Official Title: A Phase Ib/II Study Evaluating the Safety and Efficacy of Obinutuzumab in Combination With Polatuzumab Vedotin and Lenalidomide in Patients With Relapsed or Refractory Follicular Lymphoma and Rituximab in Combination With Polatuzumab Vedotin and Lenalidomide in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

NCT Number: NCT02600897

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PROTOCOL

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR *LYMPHOMA AND RITUXIMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA***
PROTOCOL NUMBER:	GO29834
VERSION NUMBER:	2
EUDRACT NUMBER:	2015-001999-22
IND NUMBER:	109409
TEST PRODUCT:	Obinutuzumab (RO5072759) *Rituximab (RO0452294)* Polatuzumab vedotin (DCDS4501A; RO5541077) Lenalidomide
MEDICAL MONITOR:	[redacted], Pharm.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 4 August 2015
DATE AMENDED:	Version 2: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	[redacted]	19-Jan-2017 19:13:19

PROTOCOL AMENDMENT, VERSION 2

Changes to the protocol, along with a rationale for each change, are summarized as follows:

- Patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) will receive polatuzumab vedotin and lenalidomide in combination with rituximab instead of obinutuzumab (see Section 3.1.3). The rationale for this change is based on the results from the Phase III GOYA study (BO21005) showing that the addition of obinutuzumab to cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone (CHOP) chemotherapy in patients with previously untreated DLBCL did not improve the primary endpoint of progression-free survival compared with the standard regimen of rituximab plus CHOP chemotherapy.

  The background (Sections 1.2 and 1.3), rationale (Sections 1.4 and 3.3), study objectives (Section 2), study design (Section 3), eligibility criteria (Section 4.1), and statistical plan (Section 6) have been updated accordingly.

  The updated study design includes a dose-escalation phase in R/R DLBCL patients to assess the maximum tolerated dose of lenalidomide when combined with rituximab (375 mg/m^2) and polatuzumab vedotin at the 1.8-mg/kg dose (Sections 3.1.2 and 3.1.3).
- Rituximab will be provided by the Sponsor as an investigational medicinal product. This information has been reflected throughout the protocol in corresponding sections. Rituximab risks have been added (see Section 5.1.2), and the risks of overlapping toxicities have been updated accordingly (Section 5.1.5).
- Obinutuzumab exposure data (Section 1.2) have been updated to reflect the most up-to-date information on clinical studies based on the latest Obinutuzumab Investigator's Brochure, Version 11 (September 2016).
- Text regarding polatuzumab vedotin (Section 1.3) has been updated to reflect the most up-to-date information on clinical studies, based on the latest Polatuzumab Vedotin Investigator's Brochure, Version 7 (July 2016).
- Collection of human anti-chimeric antibodies in relation to rituximab has been added as immunogenicity objective (Section 2.4, Section 4.5.6, and Appendix 2).
- Clarification has been made that patients who experience a dose-limiting toxicity (DLT) during the DLT observation period may continue treatment if determined by investigator in consultation with Sponsor that it is safe to continue treatment and there is potential for clinical benefit in their judgment (Section 3.1.2.1).
- The definitions of DLT criteria around non-hematologic toxicities have been clarified, including exceptions for events that are considered predictable, manageable per standard of care, and reversible on the basis of experience with individual study medications (Section 3.1.2.1.1).
- Enrollment rules into the dose-escalation phase have been updated for patients' safety considerations. A sequential enrollment instead of a parallel enrollment will be used for each of the 2 dosing groups (i.e., the 3 patients in each cohort will be enrolled at least 48 hours apart; Section 3.1.2.1.3).

- Inclusion criteria have been clarified for patients with R/R DLBCL who have been treated with a chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody (Section 4.1.1).
- The pregnancy prevention plan guidelines have been clarified for patients using lenalidomide (Section 4.1.1).
- The period for contraception has been updated to align with each individual molecule (Section 4.1.1).
- The exclusion of patients with Grade 3b follicular lymphoma and a history of transformation of indolent disease to DLBCL has been added in order to focus on a more homogenous patient population (Section 4.1.2).
- The exclusion criteria of abnormal laboratory values for calculated creatinine clearance has been changed from 60 mL/min to 50 mL/min to allow patients with mild renal insufficiency to be enrolled (Section 4.1.2).
- The classification of second malignancy has been changed from a selected adverse event to an adverse event of special interest in order to more closely monitor this adverse event. The duration of reporting has been extended (Sections 5.3.1 and 5.6).
- The adverse event reporting period for Grade 3 and 4 infections has been clarified: up to 2 years after last dose of study treatment only for patients receiving obinutuzumab (Section 5.3.1).
- Guidelines for the second and subsequent infusion of obinutuzumab have been clarified (i.e., patients with no infusion-related reaction during prior infusion will receive only an analgesic/antipyretic as premedication). Figure 6 and Table 13 have been updated accordingly.
- Thyroid hormone monitoring (thyroid-stimulating hormone, triiodothyronine, thyroxine) has been added at baseline and every 3 months (Section 4.5.6, Appendix 1, and Appendix 2).
- Recommendations on management of dermatologic toxicities has been updated to consider lenalidomide dose reduction or allow resuming current dose in the case of a Grade 2 or Grade 3 rash without blistering (Table 19).
- Reasons for permanent discontinuation of all drugs in the event of certain dermatologic toxicities have been updated to align with lenalidomide labeling recommendations (Table 19).
- Populations to be analyzed have been defined (Section 6.2).
- Interim analysis has been clarified, including specification that enrollment would not be stopped in the case of higher-than-expected efficacy (Section 6.10).

Clarifications to the protocol are summarized as follows:

- The safety objective has been clarified: RP2D will not be determined for polatuzumab vedotin in patients with R/R DLBCL, as it will be a fixed dose (Section 2.1).

- The secondary efficacy objective has been clarified: Complete response (CR) at end of induction (EOI) on the basis of computed tomography (CT) alone is to be determined by the Independent Review Committee in addition to the investigator (Sections 2.2.2 and 6.6.2).
- The exploratory efficacy objective has been clarified: If a patient with DLBCL has a positive positron emission tomography (PET)-CT scan at EOI, then they should have PET-CT scan repeated at end of consolidation (Section 2.2.3, Section 6.6.3, and footnote ″jj″ in Appendix 2).
- The number of patients in the study has been updated (Sections 3.1.1, 3.1.2, and 6.1).
- The prohibited therapies have been updated to clarify that vaccination with live vaccines is not recommended during treatment with obinutuzumab or rituximab and until B-cell recovery (Section 4.4.2).
- Clarification has been made that tumor tissue samples at time of progression are only optional if investigator is unable to access the tumor site in order to promote obtaining samples (Section 4.5.6).
- The Modified Lugano Criteria has been clarified for designation of PET-CT on the basis of partial response (PR) to also include requirement of a CR or PR on CT-based response criteria (Section 4.5.5; Appendix 5).
- Post-treatment pregnancy testing time window has been clarified for lenalidomide at Days 14 and 28 following the last dose of study treatment (footnote ″p″ in Appendix 1; footnote ″p″ in Appendix 2).
- Time window has been clarified for drawing β_2 microglobiulin and quantitative IgA, IgG, and IgM as predose collections on C1D1 (footnote ″m″ in Appendix 1; footnote ″m″ in Appendix 2).
- Timing of when CBC should be monitored has been clarified to every week for first 8 weeks of lenalidomide treatment (footnote ″m″ in Appendix 1; footnote ″m″ in Appendix 2).
- Timing of when interim scan should be done has been clarified to within 7 days prior to Day 1 of Cycle 3 (footnote ″ff″ in Appendix 1; footnote ″dd″ in Appendix 2).
- Pharmacokinetic and immunogenicity sampling schedule time windows have been clarified (Appendix 3 and Appendix 4).

Substantive new information appears in italics. Additional minor changes have been made to improve clarity and consistency. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2: BACKGROUND ON OBINUTUZUMAB

Obinutuzumab is approved for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). *Obinutuzumab is also approved for use in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen.* ~~Obinutuzumab is currently being investigated in a large clinical program, including multiple head-to-head Phase III studies versus rituximab in indolent B-cell lymphoma and DLBCL~~.

SECTION 1.2.2: Clinical Studies with Obinutuzumab

~~To date,~~ *As of 4 July 2016*, clinical data from Roche-sponsored studies on obinutuzumab are available from *13 clinical studies:* 8 Phase I or II studies (BO20999, BO21003, JO21900, BO21000, GAO4915g, GAO4779g, YP25623, and GAO4768g), *and 5 Phase III studies (GAO4735g, BO21004/CLL11, MO28543, BO21223, and BO21005).* Available efficacy results from the non-Hodgkin's lymphoma (NHL) cohorts in these studies and available safety results from all patients are summarized below. ~~In addition, two Phase III studies in patients with previously untreated CLL (Study BO21004) or rituximab-refractory iNHL (Study GAO4753g) have reached their primary endpoint PFS. Studies BO21223 (in previously untreated iNHL) and BO21005 (in previously untreated DLBCL) have passed futility analyses on efficacy, are ongoing, and remain blinded.~~

SECTION 1.2.2.1: Clinical Efficacy of Obinutuzumab in Patients with B-Cell Lymphoma

In *early* studies of obinutuzumab in combination with chemotherapy (e.g., CHOP, bendamustine) in patients with previously untreated, or R/R B-cell lymphoma (Studies BO21000, GAO4915g, and GAO4753g), the proportion of patients with a CR or PR at the end of induction (EOI) treatment ranged from 69% to 96%. The CR rate was higher with combination therapy (35%–39% in previously untreated FL, 39%–50% in R/R FL, and 55% in previously untreated DLBCL) than with monotherapy.

Phase III Study GAO4753g investigated obinutuzumab plus bendamustine (G-benda) compared with bendamustine alone in patients with rituximab-refractory indolent NHL (iNHL; n =396). Patients in the G-benda arm who had not experienced disease progression at EOI received obinutuzumab monotherapy every 2 months for up to 2 years. On the basis of positive results from this study, demonstrating significant improvement in PFS in the G-benda arm, with a median investigator-assessed PFS of

29 versus 14 months (hazard ratio [HR]: 0.52; 95% CI: 0.39, 0.70; p<0.0001; Sehn et al. 2015), obinutuzumab was granted approval for use in patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen (see Section 1.2).

Phase III Study BO21223 investigated obinutuzumab plus chemotherapy (G-benda, obinutuzumab plus CVP [G-CVP], obinutuzumab plus CHOP [G-CHOP]) compared with rituximab plus chemotherapy, followed by obinutuzumab or rituximab maintenance in patients with previously untreated iNHL (FL cohort, n =1202). On the basis of positive results that demonstrated significant improvement in PFS in the obinutuzumab chemotherapy arm, the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor at a pre-planned interim analysis (Marcus et al. 2016).

Phase III Study BO21005 investigated G-CHOP compared with rituximab plus CHOP (R-CHOP) in patients with previously untreated DLBCL. The study did not meet its primary endpoint of PFS at final analysis. Based upon the BO21005 efficacy results, this study protocol is amended to cease evaluating obinutuzumab in patients with R/R DLBCL; these patients will receive instead rituximab in combination with polatuzumab vedotin and lenalidomide (Vitolo et al. 2016).

SECTION 1.2.2.2: Clinical Safety of Obinutuzumab

As of 4 July 2016 ~~To date~~, an estimated *3636*~~3484~~ patients with B-cell lymphoma (including DLBCL, indolent B-cell lymphoma, and CLL) had been treated with obinutuzumab given as monotherapy or in combination with CHOP, bendamustine, fludarabine plus cyclophosphamide, or chlorambucil, at doses ranging from 50 to 2000 mg. Overall, the safety of obinutuzumab monotherapy and obinutuzumab combination therapy was manageable.

SECTION 1.3.2: Clinical Studies with Polatuzumab Vedotin

To date, clinical data on polatuzumab vedotin are available from one completed Phase I/Ib study (DCS4968g) ~~one ongoing Phase Ib/II study (GO27834), and from one ongoing Ib/II study (GO29044)~~ *and the ongoing Phase Ib/II Studies GO27834, GO29044, GO29833, BO29561, and GO29365* in patients with B-cell lymphoma ~~or CLL~~.

DCS4968g evaluated polatuzumab vedotin as a single agent and in combination with rituximab in patients with R/R B-cell lymphoma.

GO27834 is evaluating polatuzumab vedotin in combination with either obinutuzumab or rituximab in patients with R/R FL or DLBCL.

GO29044 is evaluating polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) or obinutuzumab plus cyclophosphamide, doxorubicin, and prednisone (G-CHP) in patients with newly diagnosed or R/R B-cell lymphoma.

GO29365 is evaluating polatuzumab vedotin in combination with bendamustine plus rituximab or obinutuzumab in patients with R/R FL or DLBCL.

Available efficacy and safety results from these studies are summarized in Sections 1.3.2.1 and 1.3.2.2, respectively. ~~Data have been generated in these studies for patients treated at the 2.4 mg/kg dose; however, further investigation focusing on the 1.8 mg/kg dose is ongoing.~~

For more detailed clinical information on polatuzumab vedotin, including clinical pharmacology data, refer to the polatuzumab Vedotin Investigator's Brochure.

