Appx. A)	X	X	X		X		X	X	X	X		
Con-med review	X	X	X		X		X	X	X	X		
AE Assessment	X	X	X		X		X	X	X	X		
Pregnancy [n]	X	X	X		X			X	X			
CBC w/diff, plt & Serum chemistry [p]	X [o]	X	X		X		X	X	X	X		
PT/INR and aPTT	X											
Correlative blood [q]		X	X				X	X		(X)		
Correlative tumor tissue	X [r]	---------- X [s] ----------										
Bone marrow biopsy/ aspirate	(X) [u]	---------- X [t] ----------										

Protocol Activity	Screening [a]	Protocol therapy [b]								Follow-up (~2 years)		
		Salvage PolaR-ICE [c]					End of Salvage [h]	Consolidation Pola [d]				
		C1	C2		(C3)			C1	C2 C3 (C4)	Safety 30-days post [i]	Active 12 months & 24 months [j]	Survival [k]
		D1[e]	D1[e]	D15[g]	D1[e]	D15[g]		D1[e]	D1[e,f]			
PET-CT	X			X		X				X [v]	X [v]	
Polatuzumab vedotin for **Salvage**		D1 of each cycle										
Rituximab		D1 of each cycle										
Etoposide		D1-3 of each cycle										
Carboplatin		D2 of each cycle										
Ifosfamide (+Mesna)		D2 (Inpatient) **or** D1-3 (Outpatient) of each cycle										
Criteria to initiate Consolidation								X				
Polatuzumab vedotin for **Consolidation**								X	X			
Survival status												X

a. Screening activities to occur within 28 days prior to start of protocol therapy except for laboratory assessments and bone marrow biopsy.

b. In the absence of treatment delay, each treatment cycle lasts 21 ± 3 days.

c. All patients will receive 2 cycles of PolaR-ICE. Patients with PR after 2 cycles will receive an additional cycle of PolaR-ICE (3 cycles total). Patients with CR or SD after 2 cycles may receive an additional cycle of PolaR-ICE (3 cycles total) at the treating physician's discretion.

d. Patients must meet the criteria to receive Consolidation Pola within timelines specified in Section 5.7.1. Patients who received 2 cycles of PolaR-ICE during Salvage will receive 4 cycles of Pola Consolidation. Patients who received 3 cycles of PolaR-ICE during Salvage will receive 3 cycles of Pola Consolidation. The maximum number of Pola-containing cycles of therapy is 6.

e. Activities to be performed within 72 hours prior to initiation of the cycle.

f. Evaluations performed within 14 days prior to start of Consolidation Day 1 may serve as Day 1 evaluations.

g. Day 15 assessments have a ± 7 day window.

h. End of salvage visit to occur within 30 days from last dose. Patients eligible for AHCT will then proceed to AHCT.

i. The Safety 30 days post-last dose assessments to occur 30 (±7) days post-last dose or, if > 30 days elapsed since last dose, within 7 days after decision to end treatment. Expedited reporting will occur during this period. Safety follow-up may be extended until resolution/ stabilization of reportable AEs.

j. For participants yet to progress, Active Follow-up will occur at 12 months (± 30 days) and 24 months (± 30 days) from the start of treatment until progression or the initiation of a new anti-lymphoma therapy.

k. Participants who end Active Follow-up will enter Survival Follow-up. Survival assessment to occur bi-annually or as requested by the Study PI via medical record review, review of social security registry, or telephone call.

l. *Standard physical exam* includes weight.

m. *Vital signs*: heart rate, blood pressure, respiration rate, and temperature.

n. *Women of child bearing potential*: Pregnancy serum or urine test. For the screening time point, pregnancy test must be performed within 7 days prior to start of protocol therapy.

o. *Screening laboratory assessments* to be performed within 14 days prior to start of protocol therapy.

p. *Serum chemistry* panel to include: glucose, Blood Urea Nitrogen (BUN), creatinine, uric acid, total protein, albumin, magnesium, bicarbonate, calcium, inorganic phosphorous, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT, AST, and LDH.

q. Refer to Section 9.1.2.

r. Archival tumor tissue to be submitted post-enrollment. **Note:** If unavailable, exceptions may be granted by the Study PI. Refer to Section 9.1.1.

s. If safe and feasible, submission of left-over tissue from a standard of care tumor biopsy (fresh core or excisional biopsy) for participants who progress/relapse during study is encouraged. Refer to Section 9.1.1.

t. Bone marrow biopsies will be performed only as clinically indicated, and to confirm CR.

u. Bone marrow biopsy will be performed only as clinically indicated.

v. CT in lieu of PET-CT is allowed if patient is in CR and CR was already confirmed by PET-CT.

11.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

11.1 Assessment of Response

Lymphoma response/progression will be evaluated using 2014 Lugano Classification (see Appendix B). [38]

Disease assessment will be performed by PET-CT. For patients in CR, diagnostic quality CT is acceptable at the end of consolidation and during active Follow-up. Assessment with PET-CT is required to confirm CR. Patients with bone marrow involvement at baseline must have a bone marrow biopsy performed to confirm CR (if applicable). After CR, additional bone marrow biopsy is only required if clinically indicated. Additional necessary restaging studies including dedicated CT scans or MRI, are permitted at the investigator's discretion. PET-CT and CT results will be read by a radiologist at each study site and investigator response assessment will be performed.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy be obtained whenever possible.