SECTION 1.3.2.1: Clinical Efficacy of Polatuzumab Vedotin in Patients with B-Cell Lymphoma

Polatuzumab vedotin demonstrated clinical activity as a single agent.
In Study DCS4968g, at the 2.4-mg/kg dose, objective responses (CR or PR) were observed in 7 of 16 patients (44%) with R/R indolent B-cell lymphoma (FL, marginal zone lymphoma [MZL], or small lymphocytic lymphoma [SLL]) and 14 of 27 patients (52%) with R/R DLBCL. *At a dose of 1.8 mg/kg, a PR was observed in 2 of 4 patients with DLBCL and in 2 of 2 patients with MCL, and no objective responses were observed in the 5 patients with CLL. The median duration of response was 6.2 months (95% CI: 3.3, 19.3 months) for the 2.4-mg/kg dose and 6.6 months (95% CI: 2.3, 11.4 months) for the 1.8-mg/kg dose. At the 2.4-mg/kg dose, median PFS was 7.9 months (95% CI: 3.0, 11.6 months) for patients with indolent B-cell lymphoma and 5.0 months (95% CI: 2.3, 6.8 months) for patients with DLBCL. Median PFS was 4.6 months (95% CI: 1.4, 13.9 months) for patients with DLBCL treated at the 1.8-mg/kg dose.*

~~No objective responses were observed in patients with CLL at doses of up to 1.8 mg/kg. Median PFS at doses of ≥ 1.8 mg/kg was 7.9 months (95% CI: 3 months, not evaluable [NE]) for patients with relapsed or refractory indolent B-cell lymphoma (FL, MZL, or SLL) and 4.9 months (95% CI: 2.5, 6.7 months) for patients with relapsed or refractory DLBCL.~~

Polatuzumab vedotin also demonstrated clinical activity when administered in combination with rituximab. In Study DCS4968g, at a dose of 2.4 mg/kg, objective responses were observed in 7 of 9 patients with indolent B-cell lymphoma, DLBCL, or MCL (78%); 2 of those 7 patients had CRs. Median duration of response among these patients was 12.3 months (95% CI: 4.3, not estimable [NE]). Median PFS was 12.5 months (95% CI: 6.9, 17.4 months).

Preliminary data show that for patients in Study GO27834 who received polatuzumab vedotin (2.4 mg/kg) in combination with rituximab overall responses were observed in 14 of 20 patients with R/R FL (70%; *9* ~~8~~ patients with CRs) and *21* ~~22~~ of 39 patients with R/R DLBCL (*54* ~~56~~%;*8* ~~6~~ patients with CRs). *For patients who received polatuzumab vedotin (1.8mg/kg) in combination with rituximab, objective responses were observed in 15 of 20 patients with FL (75%; 6 patients with CRs).*

Median duration of response was 12.9 months (95% CI: 6.7, NE) and 13.2 months (95% CI: 7.2, 21.2) for patients who received polatuzumab vedotin 1.8 mg/kg (FL) or 2.4 mg/kg (FL or DLBCL), respectively. At the 2.4 mg/kg dose, median PFS was 15.1 months (95% CI: 11.8, NE) among the 20 patients with FL and 5.6 months (95% CI: 4.2, 12.7 months) among the 39 patients with DLBCL. Among the 20 patients with R/RFL treated with 1.8 mg/kg polatuzumab vedotin in combination with rituximab, the median PFS was 18.1 months (95% CI: 9.9, NE).

For patients in Study GO27834 who received polatuzumab vedotin (1.8 mg/kg) in combination with obinutuzumab, overall responses were observed in 8 of 12 patients with R/R FL (67%; 1 patient with CR) and 3 of 15 patients with R/R DLBCL (20%; 0 patients with CR).

Preliminary data from Study GO29044 in patients treated with polatuzumab vedotin (1.0–1.8 mg/kg) in combination with R-CHP showed overall responses in 29 of 31 patients (94%; 24 patients with CRs). When polatuzumab vedotin (1.4 or 1.8 mg/kg) was combined with G-CHP, overall responses were seen in 10 of 12 patients (83%; 10 patients with CRs).

Preliminary data from GO29365 in FL patients treated with polatuzumab vedotin (1.8 mg/kg) in combination with bendamustine showed overall responses in 7 of 7 patients (100%; 2 patients with CRs) when combined with rituximab and in 3 of 4 patients (75%; 1 patient with CR) when combined with obinutuzumab. Patients with DLBCL treated with polatuzumab vedotin (1.8 mg/kg) in combination with bendamustine showed overall responses in 3 of 7 patients (43%; 2 patients with CRs) when combined with rituximab and in 6 of 8 patients (75%; 2 patient with CR) when combined with obinutuzumab.

~~For patients in Study DCS4968g who received polatuzumab vedotin (2.4 mg/kg) in combination with rituximab (all histologies), median PFS was 12.5 months (95% CI: 6.9, 17.3 months).~~

SECTION 1.3.2.2: Clinical Safety of Polatuzumab Vedotin

Clinical safety data are available from ~~180~~*327* patients with B-cell lymphoma or CLL *who received polatuzumab vedotin as a single agent (DCS4968g), in combination with rituximab (DCS4968g and GO27834), in combination with obinutuzumab (GO27834), in combination with G-CHP or R-CHP (GO29044), or in combination with obinutuzumab or rituximab plus bendamustine (GO29365).*

~~86 patients treated with single-agent polatuzumab vedotin (doses ranging from 0.1 to 2.4 mg/kg) in Study DCS4968g; 88 patients treated with polatuzumab vedotin (1.8 mg/kg and 2.4 mg/kg) in combination with rituximab (375 mg/m^2) in Studies DCS4968g and GO27834; and 6 patients treated with polatuzumab vedotin (1.0 and 1.4 mg/kg) in~~

~~combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) in Study GO29044. Efficacy data from Study GO29044 are not yet available~~.

[…]

In the dose-escalation phase of Study DCS4968g, dose-limiting toxicities (DLTs) of Grade 4 neutropenia occurred in 1 of 10 DLT-evaluable patients treated with 2.4 mg/kg polatuzumab vedotin and 1 of 9 DLT-evaluable patients treated with 2.4 mg/kg polatuzumab vedotin in combination with rituximab. Polatuzumab vedotin at a dose of 2.4 mg/kg given every 3 weeks (Q3W) was chosen as the recommended Phase II dose (RP2D) when administered as a single agent and in combination with rituximab. *Due to additional information about the benefit-risk profile of polatuzumab vedotin at the 2.4 mg/kg dose, the Sponsor is no longer pursuing the clinical development of the 2.4-mg/kg dose of polatuzumab vedotin.*

[…]

In Study GO29044, Grade ≥3 adverse events were reported in 19 of 40 patients (48%) with B-cell lymphoma who received polatuzumab vedotin (1.8 mg/kg) in combination with G-CHP or R-CHP. The most frequent events (≥10% of patients) were fatigue (33%), diarrhea (33%), and nausea (30%). Serious adverse events were reported for 33% of patients in this treatment group.

In Study GO29365, Grade ≥3 adverse events were reported in 11 of 21 patients (52%) with B-cell lymphoma who received polatuzumab vedotin in combination with rituximab plus bendamustine and in 17 of 28 patients (61%) who received polatuzumab vedotin in combination with obinutuzumab plus bendamustine. The most frequent events (≥10% of patients) were nausea (43%), diarrhea (41%), and fatigue (35%). Serious adverse events were reported for 33% of patients receiving polatuzumab vedotin in combination with rituximab plus bendamustine and 39% of patients receiving polatuzumab vedotin in combination with obinutuzumab plus bendamustine.

A total of 44 deaths have been reported: 11 deaths in patients treated with single-agent polatuzumab vedotin and 33 deaths in patients treated with polatuzumab vedotin combined with rituximab or obinutuzumab. The majority of deaths were judged as related to disease progression.

~~Limited safety data from 7 patients receiving single-agent polatuzumab vedotin in an ongoing Phase I study (JO29138) are provided in the polatuzumab vedotin Investigator's Brochure.~~

SECTION 1.4: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This study will evaluate the activity of a novel triplet combination of obinutuzumab *or rituximab plus* polatuzumab vedotin and lenalidomide.

[…]

Obinutuzumab has shown superiority over rituximab in a Phase III study in first-line CLL (Goede et al. 2014). ~~Obinutuzumab is being compared with rituximab in two large Phase III studies in patients with previously untreated DLBCL (Study BO21005) or previously untreated indolent B-cell lymphomas, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab versus rituximab-containing regimens, potentially altering the standard of care in B-cell lymphoma, it will be important to also assess the safety and efficacy of incorporating obinutuzumab into treatment regimens. A fourth~~ *Obinutuzumab showed clinical benefit compared to rituximab when combined with chemotherapy in a Phase III trial (BO21223) in patients with previously untreated indolent B-cell lymphomas, including FL (Marcus et al. 2016). A* Phase III study, GAO4753g, evaluated patients with rituximab-refractory indolent B-cell lymphoma, including patients with FL, and showed improvement in PFS with obinutuzumab added to bendamustine followed by obinutuzumab maintenance compared with bendamustine alone (Sehn et al. 2015). Obinutuzumab will be included as the anti-CD20 backbone for patients with R/R FL in this study.

Obinutuzumab did not show superiority compared to rituximab in the Phase III trial (BO21005) comparing R-CHOP to G-CHOP in patients with previously untreated DLBLC (Vitolo et al. 2016). Based upon the BO21005 efficacy results, this study protocol is amended, and patients with R/R DLBCL will receive rituximab as the anti-CD20 backbone in combination with polatuzumab vedotin and lenalidomide.

[…]

On the basis of the distinct mechanisms of action (MOAs) for each molecule and the current available clinical data, there is a strong rationale to expect an improved benefit-risk profile with the triplet combination of obinutuzumab *or rituximab plus* polatuzumab vedotin and lenalidomide. This novel triplet regimen may have the potential to extend treatment-free remissions and to decrease toxicity by improving upon individual agents used as part of current standard of care, which includes traditional chemotherapy. Early clinical data that evaluated obinutuzumab*, rituximab*, polatuzumab vedotin, and lenalidomide each as single-agents has been associated with neutropenia. Rituximab and polatuzumab vedotin and rituximab and lenalidomide doublet combinations have also been associated with neutropenia. The replacement of rituximab with obinutuzumab (Study GO27834 [obinutuzumab plus polatuzumab vedotin {G+Pola}] and GALEN [obinutuzumab plus lenalidomide {G+Len}]) in these doublets is anticipated to be associated with treatment-related neutropenia. Patients with overlapping toxicities will be closely monitored; such events are expected to be manageable in the clinical setting, and drug-drug interactions (DDIs) are unlikely to occur (see Sections 5.1.5 and 5.1.6).

SECTION 2: OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of induction treatment consisting of obinutuzumab in combination with polatuzumab vedotin and lenalidomide (G+Pola+Len) in patients with R/R FL ~~or DLBCL~~ *and rituximab in combination with polatuzumab vedotin and lenalidomide (R +Pola +Len) in patients with R/R DLBCL*, followed by post-induction treatment with G+Len *(referred to as maintenance)* in patients with FL who achieve a CR, PR, or stable disease at EOI and *post-induction treatment with rituximab plus lenalidomide (R +Len; referred to as consolidation)* in patients with DLBCL who achieve a CR or PR at EOI. Specific objectives and corresponding endpoints for the study are outlined below.

In this study, "study treatment" refers to the protocol-mandated treatments under study (i.e., obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide).

SECTION 2.1: SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To determine the RP2D~~s~~ for polatuzumab vedotin and lenalidomide when given in combination with a fixed dose of obinutuzumab *and the RP2D of lenalidomide when given in combination with a fixed dose of polatuzumab vedotin and rituximab* on the basis of the following endpoint:

    Incidence of DLTs during the first cycle of study treatment

- To evaluate the safety and tolerability of G+Pola+Len *and R +Pola +Len* on the basis of the following endpoints *in the respective combinations*:

    Nature, frequency, severity, and timing of adverse events, including DLTs

    Changes in vital signs, ECGs, and clinical laboratory results during and following study treatment administration

SECTION 2.2.1: Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of induction treatment with G+Pola+Len *in R/R FL and R +Pola +Len in R/R DLBCL* on the basis of the following endpoint:

- CR at EOI, as determined by the IRC on the basis of PET-CT scans

SECTION 2.2.2: Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of induction treatment with G+Pola+Len *and maintenance treatment with G +Len in R/R FL and of induction treatment with R +Pola +Len and consolidation treatment with R +Len in R/R DLBCL* on the basis of the following endpoints:

- CR at EOI, as determined by the investigator on the basis of PET-CT scans
- CR at EOI, as determined by the *IRC and by the* investigator on the basis of CT scans alone

SECTION 2.2.3: Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of G+Pola+Len *and R +Pola +Len* on the basis of the following endpoints:

- For patients who have positive PET scans at EOI:
  - CR at 12 months, as determined by the IRC and by the investigator on the basis of PET-CT scans *in FL patients*
  - *CR at end of consolidation (EOC), as determined by the IRC and by the investigator on the basis of PET-CT scans, in DLBCL patients*

SECTION 2.3: PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the PK profiles of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide when given in combination on the basis of the following endpoints:

- Observed serum obinutuzumab concentration at specified timepoints
- *Observed serum rituximab concentration at specified timepoints*
- Observed serum and plasma concentrations of polatuzumab vedotin and relevant analytes (TAb, acMMAE, and unconjugated MMAE) at specified timepoints
- Observed plasma lenalidomide concentration at specified timepoints

SECTION 2.4: IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab*, rituximab,* and to polatuzumab vedotin on the basis of the following endpoints:

- Incidence of human anti-human antibodies (HAHAs) to obinutuzumab during the study relative to the prevalence of HAHAs at baseline
- *Incidence of human anti-chimeric antibodies (HACAs) to rituximab during the study relative to the prevalence of HACAs at baseline*
- Incidence of ATAs to polatuzumab vedotin during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential relationships between HAHAs *or HACAs, and* ~~or~~ ATAs on the basis of the following endpoint:

- Correlation between HAHA *or HACA, and* ~~or~~ ATA status and *respective* efficacy, safety, or PK endpoints

SECTION 3.1.1: Overview of Study

This Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study will evaluate the safety, efficacy, and pharmacokinetics of G+Pola+Len in patients with R/R FL ~~or~~ *and R +Pola +Len in patients with R/R* DLBCL.

The study will include an initial dose-escalation phase ~~designed to determine the RP2D for polatuzumab vedotin and the RP2D for lenalidomide in this treatment combination (see Section 3.1.2),~~ followed by an expansion phase, during which polatuzumab vedotin and lenalidomide will be given at their RP2Ds (see Sections 3.1.2 and 3.1.2.2).

Approximately ~~98–116~~*110–128* patients are expected be enrolled in this study, at approximately 20–25 investigative sites worldwide.

All patients will be closely monitored for adverse events throughout the study and for at least 90 days after the last dose of study treatment (see Section 5.3.1). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. An Internal Monitoring Committee (IMC) will be established to monitor patient safety throughout the study (see Section 3.1.4).

To characterize the PK properties of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide, blood samples will be obtained at various timepoints before and during study treatment administration.

FIGURE 1: *Study Schema*

Figure 1 has been revised to add rituximab and to clarify maintenance and consolidation treatment.

SECTION 3.1.2: OBINUTUZUMAB PLUS POLATUZUMAB VEDOTIN PLUS LENALIDOMIDE TREATMENT GROUP (PATIENTS WITH FOLLICULAR LYMPHOMA) (NEW HEADING)

This section heading has been added to differentiate the FL and DLBCL groups. Further changes to this section are summarized as follows.

SECTION 3.1.2.1: Dose-Escalation Phase

The purpose of the *FL* dose-escalation phase is to identify the RP2D for polatuzumab vedotin and the RP2D for lenalidomide when combined with a fixed dose of obinutuzumab as induction treatment. *This* ~~These~~ dose-escalation phase will include FL patients only; these patients may receive post-induction treatment if eligible (see Section 3.3.1).

Approximately 18–~~33~~*30* patients will be enrolled in the *FL* dose-escalation phase. Cohorts of 3–6 patients each will be treated in accordance with the treatment regimens and dose-escalation rules described in Section 3.1.2.1.3.

Patients will be closely monitored for adverse events during the DLT assessment window, defined as the first treatment cycle (from Day 1 of Cycle 1 to Day 1 of Cycle 2). Adverse events meeting the criteria for DLT, as defined below (see Section 3.1.2.1.1), will be reported to the Sponsor within 24 hours (see Section 5.4.2).

Patients experiencing a DLT during the DLT assessment period ~~will permanently discontinue study treatment.~~ *may continue receiving study treatment once the event has resolved, if determined by investigator in consultation with Sponsor that it is safe to continue treatment and there is potential for clinical benefit in their judgment.*

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and RP2D assessments and will be replaced by an additional patient at that same dose level. Patients who miss one or more doses of polatuzumab vedotin *or obinutuzumab* or five consecutive daily doses of lenalidomide during the DLT assessment window for reasons other than a DLT will also be replaced *and considered non-evaluable for dose-escalation decisions.* ~~Patients who do not receive all study treatment for any reason will also be replaced.~~ Patients who receive supportive care during the DLT assessment window that may confound the evaluation of DLTs may be replaced at the discretion of the Medical Monitor.

SECTION 3.1.2.1.1: Definition of Dose-Limiting Toxicity

In this study, a DLT is defined as any <u>one</u> of the following events occurring during the first cycle of treatment and assessed by the investigator as related to study treatment *that is not attributed to disease progression or another clearly identified cause*:

- ~~Adverse~~ *Any adverse* event of any grade that leads to a delay of $>$14 days in the start of the next treatment cycle
- *Any* Grade 3 or 4 non-hematologic adverse event, <u>with the following exceptions</u>:
  - Grade 3 or 4 IRRs

    Note that IRRs may occur even after a small amount of drug has been administered (i.e., IRRs are not dose dependent).
  - Grade 3 diarrhea that responds to therapy within 72 hours
  - Grade 3 nausea or vomiting that occurs in the absence of premedication and responds to adequate therapy within 72 hours
  - *Grade 3 laboratory TLS without manifestations of clinical TLS (i.e., creatinine $\geq$1.5$\times$ upper limit of normal (ULN) and/or renal dysfunction, cardiac arrhythmias, seizures, or sudden death) that resolves within 7 days (see Appendix 12)*
  - *Grade 3 fatigue that resolves to Grade $\leq$2 within 7 days*
  - *Grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator not to be clinically significant*
  - *Grade 3 elevation in ALT or AST, provided the following criteria are met:*

    ALT or AST level is no greater than 8$\times$ ULN

    ALT or AST elevation resolves to Grade $<$2 ($<$5 ULN) within 7 days

Total and direct bilirubin and other laboratory parameters of liver synthetic function (e.g., prothrombin time) are normal

No clinical signs or symptoms of hepatic injury

- *Any increase in hepatic transaminase >3 ×baseline AND an increase in direct bilirubin >2 ×ULN, WITHOUT any findings of cholestasis or jaundice or signs of hepatic dysfunction AND in the absence of other contributory factors (e.g., worsening of metastatic disease or concomitant exposure to known hepatotoxic agent or of a documented infectious etiology) is suggestive of potential drug-induced liver injury (according to Hy's Law) and will be considered a DLT.*
- *In patients with Grade 1 ALT or AST elevation at baseline as a result of liver metastases, only a Grade ≥3 elevation that is also ≥3 ×baseline lasting >7 days will be considered a DLT.*
- Hematologic adverse event that meets <u>any</u> of the following criteria:

  Grade 3 or 4 neutropenia in the presence of sustained fever of > 38°C (lasting > 5 days) or a documented infection

  Grade 4 neutropenia lasting > 7 days

  Grade 3 or 4 thrombocytopenia that results in significant bleeding per investigator judgment

  Grade 4 thrombocytopenia lasting > 7 days

Other toxicities occurring during the first cycle that are considered to be clinically relevant and related to study treatment, as determined by the investigator and the Medical Monitor may also be considered DLTs.

SECTION 3.1.2.1.1: Treatment Regimens for the *Follicular Lymphoma* Dose-Escalation Phase

The section title was revised to clarify that this phase is specific to the FL cohort.

TABLE 1: Post-Induction Treatment for the *Follicular Lymphoma* Expansion Phase

The Table 1 title was revised to clarify that this phase is specific to the FL cohort.

TABLE 2: Maintenance Treatment for the *Follicular Lymphoma* Dose-Escalation Phase

The Table 2 title was revised to clarify that this phase is specific to the FL cohort.

SECTION 3.1.2.1.3: Dose-Escalation Rules

A standard 3+3 dose-escalation schema will be used. The obinutuzumab dose will remain fixed at 1000 mg during the dose-escalation phase. The starting doses in Cohort 1 are 1.4 mg/kg for polatuzumab vedotin and 10 mg for lenalidomide. In Cohorts 2–6, dose escalation of polatuzumab vedotin and lenalidomide will proceed in increments that parallel the magnitude of dose increases tested in ongoing Phase Ib studies (see Sections 3.3.3.2 and 3.3.3.2.2). For polatuzumab vedotin, there are two

possible dose levels: 1.4 or 1.8 mg/kg. For lenalidomide, there are three possible dose levels (10, 15, or 20 mg). Intrapatient dose escalation is not allowed. The ~~overall~~ *FL* dose-escalation plan is depicted in Figure 2, and the doses for each cohort are summarized in Table 3.

[…]

Dose escalation will occur in accordance with the rules listed below.

- A minimum of 3 patients will initially be enrolled in each cohort. *The first 3 patients in each cohort will be sequentially enrolled and dosed at least 48 hours apart.*

[…]

Relevant demographic, adverse event, laboratory, dose administration/intensity, and PK (if available) data will be reviewed *throughout the study by the Clinical Study Team and* prior to dose-escalation decisions, which will be made by the *Medical Monitor* ~~IMC~~ in consultation with the Principal Investigator *and participating investigators.*

Although the DLT assessment window is defined as the first treatment cycle, cumulative *or late* toxicities occurring beyond the first cycle may be considered when determining the RP2Ds. *Prior to opening the R/R FL expansion phase, the Clinical Study Team and the Medical Monitor will review the cumulative data, recommend the RP2D, and review this with the IMC for approval.*

FIGURE 2: *Follicular Lymphoma* Dose-Escalation Plan

The Figure 2 title was revised to clarify that this phase is specific to the FL cohort.

TABLE 3: *Follicular Lymphoma* Dose-Escalation Cohorts

The Table 3 title was revised to clarify that this phase is specific to the FL cohort.

SECTION 3.1.2.2: *Follicular Lymphoma* Expansion Phase

The expansion phase is designed to further assess the safety and efficacy of polatuzumab vedotin and lenalidomide at their respective RP2Ds when combined with a fixed dose of obinutuzumab *in FL patients*.

Approximately ~~80 patients (~~40 patients with FL ~~and 40 patients with DLBCL)~~ will be enrolled during the expansion phase and treated as described below.

[…]

~~Patients with DLBCL who achieve a CR or PR at EOI will receive post induction treatment (referred to as consolidation) with obinutuzumab and lenalidomide, and p~~ *P*atients with FL who achieve a CR, PR, or stable disease at EOI will receive post-induction treatment (referred to as maintenance) with obinutuzumab and lenalidomide, as outlined in Table 5. Polatuzumab vedotin will not be given during the

post-induction phase. Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity, for up to ~~6 months for consolidation treatment and~~ 24 months for maintenance treatment.

TABLE 4: Induction Treatment for *Follicular Lymphoma* Expansion Plan

The Table 4 title was revised to clarify that this phase is specific to the FL cohort.

TABLE 5: Post-Induction Treatment for the *Follicular Lymphoma* Expansion Phase

Table 5 has been revised to clarify that this phase is specific to the FL cohort and to remove the regimen for patients with DLBCL.

SECTION 3.1.3: *Rituximab plus Polatuzumab Vedotin plus Lenalidomide Treatment Group (Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma)* (NEW SECTION)

Based on the safety and efficacy results from the Phase III BO21005 study in patients with DLBCL, the protocol has been amended to explore dose-finding of lenalidomide in combination with fixed doses of polatuzumab vedotin and rituximab instead of obinutuzumab for patients with R/R DLBCL.

SECTION 3.1.3.1: *Dose-Escalation Phase* (NEW SECTION)

The DLBCL dose-escalation phase will open with the purpose of identifying the RP2D for lenalidomide when combined with polatuzumab vedotin at 1.8 mg/kg and rituximab at 375 mg/m^2 as induction treatment in patients with R/R DLBCL. The dose escalation will initiate at the lenalidomide 10-mg dose level and increase through Cohorts A, B, and C (see Figure 3).

Approximately 12–18 patients will be enrolled in the R/R DLBCL dose-escalation phase. Cohorts of 3–6 patients each will be treated in accordance with the treatment regimens and dose-escalation rules described below.

Patients will be closely monitored for adverse events during the DLT assessment window, defined as the first treatment cycle (from Day 1 of Cycle 1 to Day 1 of Cycle 2). Adverse events meeting the criteria for DLT, as defined below (see Section 3.1.2.1.1), will be reported to the Sponsor within 24 hours (see Section 5.4.2).

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and RP2D assessments and will be replaced by an additional patient at that same dose level. Patients who miss one or more doses of polatuzumab vedotin or rituximab or five consecutive daily doses of lenalidomide during the DLT assessment window for reasons other than a DLT will also be replaced and considered non-evaluable for dose-escalation decisions. Patients who receive supportive care

during the DLT assessment window that may confound the evaluation of DLTs may be replaced at the discretion of the Medical Monitor.

Patients will receive induction treatment with R +Pola +Len for a total of six cycles. Patients achieving a CR or PR at EOI will be eligible to receive consolidation treatment with R +Len. A study schema is provided in Figure 1.

Treatment Regimens for DLBCL Dose-Escalation Phase

Patients enrolled in the DLBCL-dose-escalation phase will receive induction treatment, administered in 28-day cycles as shown in Table 6. When study treatments are given on the same day, they will be administered sequentially in the following order: lenalidomide, rituximab, and polatuzumab vedotin.

Patients who achieve a CR or PR at EOI will receive consolidation treatment with R +Len, as outlined in Table 7. Polatuzumab vedotin will not be given as maintenance treatment. Consolidation treatment should start 8 weeks (±1 week) after Day 1 of Cycle 6 and will continue for 6 months until disease progression or unacceptable toxicity.

Dose-Escalation Rules

A standard 3 +3 dose-escalation schema will be used. The rituximab and polatuzumab dose levels will remain fixed during the dose-escalation phase, and only the lenalidomide will be dose escalated. The polatuzumab dose of 1.8 mg/kg is based on ongoing Phase II trials (see Sections 1.3.2 and 3.3.3.3). Intrapatient dose escalation is not allowed. The overall DLBCL dose-escalation plan is depicted in Figure 3.

Dose escalation will occur in accordance with the rules listed below.