11.2 Primary Endpoint(s)

Unacceptable Toxicity: defined as any of the following events occurring during the first 2 cycles of treatment that is at least possibly related to study treatment:

- Any Grade 3 or higher non-hematologic toxicity that does not resolve to Grade 1 or better within 7 days with the exception of:
    - Grade 3 asymptomatic laboratory abnormalities, including lipase or amylase, that are not clinically relevant, not requiring hospitalization or delay of treatment
    - Grade 4 isolated electrolyte abnormalities that are not clinically significant including, but not limited to, hypo-or hyperglycemia, hypo-or hypernatremia, hypo-or hyperkalemia, hypo-or hypermagnesemia, or hypo-or hypophosphatemia, that resolve, with or without intervention, to Grade 2 in less than 72 hours
    - Grade 3 nausea, vomiting, or fatigue controlled with supportive measures (and does not require hospitalization, TPN, or tube feeding)
    - Grade 3 infusion reaction that resolves with appropriate management to Grade 1 or better within 24 hours
    - Alopecia of any grade
- Any Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding.
- Any Grade 4 neutropenia (despite the use of growth factor) or grade 4 thrombocytopenia (without clinically significant bleeding) that lasts > 21 days.
- Any Grade 4 anemia unexplained by underlying disease.
- Any treatment-related toxicity that delays cycle 2 treatment for >2 weeks.
- Any Grade 5 toxicity.

Complete response (CR) rate: defined as the proportion of response-evaluable participants (see Section 12.2) that achieve a CR after 2 cycles of PolaR-ICE therapy.

11.3 Secondary Endpoint(s)

Overall response rate (ORR): defined as the proportion of response-evaluable participants (see Section 12.2) that achieve a best response of either CR or PR at the end of PolaR-ICE therapy.

Progression-Free Survival (PFS): defined as the duration of time from start of protocol treatment to time of disease relapse/progression or death due to any cause, whichever occurs earlier. For patients who are alive and have not had disease relapse/progression at the last follow-up, it is censored at the time of last follow-up. If a patient starts non-protocol anti-lymphoma therapy without disease relapse/progression, it will be censored at the start of the non-protocol anti-lymphoma therapy.

Overall Survival (OS): defined as the duration of time from start of protocol treatment to time of death due to any cause. For patients who are alive at last follow-up, it will be censored at the time of last follow-up.

CR rate among patients who were PR at ASCT: defined as the proportion of patients that achieve CR after Pola consolidation among those who were PR at ASCT.

Stem cell mobilization failure rate: defined as the portion of patients who failed to collect adequate CD34 stem cells (within 2 attempts) among those who attempt stem cell collection.

11.4 Exploratory Endpoint(s)

Exploratory endpoints include ctDNA measures and other biomarkers.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a multicenter, single-arm Phase 2 study evaluating PolaR-ICE as initial salvage therapy before ASCT for relapsed and refractory DLBCL. PolaR-ICE salvage therapy will be given in 21-day cycles. Patients will first receive 2 cycles of PolaR-ICE; patients in CR after 2 cycles may proceed to ASCT or may receive a 3rd salvage cycle of PolaR-ICE at the treating physician's discretion. Patients in PR after 2 cycles will receive a 3rd salvage cycle of PolaR-ICE. Patients in SD after 2 cycles may receive a 3rd salvage cycle of PolaR-ICE at the treating physician's discretion. A patient may proceed to ASCT if patient is CR/PR after 3 cycles, otherwise the patient will go off protocol. After ASCT, patients who received 2 salvage cycles of PolaR-ICE will receive 4 cycles of single-agent Pola (21-day cycles) as consolidation therapy, while patients who received 3 salvage cycles of PolaR-ICE will receive 3 consolidation cycles of single-agent Pola.

The primary endpoint is complete response (CR) rate after 2 cycles of PolaR-ICE salvage therapy. Secondary endpoints include toxicities of PolaR-ICE salvage therapy, toxicities of single-agent Pola consolidation therapy, overall response rate to PolaR-ICE, the rate of stem cell mobilization and collection failure in patients who attempt stem cell collection, progression free survival, overall survival, and CR rate after Pola consolidation among patients who were PR at ASCT.

The first 5-16 patients will be monitored as part of the Safety Lead-in portion as described below in Section 12.1.1 to confirm the tolerable dose of PolaR-ICE. Once the tolerable dose level of PolaR-ICE is confirmed, the study will go into the Phase 2 portion with a 2-stage design and a total sample size of 40 patients for the Phase 2 response evaluation.

12.1.1 Safety Lead-in

Prior to formally initiating the Phase 2 response assessment, a patient safety lead-in portion will be conducted to ensure there are no unexpected toxicities with PolaR-ICE salvage therapy. The decision to open to Phase 2 will primarily be based on the number of safety lead-in patients experiencing unacceptable toxicities during the first 2 cycles of PolaR-ICE salvage, but will also take into consideration other data available at the time of decision making, including toxicities observed in cycle 3, the ability to

proceed to transplant after PolaR-ICE and delays due to study treatment-related toxicity between PolaR-ICE and transplant. The unacceptability toxicities are defined in Section 11.2. Patients evaluable for unacceptable toxicities during the Safety Lead-in are defined in Section 12.2.

During the safety lead-in portion of the study, a design that is slightly modified from the IQ rolling 6 design will be used.[7] In this design, up to 8 evaluable patients may be treated at each dose level, and the highest dose level with <33% evaluable patients having unacceptable toxicities will be considered tolerable with respect to unacceptable toxicities. Given the expected safety profile of PolaR-ICE, we adopt this design which may allow up to 6 patients at risk at any time instead of some other designs which allow up to 3 at risk. The rules of the proposed design are outlined below.

1) When there is no patient with unacceptable toxicities, accrual can continue for up to 8 patients with up to 6 patients at risk (i.e., under unacceptable toxicity observation) at the same time.

2) If there is no DLT in 5+ evaluable patients with no others at risk, (i.e., 0/5, 0/6, 0/7, or 0/8), the current dose level will be considered tolerable.

3) After 1 patient with unacceptable toxicity is reported, accrual can continue to up to 6 patients (i.e. <6 at risk); to accrue the 7^{th} or the 8^{th} patient, there must be ≤3 patients at-risk.

4) If there is 1 patient with unacceptable toxicity in 6-8 evaluable patients with no others at risk (i.e., 1/6, 1/7, or 1/8), the current dose level will be considered tolerable.

5) If there are 2 patients with unacceptable toxicities when ≤6 patients are treated, the current dose level will be considered intolerable (and dose de-escalated if at dose level 1).

6) If there are 2 patients with unacceptable toxicities when 7 or 8 patients are treated, accrual to this dose level will be on hold if there are still any patients at risk. If the rate of unacceptable toxicity is ≥33% (i.e., 2 out of ≤6, 3/7, or 3/8 evaluable), the current dose level will be considered intolerable (and the dose de-escalated if at dose level 1); if the rate of unacceptable toxicity is <33% (i.e., 2/7 or 2/8 evaluable), the dose level will be considered tolerable.

7) Any time 3+ patients with unacceptable toxicities occur, the current dose level will be considered intolerable (and dose de-escalated if at dose level 1).

12.1.2 Phase 2 design

The Phase 2 portion of the study adopts a two-stage design. Patients who were enrolled during the safety lead-in portion at the final dose level deemed tolerable for Phase 2 will also be included in the Phase 2 response evaluation if they are evaluable for response.

At the first stage, 20 patients will be enrolled. If <8 complete responses are seen, the accrual will be terminated. If at least 8 patients achieve a complete response, the trial will continue to the second stage. At the second stage, 20 additional patients will be entered. At the end of stage 2, if 21 or more patients out of the total 40 patients experience a complete response, the combination will be considered worthy of further study. If <21 patients experience a complete response then no further investigation of the combination is warranted.

The 2-stage design aims to differentiate between the null hypothesis (disappointing rate) of 40% CR rate and an alternative hypothesis (promising rate) of 60% CR rate. The null hypothesis of 40% CR rate is based on a large randomized study comparing R-ICE with R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) as salvage regimen followed by ASCT for relapsed/refractory DLBCL.[8] Similar complete

response rates were observed after 3 cycles of R-ICE (37%, n=197) vs. 3 cycles R-DHAP (40%, n=191). Therefore, we would consider a 40% CR rate a discouraging rate and 60% a promising CR rate for this regimen to merit further study. The design has a 1-sided type I error of 7.3% and a power of 87%. The expected sample size under the null hypothesis is 31.7, and the design has a 42% chance of early termination after Stage I if the true CR rate is 40%.

12.2 Evaluable Participants and Participant Replacement

- ***Evaluable for toxicity***: Patients who receive at least one dose of protocol therapy are evaluable for toxicity.
- ***Evaluable for unacceptable toxicity during Safety Lead-in***: Patients evaluable for unacceptable toxicity (defined in Section 11.2) are:

    1) Those who receive the full dose of Pola, the full doses of rituximab and carboplatin, and at least 67% of the doses of etoposide and ifosfamide during the first 2 cycles of Salvage, OR

    2) Those who experience any unacceptable toxicity during the first 2 cycles of Salvage regardless of actual dose of protocol therapy received.

  During safety lead-in, patients who are not evaluable for unacceptable toxicities will be replaced.

- ***Evaluable for response during Phase 2:***

  Evaluable patients are defined as eligible participants who have received at least one cycle of PolaR-ICE salvage therapy and have at least one disease evaluation post-baseline.

  Patients will be evaluable and be considered non-CR in the primary response evaluation if they discontinued study therapy prior to having a response assessment after 2 cycles of PolaR-ICE because of progressive disease or unacceptable toxicity (rather than due to withdrawal of consent or investigator decision). If a patient discontinues study treatment prior to the first response assessment after 2 cycles of PolaR-ICE due to progressive disease, the treating physician is encouraged to obtain imaging to confirm progression.

  During Phase 2 enrollment, participants who are not evaluable for response will be replaced and excluded from Phase 2 efficacy analyses, but will be included in the general toxicity analyses if they receive any protocol treatment.

12.3 Sample Size and Accrual Rate

The minimum study accrual will be 4 patients, when both dose levels are found to be not tolerable during the safety lead-in portion. The expected total sample size for the study is 40 evaluable patients, assuming that dose level 1 (starting dose level) is safe and passes the first stage response evaluation in Phase 2, and safety lead-in patients are also evaluable for response. However if dose level 1 is not tolerable and dose level -1 is tolerable, the study will need to accrue up to 48 evaluable patients for the safety lead-in and phase 2 evaluations. Accounting for up to 10% inevaluable patients for unacceptable toxicity evaluation during Safety lead-in or inevaluable for response during Phase 2, the maximum accrual for the study is estimated to be 53 patients. Given that this is a multicenter study including high-volume DLBCL centers, we anticipate completing study accrual within 24 months.

12.4 Monitoring for Stem Cell Mobilization Failure and Non-relapse Mortality after ASCT

The rate for failure to collect adequate CD34 stem cells (after 2 attempts) for autologous transplantation will be monitored in patients who proceed to stem cell collection (regardless of the dose level of PolaR-

ICE they were enrolled on). Routine collection failure rate for RICE would be around 15%. A Bayesian rule will be used for this monitoring. The prior distribution of the failure rate is assumed to be Beta (0.15, 0.85) with a mean of 15%. If based on the observed collection failure data, the posterior probability of the failure rate being greater than 15% is 90% or higher, the stopping rule will be triggered. Operationally, the rule will be triggered if at least 3/5, 4/10, 6/20, 8/30, or 10/40 patients fail to mobilize adequate CD34 cells within 2 attempts.

The incidence of non-relapse mortality in the first 100 days after ASCT will also be monitored among patients who went to ASCT, regardless of the dose level of PolaR-ICE they were enrolled on. A second case of such death within 100 days following ASCT will trigger a stopping rule.