- *A minimum of 3 patients will initially be enrolled in each cohort. The first 3 patients in each cohort will be sequentially enrolled and dosed at least 48 hours apart.*
- *If none of the first 3 DLT-evaluable patients experiences a DLT, the doses in that cohort will be deemed safe and tolerable, and escalation may continue per the dose-escalation plan described above.*
- *If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, the doses in that cohort will be deemed safe and tolerable, and escalation may continue per the dose-escalation plan described above.*
- *If a DLT is observed in ≥33% of patients (e.g., 2 or more of up to 6 DLT-evaluable patients), the dose combination at which this occurs will be considered intolerable and the MTD will have been exceeded for lenalidomide in the R +Pola +Len treatment combination.*
- *If the MTD is exceeded in any cohort, the highest dose combination at which <33% of patients (e.g., 2 of 6 DLT-evaluable patients) experience a DLT will be declared*

the combination MTD (i.e., the MTDs lenalidomide in the R +Pola +Len treatment combination).

- *If the MTD is not exceeded at any dose level, the highest dose combination administered in this study will be declared the maximum administered dose for polatuzumab vedotin and lenalidomide in the R +Pola +Len treatment combination.*

If the MTD is exceeded in any cohort, de-escalation of the lenalidomide dose and/or polatuzumab vedotin dose, and/or adjustment of treatment schedules (e.g., lenalidomide treatment on Days 1–10) may occur. Additional patients may be enrolled in a given cohort in the absence of DLTs to acquire additional safety data for the appropriate dose levels in the expansion phase of the study.

On the basis of a review of real-time safety data and available preliminary PK data, dose escalation may be halted or modified by the Sponsor as deemed appropriate.

Relevant demographic, adverse event, laboratory, dose administration/intensity, and PK (if available) data will be reviewed prior to dose-escalation decisions, which will be objectively reviewed throughout the study by the Clinical Study Team and prior to dose-escalation decisions, which will be made by the Medical Monitor in consultation with the Principal Investigator and participating investigators.

Although the DLT assessment window is defined as the first treatment cycle, cumulative or late toxicities occurring beyond the first cycle may be considered when determining the RP2Ds. Prior to opening the R/R DLBCL expansion phase, the Clinical Study Team and the Medical Monitor will review the cumulative data, determine the RP2D, and review this with the IMC for approval.

TABLE 6: ***Induction Treatment for the DLBCL Dose-Escalation Phase***

Table 6 has been added. Subsequent tables have been renumbered accordingly.

TABLE 7: ***Consolidation Treatment for the Dose-Escalation Phase***

Table 7 has been added. Subsequent tables have been renumbered accordingly.

FIGURE 3: ***DLBCL Dose-Escalation Plan***

Figure 3 has been added. Subsequent figures have been renumbered accordingly.

TABLE 8: ***DLBCL Dose-Escalation Cohorts***

Table 8 has been added. Subsequent tables have been renumbered accordingly.

SECTION 3.1.3.2: ***DLBCL Expansion Phase*** **(NEW SECTION)**

The expansion phase is designed to further assess the safety and efficacy of lenalidomide when combined with a fixed dose of rituximab and polatuzumab vedotin in DLBCL patients.

Approximately 40 patients with DLBCL will be enrolled during the expansion phase and treated as described below.

All patients enrolled in the expansion phase will receive induction treatment as outlined in Table 9. When study treatments are given on the same day, they will be administered sequentially in the following order: lenalidomide, rituximab, and polatuzumab vedotin.

Patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with rituximab and lenalidomide as outlined in Table 10. Polatuzumab vedotin will not be given during the post-induction phase. Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity, for up to 6 months for consolidation treatment.

TABLE 9: *Induction Treatment for the DLBCL Expansion Phase*

Table 9 has been added. Subsequent tables have been renumbered accordingly.

TABLE 10: *Post-Induction Treatment for the DLBCL Expansion Phase*

Table 10 has been added. Subsequent tables have been renumbered accordingly.

SECTION 3.2: End of Study and Length of Study

The end of this study is defined as the time when both of the following criteria are met:

- All enrolled patients with FL have *been followed for at least 90 days after they have* completed or discontinued study treatment (including induction treatment and maintenance treatment as applicable).

SECTION 3.3.1: Rationale for Patient Population

On the basis of a compelling biologic and clinical rationale, as presented in Section 1.4, the addition of polatuzumab vedotin to obinutuzumab *or rituximab* and lenalidomide is a promising approach to expand the number of patients with R/R FL and DLBCL who achieve remission and to prolong response duration in these patients.

The study will include an initial dose-escalation phase followed by an expansion phase. The objective of the dose-escalation phase is to define the RP2D for lenalidomide and the RP2D dose for polatuzumab vedotin when given with obinutuzumab *in patients with R/R FL and the RP2D for lenalidomide when given in combination with polatuzumab at 1.8 mg/kg and rituximab at 375 mg/m² in patients with R/R DLBCL.* Although the DLT assessment window is the first cycle of treatment, long-term or cumulative toxicities will also be assessed and considered for the dose definition. ~~As relapsed or refractory DLBCL has a more aggressive course, with an expected higher risk of early progression than FL, patients with DLBCL will not be enrolled in the dose escalation phase in an attempt to minimize the number of patients not evaluable for DLTs and increase the chances for assessing toxicities with later onset during treatment. The doses identified~~

~~in patients with FL during the dose escalation phase will then be applied to patients in the expansion phase (including patients with FL and DLBCL), where efficacy data will be collected and safety will be continually monitored.~~

SECTION 3.3.2: Rationale for the Triplet Combination

As discussed in Section 1.4, there is a strong MOA and clinical rationale to expect an improved benefit-risk profile with the triplet combination of obinutuzumab *or rituximab*, polatuzumab vedotin, and lenalidomide over standard immunochemotherapy regimens. The hypothesis is that this novel triplet regimen may have the potential to extend treatment-free remissions and decrease toxicity by improving upon individual agents in the current standard of care. Overlapping toxicities are anticipated and expected to be manageable in the clinical setting (see Section 5.1.5).

As discussed in Section 1.4, the development of obinutuzumab in B-cell malignancies is based on the hypothesis that obinutuzumab will be a superior anti-CD20 agent compared to rituximab *in patients with FL*. This has been demonstrated in CLL (Goede et al. 2014) and *has been studied in* ~~is anticipated to be demonstrated in~~ two additional Phase III studies in DLBCL and FL.

Study BO21223 investigated obinutuzumab plus chemotherapy (G-benda, G-CVP, G-CHOP) compared with rituximab plus chemotherapy, followed by obinutuzumab or rituximab maintenance in patients with previously untreated iNHL (FL cohort, n =1202) and demonstrated positive results, showing a significant improvement in PFS in the obinutuzumab chemotherapy arm.

Study BO21005, investigated G-CHOP compared with R-CHOP in patients with previously untreated DLBCL and this study did not meet its primary endpoint of PFS at final analysis.

On the basis of the results of these Phase III studies evaluating obinutuzumab in combination with chemotherapy in both FL and DLBCL, patients with R/R FL in this current protocol amendment will continue to receive obinutuzumab in combination with polatuzumab vedotin and lenalidomide, while patients with R/R DLBCL will instead receive rituximab in combination with polatuzumab vedotin and lenalidomide.

SECTION 3.3.2.1: Rituximab and Polatuzumab Vedotin Combination

During its early development, polatuzumab vedotin treatment has been investigated as a single agent and in combination with rituximab. On the basis of available Phase I and II data (see Section 3.3.3.2 and Appendix 11), polatuzumab vedotin as a single agent and combined with rituximab has shown clinical activity in heavily pretreated patients with R/R B-cell lymphoma (Palanca-Wessels et al. 2012; Morschhauser et al. 2014a). In both studies, patients received rituximab 375 mg/m^2 and polatuzumab vedotin up to 2.4 mg/kg Q3W for up to 1 year, progression, or unacceptable toxicity. *The ongoing Study*

GO27834 has also shown preliminary safety and efficacy results evaluating the combination of rituximab and polatuzumab vedotin 1.8 mg/kg.

SECTION 3.3.2.2: Obinutuzumab and Polatuzumab Vedotin Combination

The combination of obinutuzumab with polatuzumab vedotin is being evaluated in several ongoing studies (see Table 11), including two Phase Ib/II trials in patients with R/R FL. ~~and relapsed or refractory DLBCL and in relapsed or refractory B-cell lymphoma and previously untreated DLBCL.~~ ~~As these new data emerge, these will be assessed and applied to update this study, if required.~~ *Preliminary results from these studies show safety and efficacy at the polatuzumab vedotin 1.8-mg/kg dose level when combined with obinutuzumab, every 3 weeks for 6–8 cycles as described in Section 1.3.2.*

SECTION 3.3.3.1: Rationale for Obinutuzumab Dose and Schedule *in Patients with Follicular Lymphoma*

The dose and schedule for obinutuzumab in this study will be fixed for the induction and the maintenance ~~(FL) or consolidation (DLBCL)~~ components of the study, and obinutuzumab will not be dose-escalated. This is based on the recommended dose and schedule (6–8 cycles depending on the trial) of obinutuzumab ~~in the ongoing~~ *from the* Phase III program in patients with B-cell lymphoma.

[…]

The dose and schedule of obinutuzumab in the maintenance regimen (FL) will be 1000 mg IV administered every 2 months for 2 years. This dosing administration is based on the obinutuzumab maintenance regimen that was administered in the Phase III Study GAO4753g (Sehn et al. 2015). ~~The dose and schedule of obinutuzumab in the consolidation regimen (DLBCL) will be 1000 mg IV administered every 2 months for a total of 3 doses. The consolidation regimen was modeled after the FL maintenance therapy.~~

SECTION 3.3.3.2.1: *Rationale for Polatuzumab Vedotin Dose in Patients with Follicular Lymphoma*

For this study, dose escalation of polatuzumab vedotin *for patients with R/R FL* will begin at a dose level of 1.4 mg/kg (one dose level below the highest ~~allowed~~ polatuzumab vedotin dose *currently under development*) and will escalate to a final dose of 1.8 mg/kg, if tolerated. The *initial* polatuzumab vedotin dose and schedule for this study were based on the experience from the Phase I study (DCS4968g) with single-agent polatuzumab vedotin and the Phase II study (GO27834) with polatuzumab vedotin in combination with rituximab in patients with relapsed and refractory B-cell lymphoma, the majority of which had FL or DLBCL. Most evidence of anti-tumor activity was observed at doses ≥1.8 mg/kg alone or in combination with rituximab.

[…]

The combination of obinutuzumab with polatuzumab vedotin is being evaluated in several ongoing studies (see Table 11), including two Phase Ib/II trials in patients with R/R FL. ~~and relapsed or refractory DLBCL and in relapsed or refractory B-cell lymphoma and previously untreated DLBCL.~~

[…]

In Study GO29044, the starting dose of polatuzumab vedotin ~~is~~ *was* 1.4 mg/kg and ~~will be~~ *was* escalated to 1.8 mg/kg, ~~if tolerated, when combined~~*in combination* with G-CHP. In Study GO29365, the starting dose of polatuzumab vedotin is 1.8 mg/kg when combined with obinutuzumab and bendamustine. Since polatuzumab vedotin is being combined with obinutuzumab and chemotherapy (CHP or bendamustine) at 1.4 or 1.8 mg/kg, *for patients with R/R FL in this study,* dose escalation of polatuzumab vedotin will begin at a dose level of 1.4 mg/kg (one dose level below the highest ~~allowed~~ polatuzumab vedotin dose *level in clinical development*) and will escalate to a final dose of 1.8 mg/kg, if tolerated. This novel triplet, G+Pola+Len, substitutes out the standard chemotherapy components with lenalidomide, which in this combination may have the potential to extend treatment-free remissions and decrease toxicity, compared to combinations with standard chemotherapy components.

TABLE 11: Polatuzumab Vedotin+Obinutuzumab–Containing Regimens for the Treatment of *Follicular* Lymphoma

Table 11 has been revised to specify the FL patient population and remove the DLBCL patient population. Subsequent tables have been renumbered accordingly.

SECTION 3.3.3.2.2: *Rationale for Polatuzumab Vedotin Dose in Patients with DLBCL* (NEW SECTION)

On the basis of the preliminary data from the patients with DLBCL treated in Studies GO29044 and GO29365, the dose level of polatuzumab vedotin at 1.8 mg/kg has been shown to be safe and tolerable in combination with rituximab and chemotherapy.

Due to the aggressive nature of DLBCL and the evidence that anti-tumor activity was observed at doses ≥1.8 mg/kg alone or in combination with rituximab, the higher dose level of polatuzumab vedotin is preferred to maximize clinical benefit for the R/R DLBCL population, which has no standard of care.

The safety profile of rituximab differs slightly in comparison with obinutuzumab and is expected to be tolerated when combined with polatuzumab vedotin at 1.8 mg/kg and lenalidomide; hence, in this amendment, the R/R DLBCL dose-escalation phase will start at the dose level of 1.8 mg/kg and only the lenalidomide dose will be escalated to determine an RP2D in this population.

SECTION 3.3.3.2.3: *Rationale for Polatuzumab Vedotin Dosing Schedule in Patients with Follicular Lymphoma and DLBCL*

The number of induction cycles (six ~~21~~*28*-day cycles) ~~of the G+Pola+Len regimen that will be evaluated in this study is consistent with rituximab plus lenalidomide and obinutuzumab plus lenalidomide regimens used to treat B-cell lymphoma.~~ *is in line with other anti-CD20 plus polatuzumab vedotin regimens studied in R/R NHL.*

SECTION 3.3.3.4: Rationale for Treatment Duration

Patients with R/R DLBCL who are not suitable for or do not benefit from consolidative autologous transplantation exhibit a poor prognosis. Responses obtained with different rituximab treatment regimens tested in clinical trials (e.g., rituximab in combination with bendamustine, with gemcitabine plus oxaliplatin, or with lenalidomide) have been of short duration, with the longest reported median PFS of approximately 7 months observed in one study of BR (Ohmachi et al. 2013). Thus, 6 months of consolidation treatment, for a total treatment duration of approximately 12 months, is considered to be a reasonable exploratory therapeutic approach in patients with R/R DLBCL with an anticipated positive benefit-risk ratio. On the basis of the complementary mechanism of action between all three study drugs and considering the aggressiveness of R/R DLBCL, the study was designed to investigate the safety and efficacy of the triple combination in the consolidation setting.

SECTION 4.1.1: Inclusion Criteria

- ~~For patients enrolled in the dose escalation phase~~ *For G + Pola + Len treatment group: R/R* FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator
- ~~For patients enrolled in the expansion phase lymphoma classified as either of the following:~~*For R + Pola + Len treatment group:*

  ~~Relapsed or refractory FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator~~

  R/R DLBCL after treatment with at least one prior chemoimmunotherapy regimen *that included an anti-CD20 monoclonal antibody* in patients who are not eligible for autologous stem-cell transplantation or who have experienced disease progression following treatment with high-dose chemotherapy plus autologous stem-cell transplantation

- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL

  If the archival tissue is unavailable or unacceptable, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

If the patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, a repeat core-needle biopsy is strongly recommended.

Further details are provided in Section 4.5.6.

- Agreement to comply with all local requirements of the lenalidomide risk minimization plan

  In every country where lenalidomide has been approved, a risk minimization plan, which includes a pregnancy prevention program, is in place. The risk minimization plan should be followed by patients using lenalidomide.

  US sites only: *Per standard Revlimid REMS™ requirements, all physicians who prescribe lenalidomide for research subjects enrolled in this study and all research subjects enrolled in this study must be registered in and must comply with all requirements of the Revlimid REMS™ program.*

  For Ex-US sites only: *Subjects will be counseled on pregnancy prevention prior to medication being dispensed to ensure that the subject has complied with all requirements, including use of birth control and pregnancy testing, and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Education and Counseling Guidance Document (refer to Lenalidomide Pregnancy Prevention Risk Management Plans), and no drug will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (refer to Lenalidomide Pregnancy Prevention Risk Management Plans) will be supplied with each medication dispensed. All requirements must be followed by each site as noted within the Lenalidomide Pregnancy Prevention Risk Management Plans.*

  In addition, because lenalidomide will be administered in combination with obinutuzumab, *rituximab,* and polatuzumab vedotin, patients must comply with contraceptive measures designed to ensure safe administration of all ~~three~~ study treatments as outlined below.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use <u>two</u> adequate methods of contraception, including at least one method with a failure rate of $<1\%$ per year, for at least 28 days prior to Day 1 of Cycle 1, during the treatment period (including periods of treatment interruption), and for at least *12 months after the last dose of polatuzumab vedotin, 28 days after the last dose of lenalidomide, 12 months after the last dose of rituximab, and* 18 months after the last dose of *obinutuzumab* ~~study treatment~~
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of *polatuzumab vedotin, 28 days after the last dose of lenalidomide, and 3 months after the last dose of obinutuzumab or rituximab.* ~~study treatment.~~ Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 5 months after the last dose of *polatuzumab vedotin, 28 days after the last dose of lenalidomide, and 3 months after the last dose of obinutuzumab or rituximab* ~~study treatment~~ to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

SECTION 4.1.2: Exclusion Criteria

- *Grade 3b follicular lymphoma*
- *History of transformation of indolent disease to DLBCL*
- Prior standard or investigational anti-cancer therapy as specified below:

  Lenalidomide, fludarabine, or alemtuzumab within 12 months prior to Day 1 of Cycle1

  Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1

  Monoclonal antibody or ADC therapy within *5 half-lives or* 4 weeks prior to Day 1 of Cycle 1*, whichever is longer*

  Radiotherapy, chemotherapy, hormonal therapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1
- Known sensitivity or allergy to murine products or any component of obinutuzumab, *rituximab,* polatuzumab vedotin, or lenalidomide formulations
- Active bacterial, viral, fungal, or other infection

  Caution should be exercised when considering the use of obinutuzumab *and rituximab* in patients with a history of recurring or chronic infections.
- Any of the following abnormal laboratory values (unless due to underlying lymphoma):

  Calculated creatinine clearance < ~~60~~*50* mL/min (using the Cockcroft-Gault formula; see Appendix 7)

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT

This is a Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study of G + Pola + Len in patients with R/R FL ~~or~~ *and R + Pola + Len in patients with R/R* DLBCL. During the dose-escalation phase, patients ~~with relapsed or refractory FL~~ will be

assigned to cohorts with varying polatuzumab vedotin *(R/R FL dose-finding only)* and lenalidomide dose combinations, through use of an interactive voice or web-based response system (IxRS). During the *FL* expansion phase, ~~all~~ patients *with R/R FL* will receive obinutuzumab in combination with lenalidomide at the *FL* RP2D and polatuzumab vedotin at the RP2D as induction treatment. *During the DLBCL expansion phase, patients with R/R DLBCL will receive rituximab and polatuzumab in combination with lenalidomide at the DLBCL RP2D.* Post-induction treatment (for eligible patients only) will depend on lymphoma histology. Patients with FL will receive maintenance treatment with obinutuzumab and lenalidomide, and patients with DLBCL will receive consolidation treatment with ~~obinutuzumab~~*rituximab* and lenalidomide (see Section 3.1.1 for details).

SECTION 4.3: STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide.

SECTION 4.3.1.2: *Rituximab* (NEW SECTION)

Rituximab will be supplied by the Sponsor as an IMP. Rituximab is packaged in 10-mL (100-mg) and 50-mL (500-mg) single-dose, pharmaceutical-grade glass vials at a concentration of 10 mg/mL of protein. The antibody is formulated for IV injection as a sterile product in a solution of sodium chloride (pH 6.5) containing polysorbate 80 and sodium citrate. For information on the formulation and handling of rituximab, see the pharmacy manual and the Rituximab Investigator's Brochure.

SECTION 4.3.2: Dosage, Administration, and Compliance

Patients enrolled in the dose-escalation phase or the expansion phase will receive six 28-day cycles of induction treatment with obinutuzumab *or rituximab*, polatuzumab vedotin, and lenalidomide. When study treatments are given on the same day, they will be administered sequentially in the following order: lenalidomide, *obinutuzumab or rituximab*, and polatuzumab vedotin.

Patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with lenalidomide and ~~obinutuzumab~~*rituximab*, and patients with FL who achieve a CR, PR, or SD at EOI will receive post-induction treatment (referred to as maintenance) with lenalidomide and obinutuzumab. When study treatments are given on the same day, lenalidomide will be administered prior to obinutuzumab *or rituximab*.

Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity for up to 2 years for maintenance treatment or ~~1 year~~ *6 months* for consolidation treatment.

Treatment regimens are summarized in Table 1, Table 2, Table 4, and Table 5 *for R/R FL patients and Table 6, Table 7, Table 9, and Table 10 for R/R DLBCL patients*

(see Section 3.1) and depicted in Figure 4. All eligible patients in both dose-escalation and expansion phases should receive induction and post-induction (if indicated) therapy.

FIGURE 4: Induction and Post-Induction Treatment Regimen

Figure 4 has been revised to include rituximab.

SECTION 4.3.2.1: Obinutuzumab

Obinutuzumab will be administered by IV infusion at an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of the first cycle and on Day 1 of each subsequent cycle during induction treatment, and on Day 1 of every other month (i.e., every 2 months) during ~~consolidation treatment (eligible patients with DLBCL only) or~~ maintenance treatment (eligible patients with FL only). A month is defined as 28 days.

FIGURE 6: *Guidelines for Obinutuzumab Infusions: Second and Subsequent Infusions*

Figure 6 has been revised to clarify second and subsequent infusions by IRR grade.

SECTION 4.3.2.2: *Rituximab* (NEW SECTION)

Rituximab will be administered by IV infusion at the dose of 375 mg/m² on Day 1 of Cycles 1−6 during induction treatment and on Day 1 of every other month (i.e., every 2 months) during consolidation treatment for patients with R/R DLBCL.

Body surface area (BSA) will be determined at screening and should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by >10% from screening, in which case BSA should be recalculated and used for subsequent dosing. In obese patients (defined as body mass index ≥30 kg/m²), there is no BSA cap and actual body weight, not adjusted weight, is recommended. Empiric dose adjustment for obese patients may be implemented per institutional guidelines.

The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden or high peripheral lymphocyte count). Administration of rituximab may be continued on the following day, if needed, for patients who experience an adverse event during the rituximab infusion.

If a dose of rituximab is split over 2 days, both infusions must occur with appropriate premedication (see Section 4.3.2.5) and at the first infusion rate (see Table 12).

Rituximab infusions will be administered according to the instructions in Table 12. During the treatment period, rituximab must be administered to patients in a setting where full emergency resuscitation facilities are immediately available. Patients should be under close supervision of the investigator at all times.

Rituximab should be administered as a slow IV infusion through a dedicated line. After the end of the first infusion, the IV line or central venous catheter should remain in

place for ≥2 hours in order to administer IV drugs, if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

No dose modification for rituximab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.6.

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.5, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 8.

TABLE 12: ***Administration of First and Subsequent Infusions of Rituximab***

Table 12 has been added. Subsequent tables have been renumbered accordingly.

SECTION 4.3.2.3: Polatuzumab Vedotin

For R/R FL, during ~~During~~ the dose-escalation phase, the dose of polatuzumab vedotin for each patient will depend on dose assignment (1.4 or 1.8 mg/kg). During the expansion phase, the dose of polatuzumab vedotin for each patient will depend on the RP2D established during the dose-escalation phase. *For R/R DLBCL, during the dose-escalation phase and the expansion phase, the dose of polatuzumab vedotin will be fixed at 1.8 mg/kg.* Polatuzumab vedotin will be administered by IV infusion on Day 1 of each cycle, during induction treatment only.

SECTION 4.3.2.5: Premedication and Other Required Medication

Lenalidomide increases the risk of thromboembolism. All patients will be required to take daily aspirin (*75*~~81~~–100 mg) for TE prophylaxis during lenalidomide treatment and until 28 days after the last dose of lenalidomide. Patients who are unable to tolerate aspirin, patients with a history of TE, and patients at high risk of TE should receive warfarin or low-molecular-weight heparin (LMWH).

Patients should receive premedication as outlined in Table 13.

TABLE 13: Premedication

Table 13 has been revised to include rituximab and to add premedication information for patients by IRR grade.

SECTION 4.3.3: <u>Investigational Medicinal Product Accountability</u>

All IMPs required for completion of this study (obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. *Lenalidomide will be dispensed to*

sites in the United States via the Celgene REMS™ system. For sites outside the United States, lenalidomide will be dispensed to sites through the study IxRS. Sites will be trained on lenalidomide specific requirements by their study monitors.

SECTION 4.3.4: Post-Trial Access to Obinutuzumab, *Rituximab,* Polatuzumab Vedotin, and Lenalidomide

Currently, the Sponsor does not have any plans to provide obinutuzumab*, rituximab,* ~~and~~ polatuzumab vedotin, or any other study treatments or interventions to patients who have completed the study. The Sponsor will evaluate whether to continue providing obinutuzumab*, rituximab, or* ~~and~~ polatuzumab vedotin in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

SECTION 4.4: CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from *7*~~28~~ days prior to the screening period to the visit at EOI or at the end of post-induction treatment, whichever occurs later. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

SECTION 4.4.2: Prohibited Therapy

Use of the following therapies (excluding protocol-specified treatments) is prohibited during the study:

- Any anti-cancer therapy, approved or investigational, other than intrathecal central nervous system prophylaxis
- Hormonal therapy other than contraceptives, stable hormone-replacement therapy, or megestrol acetate
- Biologic agents other than hematopoietic growth factors (as described in Section 4.4.1)
- *Vaccination with live vaccines is not recommended during treatment with obinutuzumab or rituximab and until B-cell recovery*

SECTION 4.5.5: Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the IRC and the investigator on the basis of PET and CT scans, using the Lugano 2014 criteria*, taking into account results of bone marrow examinations for patients with bone marrow involvement at screening.*

In this study, the Lugano 2014 criteria for a PET-CT–based CR have been slightly modified to require normal bone marrow for patients with bone marrow involvement at screening. *Additionally, designation of PET-CT-based PR requires that CT-based*

response criteria for a CR or PR be met in addition to the PET-CT-based response criteria for a PR (see Appendix 5).