If either monitoring rule is triggered, the study accrual will be halted. A full review of the study data will be undertaken by the study team, and the results will be submitted to the DSMC. The study team may propose to modify the study if deemed necessary. The DSMC will also perform their independent assessment of these events. The study accrual will not be resumed without approval from the DSMC.

12.5 Toxicity monitoring for post-HCT Pola

To assess the safety of Pola consolidation in the post-HCT setting, we will monitor the number of patients experiencing severe toxicities during post-HCT Pola consolidation, defined as any of the following AEs that is **at least possibly** attributed to Pola or to PolaR-ICE:

- Grade 3 peripheral neuropathy that does not resolve to grade 2 or better within 7 days
- Any Grade 4 AE with the **exception** of:
  - Grade 4 neutropenia (despite the use of growth factor) or grade 4 thrombocytopenia that lasts ≤ 21 days
  - Grade 4 laboratory abnormalities that resolve to Grade ≤ 2 within 10 days
  - Grade 4 metabolic laboratory abnormalities that are not clinically significant
- Any Grade 5 AE

The City of Hope Data Safety Monitoring Committee (DSMC) will review the toxicity data on this study every 6 months. The stopping rule for “severe” toxicities will start when there are at least 6 patients on the study who received post-HCT Pola (regardless of the dose level of PolaR-ICE they received or whether they were enrolled in the safety lead-in or Phase 2 portion of the study). If during such review, the proportion of patients having any of the severe toxicities is 33% or higher, the study accrual will be halted. A full review of the study data will be undertaken by the study team, and the results will be submitted to the DSMC. The study team may propose to modify the study if deemed necessary. The DSMC will also perform their independent assessment of these events. The study accrual will not be resumed without approval from the DSMC.

12.6 Statistical Analysis Plan

Patient demographics, baseline disease characteristics and prior treatment therapy will be summarized using descriptive statistics. For continuous variables, descriptive statistics such as number, mean, standard deviation, standard error, median (range) etc. will be provided. For categorical variables, patient counts and percentages will be provided.

CR rate after PolaR-ICE salvage therapy will be estimated by the proportion of response-evaluable patients achieving CR after 2 cycles of salvage therapy, along with the 95% exact binomial confidence interval. ORR after PolaR-ICE salvage therapy will be similarly estimated. PFS and OS will be estimated using the product-limit method of Kaplan and Meier along with the Greenwood estimator of standard error; 95% confidence interval will be constructed based on log-log transformation. Median PFS/OS will be estimated when

available. Observed toxicities of PolaR-ICE salvage therapy and Pola single-agent consolidation therapy will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity, and attribution.

12.7 Analysis of the exploratory objectives

For the exploratory objectives, descriptive statistics will be used to summarize the correlative study measures such as ctDNA measures or other biomarkers. For continuous variables, number, mean, standard deviation, standard error, median (range) etc., will be provided. For categorical variables, patient counts and percentages will be provided. Changes in these measures before, during, and after treatment (when measured) will also be summarized by descriptive statistics and tables/plots.

Various statistical analyses will be used to explore the association between these correlative measures (at different time points and the changes over time, when measured) with clinical outcomes. For the exploratory correlation of these endpoints with response, analyses comparing groups of participants defined by response may be conducted by various two sample tests such as two-sample t-test or Wilcoxon rank sum test for the continuous correlative endpoints, or Chi-square test/Fisher's exact test for the categorical correlative endpoints. For the exploratory correlation of these endpoints with survival outcomes, survival analysis techniques such as Log rank test will be considered. Appropriate regression models will also be considered which examine the association of these correlative measures with disease outcome adjusting for other disease risk factors, such as logistic regression for response and Cox proportional hazards models for survival outcomes. All these analyses are exploratory in nature and are intended to generate hypotheses that may be validated in larger studies; no multiple comparison adjustments will be made in these exploratory analyses.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system (EDC) that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms/Data Submission Schedule

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	**Safety Lead-in Salvage Cycles 1 & 2**: Within 7 calendar days of AE assessment/notification **Safety Lead-in remaining cycles and Phase 2**: Within 10 calendar days of AE assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (concomitant medications)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study
Follow up/Survival Forms	Within 14 calendar days of the follow up activity

13.4 Regulatory Records

The Investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

14.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy (available from the DCC). Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.

- **Unlikely –** The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.

  Definite – The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

14.2 Adverse Events of Special Interest (AESI)

AESIs are a subset of events to monitor of scientific and medical concern specific to the study, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor and industry partner 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.

14.2.1 Potential Drug-induced Liver Injury (DILI)

A potential DILI includes 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 $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

14.2.2 Suspected transmission of an infectious agent by the study drug

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

14.2.3 Tumor lysis syndrome (TLS)

TLS of any grade (irrespective of causality).

14.2.4 Secondary Malignancy

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

14.3 Pregnancies

14.3.1 Female participants:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring after the participant receives the first dose of protocol therapy up to 90 days post-last dose of polatuzumab vedotin are considered immediately reportable events. **Protocol therapy is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study PI and the DCC immediately within 24 hours of awareness (Section 14.6)**. The female subject may be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator should make every effort to follow the female participant until completion of the pregnancy per institutional policies, and should notify the Study PI.

Abnormal pregnancy outcomes, neonatal deaths that occur within 28 days of birth, and any congenital anomaly/birth defect should be reported as an SAE per expedited reporting guidelines.

Any infant death after 28 days that the Investigator suspects is related to the in utero exposure to protocol therapy should also be reported as an SAE per expedited reporting guidelines.

Follow guidelines in Section 14.8 for reporting to Genentech.

14.3.2 Male participants:

If a female partner of a male participant becomes pregnant, the male participant should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Pregnancy of a male participant's partner occurring after the participant receives the first dose of protocol therapy up to 90 days post-last dose of polatuzumab vedotin are considered immediately reportable events.

The Investigator should make every effort to follow the outcome of the pregnancy per institutional policies, and should notify the Study PI.

Follow guidelines in Section 14.8 for reporting to Genentech.

14.4 Post-Study Adverse Events

Any SAE occurring after a subject has completed or discontinued study participation if attributed to prior polatuzumab vedotin should be expeditiously reported to Genentech (see Section 14.8). If the investigator should become aware of the 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 subject, this should be adequately reported as an SAE to Genentech.

14.5 Routine AE Collection and Reporting Guidelines

Routine recording of adverse events will occur via data entry into the study eCRF. Adverse events will be collected from the signing of informed consent until ending study participation, except those occurring between the end of salvage visit and the start of consolidation for subjects proceeding to HCT. Adverse events will be monitored by the Protocol Management Team (PMT). AEs reported through expedited processes (e.g., reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

AEs recorded in the eCRF include:

- The highest grade of any toxicity for each cycle during protocol treatment and for the period of safety follow-up after end of treatment
- For Cycles 1 and 2 only, all Grade ≥2 AEs (highest grade or not) will also be collected
- All SAEs

14.6 Expedited Reporting

Table 14.6 indicates what events must be reported expeditiously.

Table 14.6 Criteria for Expedited Reporting

Time point	What to report
From signing of the consent to study completion	• All UPs
For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier	• All SAEs regardless of relationship to protocol therapy • All UPs and AEs that meet the definition of a UP • AESIs* • Secondary malignancy • Pregnancies and lactation
From Day 1 of protocol therapy up to 90 days post-last polatuzumab vedotin dose	• Pregnancies and lactation
Post Safety Follow-Up to removal from study	• All SAEs that are considered possibly, probably or definitely related to protocol therapy.

*** AESIs (except secondary malignancy) do not require an expedited report unless the event results in unplanned hospitalization or prolongation of hospitalization. However, they must still be reported through the routine mechanism in the eCRFs, and to Genentech within the timelines indicated in Section 14.8.**

NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or determined to be irreversible by the investigator.

The DCC should be consulted prior to ending the follow-up of events that have stabilized.

14.6.1 Expedited reporting guidelines **(COH only)**

14.6.1.1 To the COH DSMC/IRB

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. This includes all SAEs and UPs that meet COH DSMC/IRB expedited reporting criteria that occurred at COH and non-COH sites. For non-COH sites, the DCC will be responsible for reporting (see Section 14.6.2).

14.6.1.2 To Participating Investigators

- Report all expedited reportable AEs to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed (if applicable), and, for non-COH sites, a statement that the report should be submitted to their local IRB for review if applicable per local IRB policy.

- Forward to participating sites all IND safety reports received from Genentech, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

14.6.2 Expedited reporting guidelines **(non-COH sites only)**

14.6.2.1 To the DCC/Study PI

All events that meet the criteria specified in Table 14.6 will be reported to the DCC and Study PI within 24 hours of notification that the event met the expedited reporting criteria.

1. Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB submission and corresponding IRB response.
2. Document/describe the AE/UP on each of the following:
    a. MedWatch 3500A or local IRB submission document*
    MedWatch 3500A is downloadable form at http://www.fda.gov/medwatch/getforms.htm
    *The local IRB submission document may be used if the document template is approved by the DCC
    b. Expedited Reporting Coversheet. A modifiable Microsoft Word document is available from the DCC. An electronic signature on the document will be accepted.
3. Scan and email above documents to the Study PI (aherrera@coh.org) and DCC@coh.org with the subject title as "[PolaR-ICE as initial salvage for R/R DLBCL] SAE COH IRB #20148".
    a. If available, sites may include the local IRB submission for this event in the submission.
4. If an email receipt from DCC personnel is not received within one working day, please email DCC@coh.org.

14.7 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, regardless of the site of occurrence, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the MedWatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA **no later than 7 calendar days** after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted **no later than 15 calendar days** after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported **as soon as** the relevant information becomes available. [21 CFR 312.32(d)(3)]

The final IND report will be distributed to the Study PI and DCC. If it is determined that the IND safety report requires a change to the protocol or the consent form, the DCC will include instructions to participating sites for local IRB reporting.

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days of the anniversary of the date the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

14.8 Reporting to Industry Partner

The Study PI (or designee) will:

- Report to Genentech per the guidelines provided in Table 14.8.
  Email: usds_aereporting-d@gene.com; Fax: 650-238-6067

Table 14.8 Timeframes for Reporting to Genentech

Type of Report	Reporting Timeframes to Genentech
Pregnancy	**Within 30 calendar days** of being aware of the event using the Genentech Pregnancy Reporting Form.
All expedited SAE reports Post-study SAE reports	**Within 15 calendar days** of being aware of the event via a MedWatch 3500A form.
AESIs	**Within 15 calendar days** of the awareness event.
Aggregate safety reports	Forward to Genentech every 6 months (e.g. at time of COH PMT report).
Special Situation Reports*	**Within 30 calendar days** of the awareness event.
Product complaints**	**Within 15 calendar days** of the awareness event. Product complaints ***without an AE*** should be reported by calling: PC Hotline Number : (800)-334-0290 (M-F : 5am to 5pm PST)

- Assist Genentech in investigating any SAE and will provide any follow-up information reasonably requested by Genentech.
- *Special Situations Reports: In addition to all SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:
  - Data related to polatuzumab vedotin 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 patient, in order to be able to identify potential safety signals specific to a particular population
- **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.

- Fax to Genentech/Roche Safety **copies of all written IND safety reports** submitted to the FDA:

  Fax: (650) 225-4682 or (650) 225-4630

- Email to Genentech Drug Safety CTV **all IND annual reports and the final study report** submitted to the FDA:

  Email: ctvist_drugsafety@gene.com

14.9 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 the investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by the investigator 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 the investigator 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

14.10 Queries

Queries related to the Study will be answered by the investigator. 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 polatuzumab vedotin. The investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to polatuzumab vedotin independently but shall redirect such queries to Genentech.