SECTION 4.5.6: Laboratory, Biomarker, and Other Biological Samples

Local Laboratory Assessments

Samples for the following laboratory tests will be analyzed at the study site's local laboratory for analysis:

- Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, uric acid, glycosylated hemoglobin (HbA_{1c}), amylase, and lipase (amylase and lipase only during induction). HbA_{1c} will be measured only at Screening and can be obtained in a non-fasting state.
- *Thyroid-stimulating hormone, triiodothyronine, thyroxine*
- β_2 microglobulin
- Coagulation: INR, aPTT (or PTT), and PT
- Pregnancy test

  All women of childbearing potential must have two negative serum pregnancy test results (minimum sensitivity, 25 mIU/mL) prior to initiating therapy: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1. Urine pregnancy tests will be performed at specified subsequent visits (see Appendix 1 and Appendix 2). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Viral serology

  Hepatitis B testing includes HBsAg and total HBcAb

  Hepatitis C testing includes HCV antibody

  HIV testing (if required per local regulatory requirements)
- Quantitative immunogloblulins: IgA, IgG, and IgM

Central Laboratory Assessments

The following samples will be sent to one or several Sponsor-designated central laboratories or to the Sponsor for analysis:

- Serum samples for obinutuzumab PK analysis using a validated assay
- *Serum samples for rituximab PK analysis using a validated assay*
- Serum and plasma samples for polatuzumab vedotin PK analysis using a validated assay
- Plasma samples for lenalidomide PK analysis using a validated assay
- Serum samples for assessment of obinutuzumab HAHAs using a validated assay

- *Serum samples for assessment of rituximab HACAs using a validated assay*
- Serum samples for assessment of polatuzumab vedotin ATAs using a validated assay
- Tumor tissue samples (obtained within 6 months prior to the initiation of study treatment for DLBCL or within 12 months prior to the initiation of study treatment for FL) and the corresponding pathology report for retrospective central confirmation of the ~~original~~ diagnosis of FL or DLBCL and for exploratory research on candidate biomarkers (see Table 14)

  The specimen must contain adequate evaluable tumor cells (≥ 20% for excisional biopsy and ≥ 50% for core biopsy).

  Formalin-fixed paraffin-embedded tissue blocks are preferred over slides. Tissue blocks that are not formalin fixed will be accepted in countries that use a fixative other than paraformaldehyde, but information on the type of fixative should be included. If a tissue block is not available, a minimum of 20 serial, freshly cut, unstained slides accompanied by a tumor block punch may be sent. A tumor block or tumor block punch is required for construction of a tissue microarray.

  If archival tissue is unavailable or unacceptable according to above criteria, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

  If the available biopsy was performed more than 12 months prior to Day 1 of Cycle 1, or the patient received anti-lymphoma treatment between the time of the most recent available biopsy and Day 1 of Cycle 1, a core-needle biopsy is strongly recommended.

  The sample should be shipped according to instructions provided in the laboratory manual. The remainder of the archival tissue blocks will be returned to the local pathology laboratory, according to country-specific procedures after the clinical study report has been published or upon request.
- ~~Optional t~~*T*umor biopsy samples obtained at the time of progression (unless no adequate tumor site is accessible) for exploratory research on candidate biomarkers (see Table 14)
- Plasma samples for exploratory research on candidate biomarkers (see Table 14)
- Whole blood samples for exploratory research on candidate biomarkers (see Table 14)
- ~~Whole blood samples for isolation of peripheral blood mononuclear cells for exploratory research on candidate biomarkers (see Table 14).~~
- Whole blood for lymphocyte immunophenotyping (see Table 14)

Samples collected for PK and immunogenicity analyses may be used for assay development purposes and additional safety and immunogenicity assessments, as appropriate.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research, biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception(s):

- *Serum [or plasma] samples collected for PK and immunogenicity (ATA) analysis may be needed for additional PK and ATA assay development and validation, and additional immunogenicity characterization; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed* ~~Biological samples will be destroyed when the final clinical study report has been completed, unless the patient gives specific consent for the leftover samples to be stored for optional exploratory research~~ (see Section 4.5.8).

TABLE 14: Proposed Non-Inherited Biomarkers

Table 14 has been revised to remove information about peripheral blood mononuclear cells.

SECTION 4.5.8.3: Sample Collection

The following samples and derivatives thereof (e.g., DNA, RNA, proteins, peptides) will be collected for research purposes, including, but not limited to, research on dynamic (non-inherited) and genetic (inherited) biomarkers related to obinutuzumab, *rituximab,* polatuzumab vedotin, lenalidomide, B-cell lymphoma, or other types of cancer:

- Peripheral blood (i.e., whole blood)
- Remaining tumor tissue from lymph node biopsy (archival and/or fresh biopsy)
- Remaining peripheral blood (e.g., whole blood~~, peripheral blood mononuclear cells [PBMCs]~~, plasma, and serum)

SECTION 4.6.2: <u>Study Treatment Discontinuation</u>

Patients who discontinue study treatment will not be replaced, except as outlined below:

- During the dose-escalation phase, patients who discontinue study treatment prior to completing the DLT assessment window for reasons other than a DLT will be replaced by an additional patient at that same dose level.
- ~~During the expansion phase, p~~*P*atients who discontinue ~~study treatment~~ prior to receiving at least one dose of each component of the combination will be replaced.

SECTION 5.1: SAFETY PLAN

Polatuzumab vedotin is not a marketed product, and ~~obinutuzumab and~~ *lenalidomide is*~~are~~ not approved for the treatment of patients with R/R FL. *Obinutuzumab is only approved in combination with bendamustine for the treatment of R/R FL. Rituximab and lenalidomide are not approved for the treatment of patients with R/R DLBCL.* Clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide in completed and ongoing studies. The anticipated important safety risks of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide are outlined below. Please refer to the Obinutuzumab, *Rituximab,* and Polatuzumab Vedotin Investigator's

Brochures and the lenalidomide Summary of Product Characteristics (SmPC) for a complete summary of safety information.

SECTION 5.1.1: Risks Associated with Obinutuzumab

To date, the following adverse events are considered to be important *identified* risks associated with obinutuzumab: IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), infections (including PML and HBV reactivation), prolonged B-cell depletion, impaired immunization response, worsening of preexisting cardiac conditions, and gastrointestinal perforation.

SECTION 5.1.1.6: Immunizations

The safety of immunization with live *or attenuated viral* ~~virus~~ vaccines following obinutuzumab therapy has not been studied *and* ~~. Thus,~~ vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

SECTION 5.1.2: *Risks Associated with Rituximab* (NEW SECTION)

The following adverse events are considered to be important risks associated or potentially associated with rituximab: IRRs, infections (including severe infections), PML, hepatitis B reactivation, neutropenia (including prolonged neutropenia), TLS, impaired immunization response, severe skin reactions (Stevens-Johnson syndrome [SJS]/toxic epidermal necrolysis [TEN]), and GI perforation. Details for these risks are provided below; refer to the Rituximab Investigator's Brochure for full information.

SECTION 5.1.2.1: *Infusion-Related Reactions* (NEW SECTION)

Acute IRRs are very common in patients receiving rituximab (occurring in ≥10% of patients) based on clinical trial experience. However, serious IRRs are uncommonly reported (occurring in ≥1 of 1,000 and <1 of 100 patients) and are rarely fatal (occurring in ≥1 of 10,000 and <1 of 1,000 patients). Most IRRs occur with the first administration of rituximab. Most IRRs are mild to moderate in severity (Grades 1 or 2) and can be managed by slowing or stopping the rituximab infusion. IRRs can be severe and, in rare cases, can result in death. Rituximab-induced IRRs consist of a cluster of symptoms and signs occurring during or within 24 hours of a rituximab infusion that may be related to cytokine release and/or other chemical mediators, and these acute IRRs overlap with "cytokine release syndrome." Anaphylactic and other hypersensitivity reactions have been reported following rituximab administration, and clinical manifestations of these reactions are similar to cytokine release syndrome. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the rituximab infusion.

SECTION 5.1.2.2: *Infections (Including Serious Infections)* (NEW SECTION)

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy.

SECTION 5.1.2.3: *Hepatitis B Reactivation* (NEW SECTION)

Reactivation of hepatitis B ranges from asymptomatic reactivations (detected by changes in laboratory parameters only) to fulminant liver failure and death. Patients with chronic hepatitis B (HBsAg positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and anti-HBcAb positive) are at a lower risk for reactivation. Patients who demonstrate evidence of reactivation while receiving an appropriate anti-viral therapy will be discontinued from study treatment.

SECTION 5.1.2.4: *Progressive Multifocal Leukoencephalopathy* (NEW SECTION)

Rare cases of PML have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson and Bennett 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is rare, but it should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic SCT. Most cases of PML were diagnosed within 12 months of the patients' last infusion of rituximab.

SECTION 5.1.2.5: *Neutropenia (Including Prolonged Neutropenia)* (NEW SECTION)

Neutropenia is very common in patients receiving rituximab (occurring in ≥ 10% of patients) based on clinical trial experience. However, delayed onset neutropenia is very rare (occurring in < 1 of 10,000 patients), and the incidence of prolonged neutropenia is unknown. Neutropenia may lead to serious or overwhelming infection, especially if profound (Grades 3–4), prolonged, associated with breaches in natural mucosal barriers (e.g., diarrhea and/or mucositis), and/or other immunological defects (e.g., lymphopenia, hypogammaglobulinemia, and acquired immunodeficiency syndrome). Despite an increase in incidence of neutropenia and Grade 3–4 neutropenia associated with rituximab, most studies have not reported a significant increase in serious neutropenic infections.

SECTION 5.1.2.6: *Tumor Lysis Syndrome* (NEW SECTION)

Patients treated with rituximab may be at risk for TLS. Severe tumor TLS is very rare in patients receiving rituximab (occurring in < 1 of 10,000 patients), based on postmarketing experience. Signs and symptoms (e.g., hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated LDH) that are consistent with TLS have been reported to occur after the first rituximab IV infusion in patients with high numbers of circulating malignant lymphocytes. A high number of circulating malignant cells (≥ 25,000/mm^3) or high tumor burden confers a greater risk of TLS. For patients with evidence of TLS, rituximab should be discontinued, and the patient should be treated as clinically indicated.

SECTION 5.1.2.7: *Impaired Immunization Response* (NEW SECTION)

B-cell depletion is expected (and desired) during rituximab therapy and is directly related to its mechanism of action. In theory, peripheral B-cell depletion may reduce the effectiveness of immunization, as patients may not be able to mount an effective humoral immune response to foreign antigens.

SECTION 5.1.2.8: *Severe Skin Reactions: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis* (NEW SECTION)

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. The onset of these reactions in patients treated with rituximab has varied from 1to 13 weeks following rituximab exposure. The majority of the Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) cases reported with rituximab were associated with additional risk factors. Fatal outcome also appeared to increase in patients who were exposed to multiple risk factors for SJS/TEN.

SECTION 5.1.2.9: *Gastrointestinal Perforation*(NEW SECTION)

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy.
In postmarketing reports of rituximab, the mean time to documented GI perforation was 6 days (range: 1–77 days) in patients with NHL.

SECTION 5.1.3.1: *Identified Risks* ~~Known Risks Associated with Polatuzumab Vedotin~~

The title of this section was revised.

SECTION 5.1.3.2: Potential Risks ~~Associated with Polatuzumab Vedotin~~ Infections

Neutropenia is a known risk for polatuzumab vedotin. Reports in the literature state that granulocytopenia is a major predisposing factor to infections in patients with B-cell lymphoma. Patients receiving chemotherapy for B-cell lymphoma with a granulocyte count of < 500 cells/μL experienced a higher incidence of infections than those with a count of > 500 cells/μL.

Progressive Multifocal Leukoencephalopathy (NEW SECTION)

One case of PML was reported in an [redacted]-year-old female with R/R FL after receiving one cycle of polatuzumab vedotin in combination with obinutuzumab and bendamustine. MRI showed changes suggestive of PML. Cerebrospinal fluid test for JC virus by PCR was negative. Confounders included previous lines of anti-CD20 therapies and concurrent use of obinutuzumab. Additional details of the case can be found in the Polatuzumab Vedotin Investigator's Brochure.

Infusion-Related Events

Because of the potential for infusion reactions, administration of polatuzumab vedotin will be performed in a setting with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies. All patients will be monitored for infusion reactions during the infusion and immediately afterward ~~(for additional instructions on the monitoring and management of infusion reactions, see Section 4.3.2.3)~~. Precautions for suspected anaphylactic reaction during study drug infusions are provided in Section 4.3.2.3. The initial dose of polatuzumab vedotin may be administered with premedication with acetaminophen, antihistamines, or corticosteroids per institutional standard practice at the discretion of the Investigator. Premedication should be instituted for subsequent doses if IRRs are observed in patients who receive their first dose of polatuzumab vedotin without premedications (see Section 4.3.2.3). Significant issues with polatuzumab vedotin IRRs have not been observed.

Similar considerations regarding infusion reactions are applicable for obinutuzumab. Refer to Section 4.3.2.1 for additional information.

Tumor Lysis Syndrome

There is the *potential* ~~theoretical~~ risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, tumor lysis prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/L or bulky lymphadenopathy) and who are considered to be at risk for tumor lysis by the investigator will receive tumor lysis prophylaxis (e.g., allopurinol $\geq$ 300 mg/day orally or a suitable alternative treatment [according to institutional practice] starting 12–24 hours before study treatment) and must be well hydrated before the initiation of study treatment on Day 1 of Cycle 1. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration before each subsequent infusion, as deemed appropriate by the investigator.

One case of TLS attributed to polatuzumab vedotin has been reported (Study GO27834); however, the laboratory elevations did not meet the Howard criteria for TLS (see Appendix 12). The suspected TLS event resolved after 3 days of supportive care. One case of Grade 3 Laboratory TLS was reported in the ongoing Phase Ib/II Study GO29833 combining polatuzumab vedotin, obinutuzumab, and venetolax.

The patient was at high risk for TLS due to bulky disease and decreased renal function. Potassium and phosphorous levels were elevated, while serum creatinine levels remained normal and the patient was asymptomatic. The TLS event was considered related to all three study treatments and resolved in 4 days with supportive care (see Polatuzumab Vedotin Investigator's Brochure for case details.