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.

14.11 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 polatuzumab vedotin 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 polatuzumab vedotin. The investigator agrees that it shall not answer such queries from media and other sources relating to polatuzumab vedotin but shall redirect such queries to Genentech.

14.12 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.

15.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the City of Hope Clinical Research Protocol Deviation policy.

Non-COH Sites:

Deviations meeting the criteria specified in the City of Hope Clinical Research Protocol Deviation policy (available from the DCC) will be reported to the DCC and Study PI within **24 hours** of notification that the event occurred.

Procedure for reporting deviations to the COH DCC:

1. Document the deviation on the Deviation Reporting Coversheet or submit your site-specific protocol deviation log if the log format has been approved for use by the DCC. This modifiable Microsoft Word document is available from the DCC. An electronic signature on this document will be accepted.
2. Scan and email the Deviation Reporting Coversheet or protocol deviation log to the Study PI (aherrera@coh.org) and DCC@coh.org **within 24 hours** of notification of the deviation with the email subject title of "[PolaR-ICE as initial salvage for R/R DLBCL] Deviation COH IRB #20148". If an email receipt from the DCC is not received within one working day, please email DCC@coh.org.

Sites are to report to their local IRB and DSMC per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB and/or DSMC submission and corresponding response(s).

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, site investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

16.4 Quality Assurance

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

16.5 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because this study involves a COH IND.

16.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Each participating non-COH institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federal wide Assurance issued by and registered with the Office for Human Research Protections (OHRP). The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator, and, for external sites, the possession of the DCC, before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the

safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

All participating sites must follow the lead institution's IRB-approved protocol.

17.4 Informed Consent

Each participating non-COH institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the site's IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or participating institution or any relationship they have with City of Hope or participating institution. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the site investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the study drugs have been determined to be embryotoxic and teratogenic in animal testing.

17.6.2 Pediatric Population

Pediatric participants (< 18 years of age) are excluded from this study because safety and effectiveness of protocol therapy has not yet been defined for the study population. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult study population.

17.6.3 HIV Positive Individuals

Participants with HIV are included based on specifications outlined in inclusion criteria.

17.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

Source documents provided to the DCC for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The Investigator/Institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved biorepository with some clinical information and potentially PHI attached or (b) discarded.

With regard to which option will apply, each site IRB may choose to either: (a) leave the determination to the participant via a question in the informed consent document, which would be communicated to the study registrar (DCC) at the time of participant registration, OR b) may choose to make a single determination on behalf of their respective participants, and communicate that determination to their respective participants via the informed consent.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Polatuzumab vedotin will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible

for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope or at the non-COH site to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and Genentech, and participating non-COH institutions. City of Hope will forward a copy of the publication to Genentech/Roche upon completion of the study. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov. Results will be reported on ClinicalTrials.gov generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

18.0 REFERENCES

1. Dickinson, M., et al., *Improved survival for relapsed diffuse large B cell lymphoma is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy.* Br J Haematol, 2010. **150**(1): p. 39-45.

2. Johnston, P.B., G.A. Wiseman, and I.N. Micallef, *Positron emission tomography using F-18 fluorodeoxyglucose pre- and post-autologous stem cell transplant in non-Hodgkin's lymphoma.* Bone Marrow Transplant, 2008. **41**(11): p. 919-25.

3. Terasawa, T., I.J. Dahabreh, and T. Nihashi, *Fluorine-18-fluorodeoxyglucose positron emission tomography in response assessment before high-dose chemotherapy for lymphoma: a systematic review and meta-analysis.* Oncologist, 2010. **15**(7): p. 750-9.

4. Sehn LH, Herrera AF, Matasar MJ, et al. Addition of polatuzumab vedotin to bendamustine and rituximab (BR) improves outcomes in transplant-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) versus BR alone: Results from a randomized phase 2 study. Poster presented at: 59th Annual Meeting & Exposition for the American Society of Hematology; December 10, 2017; Atlanta, GA.

5. Moskowitz, C.H., et al., *Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2015.

6. Sehn LH, Herrera AF, Matasar MJ, et al. Addition of polatuzumab vedotin to bendamustine and rituximab (BR) improves outcomes in transplant-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) versus BR alone: Results from a randomized phase 2 study. Poster presented at: 59th Annual Meeting & Exposition for the American Society of Hematology; December 10, 2017; Atlanta, GA.

7. Frankel, P.H., et al., *Model of a Queuing Approach for Patient Accrual in Phase 1 Oncology Studies.* JAMA Network Open, 2020. **3**(5): p. e204787-e204787.

8. Gisselbrecht, C., et al., *Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era.* J Clin Oncol, 2010. **28**(27): p. 4184-90.

9. Swerdlow, S.H., et al., *Chapter 10: Mature B-cell Neoplasms. WHO classification of tumours of haematopoietic and lymphoid tissues*, ed. F. Lyon, International Agency for Research on Cancer. 2008.

10. Ghielmini, M., et al., *ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL).* Ann Oncol, 2013. **24**(3): p. 561-76.

11. Network, N.C.C., *NCCN Guidelines Version I.2015: Non-Hodgkin's Lymphomas. http://www.nccn.org/ Accessed: 1/9/2015.* 2015.

12. Morschhauser, F., et al., *Updated Results of a Phase II Randomized Study (ROMULUS) of Polatuzumab Vedotin or Pinatuzumab Vedotin Plus Rituximab in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma.* Blood, 2014. **124**(21): p. 4457-4457.

13. Sehn LH, Herrera AF, Matasar MJ, et al. Addition of polatuzumab vedotin to bendamustine and rituximab (BR) improves outcomes in transplant-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) versus BR alone: Results from a randomized phase 2 study. Poster presented at: 59th Annual Meeting & Exposition for the American Society of Hematology; December 10, 2017; Atlanta, GA.

14. Tilly, H., et al., *POLA-R-CHP: POLATUZUMAB VEDOTIN COMBINED WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, PREDNISONE FOR PATIENTS WITH PREVIOUSLY UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA.* Hematological Oncology, 2017. **35**: p. 90-91.

15. Moskowitz, C.H., et al., *Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma.* J Clin Oncol, 1999. **17**(12): p. 3776-85.

16. Sehn LH, Herrera AF, Matasar MJ, et al. Addition of polatuzumab vedotin to bendamustine and rituximab (BR) improves outcomes in transplant-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) versus BR alone: Results from a randomized phase 2 study. Poster presented at: 59th Annual Meeting & Exposition for the American Society of Hematology; December 10, 2017; Atlanta, GA.

17. Sehn LH, Herrera AF, Matasar MJ, et al. Addition of polatuzumab vedotin to bendamustine and rituximab (BR) improves outcomes in transplant-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) versus BR alone: Results from a randomized phase 2 study. Poster presented at: 59th Annual Meeting & Exposition for the American Society of Hematology; December 10, 2017; Atlanta, GA.

18. Armand, P., et al., *Detection of circulating tumour DNA in patients with aggressive B-cell non-Hodgkin lymphoma.* Br J Haematol, 2013. **163**(1): p. 123-6.

19. Oki, Y., et al., *Detection of classical Hodgkin lymphoma specific sequence in peripheral blood using a next-generation sequencing approach.* Br J Haematol, 2015. **169**(5): p. 689-93.

20. Roschewski, M., et al., *Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study.* Lancet Oncol, 2015. **16**(5): p. 541-9.

21. Kurtz, D.M., et al., *Noninvasive monitoring of diffuse large B-cell lymphoma by immunoglobulin high-throughput sequencing.* Blood, 2015. **125**(24): p. 3679-87.

22. Scherer F, K.D., Newman AM, et al. *Noninvasive Genotyping And Assessment of Treatment Response in Diffuse Large B-Cell Lymphoma*. in *ASH 2015, abstract #126*.

23. Kurtz DM, S.F., Newman AM, et al. *Dynamic Noninvasive Genome Monitoring for Outcome Prediction in Diffuse Large B-Cell Lymphoma*. in *ASH 2015, abstract #130*.

24. Scherer, F., et al., *Distinct biological subtypes and patterns of genome evolution in lymphoma revealed by circulating tumor DNA.* Sci Transl Med, 2016. **8**(364): p. 364ra155.

25. Rossi, D., et al., *Diffuse large B-cell lymphoma genotyping on the liquid biopsy.* Blood, 2017.

26. Bohers, E., et al., *Somatic mutations of cell-free circulating DNA detected by next-generation sequencing reflect the genetic changes in both germinal center B-cell-like and activated B-cell-like diffuse large B-cell lymphomas at the time of diagnosis.* Haematologica, 2015. **100**(7): p. e280-4.

27. Assouline, S.E., et al., *Phase 2 study of panobinostat with or without rituximab in relapsed diffuse large B-cell lymphoma.* Blood, 2016. **128**(2): p. 185-94.

28. Kurtz, D.M., et al., *Circulating Tumor DNA Measurements As Early Outcome Predictors in Diffuse Large B-Cell Lymphoma.* J Clin Oncol, 2018. **36**(28): p. 2845-2853.

29. Alizadeh, A.A., et al., *Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling.* Nature, 2000. **403**(6769): p. 503-11.

30. Rosenwald, A., et al., *The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma.* N Engl J Med, 2002. **346**(25): p. 1937-47.

31. Ennishi, D., et al., *Double-Hit Gene Expression Signature Defines a Distinct Subgroup of Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma.* J Clin Oncol, 2019. **37**(3): p. 190-201.

32. Chapuy, B., et al., *Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes.* Nat Med, 2018. **24**(5): p. 679-690.

33. Reddy, A., et al., *Genetic and Functional Drivers of Diffuse Large B Cell Lymphoma.* Cell, 2017. **171**(2): p. 481-494 e15.

34. Schmitz, R., et al., *Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma.* N Engl J Med, 2018. **378**(15): p. 1396-1407.

35. Carey, C.D., et al., *Topological analysis reveals a PD-L1-associated microenvironmental niche for Reed-Sternberg cells in Hodgkin lymphoma.* Blood, 2017. **130**(22): p. 2420-2430.

36. Jung, S.H., et al., *Admissible two-stage designs for phase II cancer clinical trials.* Stat Med, 2004. **23**(4): p. 561-9.

37. Skolnik, J.M., et al., *Shortening the timeline of pediatric phase I trials: the rolling six design.* J Clin Oncol, 2008. **26**(2): p. 190-5.

38. Cheson, B.D., et al., *Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.* Journal of Clinical Oncology, 2014. **32**(27): p. 3059-3067.

39. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* Am J Clin Oncol, 1982. **5**(6): p. 649-55.

40. Dolgin, M., et al., *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* 9 edn (Boston, Little, Brown and Company). 1994.