SECTION 5.1.4.1: Embryo-Fetal Toxicity

Lenalidomide must not be taken by patients who are pregnant. In every country where lenalidomide has been approved, a risk minimization plan, which includes a pregnancy prevention program, is in place. Investigators must ensure that all specific local requirements that are applicable to the safe and effective use of lenalidomide are fulfilled prior to administration to patients. The risk minimization plan should be followed by prescribers and by patients using lenalidomide, with one exception: Because lenalidomide will be administered in combination with polatuzumab vedotin and obinutuzumab *or rituximab*, patients must comply with contraceptive measures designed to ensure safe administration of all *four*~~three~~ study treatments, as outlined in Section 4.1.1. Pregnancy testing and counseling should be performed if a patient misses her period or has unusual*/irregular* menstrual bleeding. Treatment with lenalidomide must be discontinued until it is confirmed that the patient is not pregnant

SECTION 5.1.4.8: Renal Impairment

Lenalidomide is substantially excreted by the kidney. Patients with renal impairment (i.e., calculated creatinine clearance <~~60~~ *50* mL/min) will not be enrolled in this study.

SECTION 5.1.4.12: *Cardiovascular Reactions* (NEW SECTION)

Cases of serious adverse cardiovascular events, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in patients with CLL treated with lenalidomide compared to single agent chlorambucil. Patients will be monitored for the development of cardiac toxicities.

SECTION 5.1.4.13: *Impaired Stem Cell Mobilization* (NEW SECTION)

Patients have been reported to show a decrease in the number of CD34+ cells collected after treatment with lenalidomide. Early referral to a transplant center is recommended in patients who are autologous SCT candidates.

SECTION 5.1.5: Risk of Overlapping Toxicities

The anticipated toxicities from the combined administration of obinutuzumab *or rituximab with* polatuzumab vedotin and lenalidomide are expected to be manageable in the clinical setting and will be closely monitored throughout the study.

[…]

Both rituximab and lenalidomide have been associated with dermatologic reactions such as SJS and TEN, and the risk of overlapping toxicities will be monitored. Guidelines

for management of patients who develop dermatologic toxicities are provided in Table 19.

SECTION 5.1.6: Risk of Overlapping Toxicities

The risk for clinically relevant PK DDIs between study treatments is low. First, obinutuzumab, *rituximab,* and polatuzumab vedotin are not anticipated to interact directly with CYP isoforms or other drug–metabolizing enzymes or drug transporters. Cytokine modulation may be considered as an indirect mechanism through which a monoclonal antibody could alter CYP expression. However, treatment with obinutuzumab results in only transient increases in cytokine levels after the first infusion, and no increases are observed after subsequent infusions. In vitro (human PBMCs) and in vivo (cynomolgus monkeys) treatment with anti-CD79 antibodies (i.e., the same antigen target as polatuzumab vedotin) showed a low risk for release of systemic pro-inflammatory cytokines. Taken together, these results suggest that both obinutuzumab and polatuzumab vedotin are unlikely to precipitate DDIs via indirect effects on cytokines.

Second, lenalidomide is primarily excreted in the urine. Lenalidomide is not a substrate, inhibitor, or inducer of the CYP group of enzymes (Kumar et al. 2009). In vitro, the MMAE component of polatuzumab vedotin is mainly metabolized by CYP3A4, and it is mainly eliminated by biliary secretion in vivo. Both lenalidomide and MMAE are substrates but not inhibitors of P-gp. Owing to the different elimination pathways for lenalidomide and MMAE, the risk of CYP-mediated and transporter-mediated DDI risk is low when polatuzumab vedotin is combined with lenalidomide.

In addition, simulation results suggest that unconjugated MMAE exposure is likely to be altered by $<50\%$ when polatuzumab vedotin is co-administered with strong CYP3A inhibitors or inducers. Therefore, patients who receive concomitant medications that are strong CYP3A or P-gp inhibitors should be closely monitored for adverse reactions.

In summary, clinically relevant PK DDIs are unlikely to occur between lenalidomide, obinutuzumab, *rituximab,* and polatuzumab vedotin.

SECTION 5.1.7: Management of Specific Adverse Events

Treatment delays apply to all toxicities described below; dose modifications apply only to toxicities that are considered to be related to lenalidomide or polatuzumab vedotin (only for peripheral neuropathy). There will be no dose reductions of obinutuzumab *or rituximab. For patients receiving obinutuzumab, if toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses of obinutuzumab will not be skipped but given after resolution of toxicity.*

SECTION 5.1.7.1: Polatuzumab Vedotin Dose-Reduction Steps

The dose of polatuzumab vedotin may be reduced *due to neurotoxicity only* according to the following dose reduction steps based on the starting dose (see Table 15 and Table 19).

SECTION 5.1.7.2: Lenalidomide Dose-Reduction Steps

The dose of lenalidomide may be reduced in 5-mg increments one or two times *during induction or post-induction*, depending on the starting dose, as outlined in Table 16. There will be no more than one dose reduction per treatment cycle. *If the lenalidomide dose is reduced to 5 mg during induction, the maintenance or consolidation dose may be escalated to start at 10 mg in post-induction if considered safe per investigator judgment in consultation with the Sponsor. In all other cases, i*f the lenalidomide dose is reduced, re-escalation is not permitted.

SECTION 5.1.7.3: Hematologic Toxicities during Induction Treatment

Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia is not considered a hematologic toxicity, but rather an expected outcome of therapy. Table 16 provides guidelines for management of hematologic toxicities that occur during induction treatment, with the exception of Days 8 and 15 of Cycle 1 *for patients receiving obinutuzumab.* Table 17 provides guidelines for management of hematologic toxicities that occur at Days 8 and 15 of Cycle 1, when patients are to receive treatment with obinutuzumab only.

TABLE 17: Guidelines for Management of Hematologic Toxicities That Occur during Induction Treatment (Except Days 8 and 15 of Cycle 1 *for Patients Receiving Obinutuzumab*)

The Table 17 title has been revised to specify the cohort of patients receiving obinutuzumab. The table has also been revised to include rituximab.

TABLE 18: Guidelines for Management of Hematologic Toxicities That Occur on Days 8 and 15 of Cycle 1 *for Patients Receiving Obinutuzumab*

The Table 18 title has been revised to specify the cohort of patients receiving obinutuzumab.

TABLE 19: Guidelines for Management of Non-Hematologic Toxicities *During Induction*

The Table 19 title has been revised to specify the induction period, and table content has been updated.

TABLE 20: Guidelines for Management of Toxicities that Occur during Consolidation or Maintenance Treatment

Table 20 has been revised to include rituximab and to clarify lenalidomide dose reduction.

SECTION 5.2.3: Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- *Second malignancies*

SECTION 5.2.5: Selected Adverse Events

The following adverse events are considered selected adverse events:

[…]

- ~~Secondary malignancies~~

Events for which additional data collection will be required are PML *and*~~,~~ hepatitis B reactivation~~, and secondary malignancies~~.

SECTION 5.3.1: Adverse Event Reporting Period

After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. After this period, the investigator should report any serious adverse events that are believed to be related to prior study treatment *and events of second malignancies for patients who received obinutuzumab* (see Section 5.6).

An exception is *for the FL patients, where* Grade 3 and 4 infections (both related and unrelated)~~, which~~ should be reported until up to 2 years after the last dose of ~~study treatment~~. *obinutuzumab.*

SECTION 5.3.5.8: Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An ~~independent monitoring committee (~~IMC~~)~~ will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive~~

~~and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").* ~~During survival follow up, deaths attributed to progression of lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF.~~

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:~~The following hospitalization scenarios are not considered to be adverse events:~~

[…]

An event that leads to hospitalization under the following circumstance is not considered to be a serious adverse event, but should be reported as an adverse event instead:~~The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as an adverse event instead:~~

SECTION 5.4: IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to any of the study treatments:

- Serious adverse events (see Section 5.4.2 for further details)
- ~~Non serious~~ Adverse events of special interest (see Section 5.4.2 for further details)
- *Dose-limiting toxicities (see Section 5.4.2 for further details)*
- Pregnancies (see Section 5.4.3 for further details)

SECTION 5.4.2.2: Events that Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment. *After this period, the investigator should report any serious adverse events that are believed to be related to prior study treatment (see Section 5.6).* DLTs will be reported during the DLT assessment window. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF

and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting *events after the* ~~post study~~ adverse events *reporting period* are provided in Section 5.6.

SECTION 5.6: ~~POST STUDY~~ ADVERSE EVENTS *THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of study treatment), if the event is believed to be related to prior study treatment. *The sponsor should also be notified of events of second malignancies after the end of the adverse event reporting period for patients who received obinutuzumab.*

An exception is *for patients receiving obinutuzumab, where* Grade 3–4 infections (both related and unrelated)~~, which~~ should be reported until up to 2 years after the last dose of study treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting *Form* ~~eCRF~~ using the fax number or email address provided to investigators.

During survival follow-up, deaths attributed to progression of lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF.

SECTION 5.7: EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Obinutuzumab Investigator's Brochure (Oncology)

- *Rituximab Investigator's Brochure (Oncology)*
- Polatuzumab Vedotin Investigator's Brochure
- Lenalidomide SmPC

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This Phase Ib/II, open-label, multicenter, non-randomized study will evaluate the safety, efficacy, and pharmacokinetics of G+Pola+Len in patients with R/R FL *and R+Pola+Len in patients with R/R* ~~or~~ DLBCL.

The study will include an initial dose-escalation phase followed by an expansion phase. The dose-escalation phase ~~will include~~ *in* FL patients ~~only, and it~~ is designed to determine the RP2Ds for both polatuzumab vedotin and lenalidomide when combined with fixed doses of obinutuzumab ~~in patients with relapsed or refractory FL.~~ *The dose-escalation phase in DLBCL patients is designed to determine the RP2D of lenalidomide when combined with fixed doses of polatuzumab vedotin (1.8 mg/kg) and rituximab (375 mg/m²).* During the expansion phase, additional patients with R/R FL or DLBCL will undergo treatment with polatuzumab vedotin and lenalidomide at their respective RP2Ds in combination with obinutuzumab *or rituximab*.

Study data will be summarized separately for each phase. Data from the dose-escalation phase will be summarized by cohort (assigned dose level). Data from the expansion phase will be summarized by histologic subtype (i.e., FL or DLBCL). Data will be summarized as warranted, and listings will be used in place of tables when the sample sizes are small.

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

Limited dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a standard 3+3 algorithm, as outlined in Section 3.1. It is anticipated that enrollment of 5 ~~or six~~ cohorts of 3–6 patients each, for a total of 18–*30* ~~36~~ patients, will be required to establish the RP2D during the dose-escalation phase *for patients with R/R FL. An additional 3 possible cohorts of 3–6 patients each, for a total of 12–18 patients will be required to establish the RP2D during the dose-escalation phase for patients with R/R DLBCL.*

Approximately 80 patients (40 patients with FL and 40 patients with DLBCL) will be enrolled during the expansion phase. Overall, approximately *110–128* ~~98–116~~ patients will be enrolled in the study.

The primary efficacy analysis will be the estimation of the true proportion of patients expected to obtain a PET-CT–defined CR at EOI.

Data from completed and ongoing studies in similar disease settings will be used as historical controls for comparison. Currently available data indicate that the historical CR rate based on PET-CT scans is 40% for R/R FL and DLBCL.

A sample size of 40 patients is deemed sufficient to provide adequate precision for the point estimate and for the lower bound of the two-sided 90% CI to rule out a clinically uninteresting probability of response of $<55\%$, assuming an observed PET-CT–defined CR rate of ~~65%~~ 70%.

SECTION 6.2: *DEFINITION OF ANALYSIS POPULATION*

The following populations are defined:

- *The primary safety and efficacy populations will include patients who received at least one dose of any component of the combination.*
- *The intent-to-treat population will include all patients enrolled in the study.*

SECTION 6.5: SAFETY ANALYSES

The safety analyses will include all treated patients (i.e., patients who received any amount of study treatment). Data for patients in the dose-escalation phase will be summarized by cohort *and histology type*, and data for patients in the expansion phase will be summarized by histologic subtype (FL or DLBCL).

Safety will be assessed through summaries of adverse events and changes from baseline in laboratory test results, shift-tables of ECGs findings, and vital signs.

All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE, Version 4.0 grade. All serious adverse events, adverse events of special interest, and selected adverse events will be summarized and listed.

Deaths reported during the treatment period and during post-treatment follow-up will be listed *and summarized*.

Relevant laboratory ~~and vital sign (temperature, heart rate, respiratory rate, and blood pressure) data~~ *results* will be displayed by time, with Grade 3 and 4 values identified as appropriate.

SECTION 6.6: EFFICACY ANALYSES

The primary and secondary efficacy analyses will include *the primary efficacy population and the intent-to-treat population for* ~~all~~ patients enrolled in the expansion phase, with patients grouped according to histologic subtype*, and will be performed by treatment group. In addition, patients with FL and DLBCL who received polatuzumab vedotin and lenalidomide at the RP2D during the dose-escalation phases will be pooled for analysis by histology with patients treated in the expansion phase at the same dose levels.*

SECTION 6.6.2: Secondary Efficacy Endpoint

The secondary efficacy analyses will be estimation of the proportion of patients achieving each of the following endpoints:

- CR at EOI, as determined by the investigator on the basis of PET-CT scans
- CR at EOI, as determined by the *IRC and* investigator on the basis of CT scans alone
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator on the basis of PET-CT scans
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator on the basis of CT scans alone
- Best response of CR or PR during the study, as determined by the investigator on the basis of CT scans alone

Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non-responders.