APPENDIX A: PERFORMANCE STATUS

ECOG Performance Scale [39]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: LYMPHOMA RESPONSE CRITERIA [38]

Response	Site	CT-Based Response	PET-CT Based Response
Complete Response		Complete radiologic response (all of the following)	Complete metabolic response (even with a persistent mass)
	Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤1.5 cm in longest diameter (LDi). No extralymphatic sites of disease.	Score ≤ 3* with or without a residual mass on 5-point scale†. 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 inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
	Nonmeasured lesion	Absent	Not applicable
	Organ enlargement	Regress to normal	Not applicable
	New lesions	None	None
	Bone marrow	Normal by morphology; if indeterminate, IHC negative	No evidence of FDG-avid disease in marrow
Partial Response		Partial remission (all of the following)	Partial metabolic response
	Lymph nodes and extralymphatic sites	≥ 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	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease *At end of treatment, these findings indicate residual disease*

Response	Site	CT-Based Response	PET-CT Based Response
	Nonmeasured lesion	Absent/normal, regressed, but no increase	Not applicable
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No response or stable disease		Stable disease	No metabolic response
	Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasured lesion	No increase consistent with progression	Not applicable
	Organ enlargement	No increase consistent with progression	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	No change from baseline
Progressive disease		Progressive disease requires at least 1 of the following	Progressive metabolic disease
	Individual target nodes/nodal masses	PPD progression:	Score 4 or 5† with an increase in intensity of uptake from baseline and/or
	Extranodal lesions	An individual node/lesion must be abnormal with: Longest diameter (LDi) > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or shortest diameter (SDi) from nadir	New FDG-avid foci consistent with lymphoma at interim OR End-of-treatment assessment

Response	Site	CT-Based Response	PET-CT Based Response
		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	
	Nonmeasured lesion	New or clear progression of preexisting nonmeasured lesions	None
	New lesions	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
	Bone marrow	New or recurrent involvement	New or recurrent FDG-avid foci

Measured dominant lesions:

Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.

Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

Nonmeasured lesions:

Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

†*PET 5-point scale:*

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.

Abbreviations:

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.

APPENDIX C: NYHA CARDIAC GRADING CRITERIA

Modified from Dolgin et al., 1994 [40]

New York Heart Association Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

APPENDIX D: REGISTRATION COVERSHEET

COH IRB# 20148: A Phase 2 Study of Polatuzumab Vedotin with Rituximab, Ifosfamide, Carboplatin, and Etoposide (PolaR-ICE) as Initial Salvage Therapy for Relapsed/Refractory Diffuse Large B-cell Lymphoma

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: (626)-218-7904
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
	PI/ Sub-Investigator:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
☐	Black	☐	Hispanic	Codes:	
☐	Caucasian	☐	Non-Hispanic	**01** Private	**06** Military or Veterans Adm. sponsored
☐	Asian	☐	Other_____	**02** Medicare	**07** Self-pay (no insurance)
☐	American Indian			**03** Medicare & private ins.	**08** No means of payment (no insurance)
☐	Native Hawaiian/Pacific Islander			**04** Medicaid	**09** Unknown
☐	Other_____ _____			**05** Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX E: CORRELATIVE TISSUE FORM (FOR ALL SITES)

A copy of this form should accompany the sample shipments to COH Pathology Core.

Non-COH sites: refer to **Appendix F** for shipping instructions to COH Pathology Core.

COH IRB number: 20148	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

CRA/Study Coordinator/Nurse Printed Name:
CRA/Study Coordinator/Nurse Signature:
Contact Number:

APPENDIX F: TISSUE SHIPPING GUIDELINES TO CITY OF HOPE PATHOLOGY CORE

*These guidelines apply to **non-COH sites** only.*

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).

2. Notify City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org) of impending shipment. Sites must create their own FedEx shipping labels.

3. **Slides/ Blocks:** Batch ship at room temperature via FedEx. During extreme heat, include refrigerated (not frozen) gel packs or gel insulators.

   It is recommended to ship samples via FedEx overnight (for a delivery by 3 pm or earlier the next day) or FedEx 2-day (with a morning delivery). During extreme heat, ship via FedEx overnight (for a delivery ideally by 10.30 am, or 3 pm the next day).

4. **Frozen samples** should be batch shipped on dry ice via FedEx overnight (for a delivery by 10.30 am the next day). The shipment should contain enough dry ice to last at least 72 hours.

5. On the day of shipment, email the sample shipment information to City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).

6. Ship samples with a **copy of the correlative tissue form (**Appendix **E)** and a **copy of the pathology report** to:

Karen Miller
COH Pathology Core
City of Hope National Medical Center
1500 E. Duarte Road
Familian Science (Building 084), Room 1207
Duarte, CA 91010
Telephone: 626-218-8408
Email: DL-PATHCORE-BiospecimenSupport@COH.org

APPENDIX G: CORRELATIVE BLOOD COLLECTION FORM FOR NON-COH SITES ONLY

Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	

To be used by **non-COH sites** for the following blood samples being sent to **COH APCF**:

Sample #	Time point of Collection	Expected Volume	Tube Type Used	Collected Volume	Time of Collection	Date of Collection	Indicate which sample was collected
1.	Salvage Cycle 1, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
2.	Salvage Cycle 2, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
3.	End of Salvage	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
4.	Consolidation Cycle 1, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
5.	End of Consolidation (30 days post-last dose)	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
6.	At Progression/Relapse	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐

A copy of this form should accompany the sample shipments to COH APCF. **Refer to the blood shipping guidelines for shipping instructions to COH APCF (Appendix H).**

CRA/Study Coordinator/ Nurse:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

APPENDIX H: BLOOD SHIPPING GUIDELINES TO CITY OF HOPE APCF

*These guidelines apply to **non-COH sites** only.*

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with APCF (DL-APCF@coh.org). Sites must create their own FedEx shipping labels.

1. Cell-free BCT tubes should be shipped as soon as possible but no more than 3 days after being drawn via overnight courier at ambient temperature.

2. **On the day of shipment**, email APCF (DL-APCF@coh.org) the FedEx shipment #.

3. Ship samples with a **copy of the correlative blood collection form (Appendix G)** and a **copy of the latest CBC results (with differential)** and the **date of the test** to:

Dr. Tim Synold
Analytical Pharmacology Core Facility
Shapiro 1042
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010