SECTION 6.6.3: Exploratory Efficacy Endpoints

Exploratory efficacy analyses will include estimation of the proportion of patients achieving each of the following endpoints:

- For patients who have positive PET scans at EOI:
  - CR at 12 months, as determined by the IRC and by the investigator on the basis of PET-CT scans*, in FL patients*
  - *CR at EOC, as determined by the IRC and by the investigator on the basis of PET-CT scans, in DLBCL patients*

SECTION 6.7: PHARMACOKINETIC ANALYSES

Plasma/serum concentrations of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide will be tabulated, summarized, and plotted after appropriate grouping. As appropriate, PK parameters (e.g., area under the curve [AUC], time to maximum concentration [t_{max}], maximum concentration [C_{max}], half-life [$t_{1/2}$]) may also be calculated, tabulated, and summarized after appropriate grouping. Additional PK and PK/PD analyses (e.g., population modelling including pooled analyses across studies) may also be performed as appropriate. If done, these additional analyses may be reported separately from the CSR. At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of polatuzumab vedotin or lenalidomide.

SECTION 6.8: IMMUNOGENICITY ANALYSES

The numbers and proportions of post-treatment HAHA- *or HACA-,* and ATA-positive patients and HAHA- *or HACA-,* and ATA-negative patients at baseline and during both the treatment and follow-up periods will be summarized by histologic subtype. Patients

are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study treatment administration (treatment-induced ATA response) or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all post-baseline samples are negative or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between HAHA *or HACA,* and ATA status and safety, efficacy, PK, and biomarker endpoints will be explored as appropriate.

SECTION 6.10: INTERIM ANALYSES

It is anticipated that at least two interim analyses, one per histology, will be conducted during the expansion phase of the study, when at least 15 patients *in each histology* have been evaluated for PET-CT–defined CR at EOI. Additional analyses may be conducted to guide early stopping of enrollment for safety on the basis of observed toxicities and the ability to maintain chemotherapy dose intensity.

During the expansion phase, a *modified version of the* predictive probability design (Lee and Lui 2008) may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a PET-CT–defined CR at EOI in each indication-specific expansion cohort with that in historical controls. Updated estimates for the assumed historical control PET-CT–defined CR rate will be available from currently ongoing studies by the time of the first interim analysis. ~~The earliest interim analysis would occur after at least 15 patients have been evaluated for PET-CT–defined CR at EOI~~ *The design is based on Lee and Lui 2008, with the modification that the uncertainty in the historical control data is fully taken into account by utilizing a beta posterior on the control response rate. Interim analysis decision rules will be based on the predicative probability that the trial will have a positive outcome if carried out to completion and will use the historical control data available at the time of analysis.*

If, at any time, an interim analysis suggests that the proportion of patients achieving a PET-CT–defined CR for one of the indication-specific expansion cohorts is lower ~~or higher~~ than expected, the IMC will review the data and decide whether to recommend an early decision to stop enrollment in that subgroup. ~~Interim analysis decision rules will be based on the predictive probability that the trial will have a positive outcome if carried out to completion and will use the most current historical control data available at the time of analysis.~~

Additional review of safety and/or efficacy data by the IMC may be requested by and carried out at the discretion of the Medical Monitor. Further details regarding the rules and guidelines of data review will be provided to the IMC in an IMC charter.

APPENDIX 1: Schedule of Assessments for Patients with Follicular Lymphoma

The schedule of assessments for patients with follicular lymphoma has been revised to reflect the changes to the protocol.

APPENDIX 2: Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma

The schedule of assessments for patients with DLBCL has been revised to reflect the changes to the protocol.

APPENDIX 3: Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory Follicular Lymphoma Patients*

Appendix 3 has been clarified to include patients with R/R FL, removing information about patients with DLBCL.

APPENDIX 4: *Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory DLBCL Patients*

Appendix 4 has been added. Subsequent appendices have been renumbered accordingly.

APPENDIX 5: *Modified* Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

Appendix 5 has been revised to add “modified” to the title and to clarify designation of PET-CT based PR.

APPENDIX 12: *Diagnostic Criteria for Tumor Lysis Syndrome*

Appendix 12 has been added.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR *LYMPHOMA AND RITUXIMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA***
PROTOCOL NUMBER:	GO29834
VERSION NUMBER:	2
EUDRACT NUMBER:	2015-001999-22
IND NUMBER:	109409
TEST PRODUCT:	Obinutuzumab (RO5072759) *Rituximab (RO0452294)* Polatuzumab vedotin (DCDS4501A; RO5541077) Lenalidomide
MEDICAL MONITOR:	[redacted], Pharm.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR** *LYMPHOMA AND RITUXIMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA*
PROTOCOL NUMBER:	GO29834
VERSION NUMBER:	2
EUDRACT NUMBER:	2015-001999-22
IND NUMBER:	109409
TEST PRODUCT:	Obinutuzumab (RO5072759) *Rituximab (RO0452294)* Polatuzumab vedotin (DCDS4501A; RO5541077) Lenalidomide
PHASE:	Phase Ib/II
INDICATION:	Follicular or diffuse large B-cell lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Outcome Measures

This study will evaluate the safety, efficacy, and pharmacokinetics of induction treatment consisting of obinutuzumab in combination with polatuzumab vedotin and lenalidomide (G+Pola+Len) in patients with relapsed or refractory (R/R) follicular lymphoma (FL) *and rituximab in combination with polatuzumab vedotin and lenalidomide (R +Pola +Len) in patients with R/R DLBCL*, followed by post-induction treatment with obinutuzumab in combination with lenalidomide (G+Len) *(referred to as maintenance)* in patients with FL who achieve a complete response (CR), partial response (PR), or stable disease at end of induction (EOI) and *post-induction treatment with rituximab plus lenalidomide (R +Len) (referred to as consolidation)* in patients with DLBCL who achieve a CR or PR at EOI. Specific objectives and corresponding endpoints for the study are outlined below.

In this study, "study treatment" refers to the protocol-mandated treatments under study (i.e., obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide).

Safety Objective

The safety objectives for this study are as follows:

- To determine the recommended Phase II dose (RP2D) for polatuzumab vedotin and lenalidomide when given in combination with a fixed dose of obinutuzumab *and the RP2D of lenalidomide when given in combination with a fixed dose of polatuzumab vedotin and rituximab* on the basis of the following endpoint:

  Incidence of dose-limiting toxicities (DLTs) during the first cycle of study treatment

- To evaluate the safety and tolerability of G+Pola+Len *and R +Pola +Len* on the basis of the following endpoints *in the respective combinations*:

  Nature, frequency, severity, and timing of adverse events, including DLTs

  Changes in vital signs, ECGs, and clinical laboratory results during and following study treatment administration

Efficacy Objective

Response will be determined on the basis of positron emission tomography (PET) and computed tomography (CT) scans or CT scans alone, using Revised Lugano Response Criteria for Malignant Lymphoma, hereinafter referred to as the Lugano 2014 criteria. Response will be determined by an Independent Review Committee (IRC) and by the investigator.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of induction treatment with G+Pola+Len *in R/R FL and R +Pola +Len in R/R DLBCL* on the basis of the following endpoint:

- CR at EOI, as determined by the IRC on the basis of PET-CT scans

Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of induction treatment with G+Pola+Len *and maintenance treatment with G +Len in R/R FL and of induction treatment with R +Pola +Len and consolidation treatment with R +Len in R/R DLBCL* on the basis of the following endpoints:

- CR at EOI, as determined by the investigator on the basis of PET-CT scans
- CR at EOI, as determined *by the IRC and* by the investigator on the basis of CT scans alone
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator on the basis of PET-CT scans
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator on the basis of CT scans alone
- Best response of CR or PR during the study, as determined by the investigator on the basis of CT scans alone

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of G+Pola+Len *and R +Pola +Len* on the basis of the following endpoints:

- For patients who have positive PET scans at EOI: CR at 12 months, as determined by the IRC and by the investigator on the basis of PET-CT scans *in FL patients; CR at end of consolidation (EOC), as determined by the IRC and by the investigator on the basis of PET-CT scans, in DLBCL patients*
- PFS, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by investigator on the basis of CT scans alone, or death from any cause
- EFS, defined as the time from initiation of study treatment to any treatment failure, including disease progression or relapse, as determined by investigator on the basis of CT scans alone, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first
- Disease-free survival, defined, among patients achieving a CR, as the time from the first occurrence of a documented CR to relapse, as determined by the investigator on the basis of CT scans alone, or death from any cause, whichever occurs first
- Overall survival, defined as the time from initiation of study treatment to death from any cause

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the PK profiles of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide when given in combination on the basis of the following endpoints:

- Observed serum obinutuzumab concentration at specified timepoints
- *Observed serum rituximab concentration at specified timepoints*
- Observed serum and plasma concentrations of polatuzumab vedotin and relevant analytes (total antibody, antibody-conjugated mono-methyl auristatin E, and unconjugated mono-methyl auristatin E) at specified timepoints
- Observed plasma lenalidomide concentration at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab, *rituximab,* and polatuzumab vedotin on the basis of the following endpoints:

- Incidence of human anti-human antibodies (HAHAs) to obinutuzumab during the study relative to the prevalence of HAHAs at baseline
- *Incidence of human anti-chimeric antibodies (HACAs) to rituximab during the study relative to the prevalence of HACAs at baseline*
- Incidence of anti-therapeutic antibodies (ATAs) to polatuzumab vedotin during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential relationships between HAHAs *or HACAs, and* ATAs on the basis of the following endpoint:

- Correlation between HAHA *or HACA, and* ATA status and *respective* efficacy, safety, or PK endpoints

Biomarker Objective

The exploratory biomarker objective for this study is to identify non-inherited biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, can increase the knowledge and understanding of lymphoma biology or study treatment mechanism of action, or can contribute to improvement of diagnostic assays on the basis of the following endpoint:

- Association between non-inherited biomarkers and efficacy, safety, pharmacokinetics, or immunogenicity endpoints

Study Design

Description of Study

This Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study will evaluate the safety, efficacy, and pharmacokinetics of G+Pola+Len in patients with R/R FL *and R+Pola+Len in patients with R/R DLBCL*. The study will include an initial dose-escalation phase, followed by an expansion phase, during which polatuzumab vedotin and lenalidomide will be given at their RP2Ds.

All patients will be closely monitored for adverse events throughout the study and for at least 90 days after the last dose of study treatment. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. An Internal Monitoring Committee (IMC) will be established to monitor patient safety throughout the study.

To characterize the PK properties of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide, blood samples will be obtained at various timepoints before and during study treatment administration.

Response will be determined by the IRC and the investigator using the Lugano 2014 criteria. The primary efficacy endpoint will be based on IRC assessment of response.

Number of Patients

Approximately *110–128* patients are expected be enrolled in this study, at approximately 20–25 investigative sites worldwide.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- *For G + Pola + Len treatment group: R/R* FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator
- *For R + Pola + Len treatment group:* R/R DLBCL after treatment with at least one prior chemoimmunotherapy regimen *that included an anti-CD20 monoclonal antibody* in patients who are not eligible for autologous stem-cell transplantation or who have experienced disease progression following treatment with high-dose chemotherapy plus autologous stem-cell transplantation
- Histologically documented CD20-positive B-cell lymphoma as determined by the local laboratory
- Fluorodeoxyglucose-avid lymphoma (i.e., PET-positive lymphoma)
- At least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan or magnetic resonance imaging)
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL

  If the archival tissue is unavailable or unacceptable, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

  If the patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, a repeat core-needle biopsy is strongly recommended.
- Agreement to abstain from donating blood during the treatment period (including periods of treatment interruption) and for 28 days after the last dose of study treatment
- Agreement not to share study medication with another person
- Agreement to comply with all local requirements of the lenalidomide risk minimization plan

  In every country where lenalidomide has been approved, a risk minimization plan, which includes a pregnancy prevention program, is in place. The risk minimization plan should be followed by patients using lenalidomide.

  US sites only: *Per standard Revlimid REMS™ requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this study, and all research subjects enrolled into this study, must be registered in and must comply with all requirements of the Revlimid REMS™ program.*

  For Ex-US sites only: *Subjects will be counseled on pregnancy prevention prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing and that the subject understands the risks associated with lenalidomide. This step will be*

documented with a completed Education and Counseling Guidance Document (refer to Lenalidomide Pregnancy Prevention Risk Management Plans), and no drug will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (refer to Lenalidomide Pregnancy Prevention Risk Management Plans) will be supplied with each medication dispense. All requirements must be followed by each site as noted within the Lenalidomide Pregnancy Prevention Risk Management Plans.

In addition, because lenalidomide will be administered in combination with obinutuzumab, *rituximab,* and polatuzumab vedotin, patients must comply with contraceptive measures designed to ensure safe administration of all study treatments as outlined below.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use <u>two</u> adequate methods of contraception, including at least one method with a failure rate of $<1\%$ per year, for at least *12 months after the last dose of polatuzumab vedotin, 28 days after the last dose of lenalidomide, 12 months after the last dose of rituximab, and* 28 days prior to Day 1 of Cycle 1, during the treatment period (including periods of treatment interruption), and for at least 18 months after the last dose of *obinutuzumab.*

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 24 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of progestogen-only hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Combined oral contraceptives are not recommended because of the increased risk of venous and arterial thromboembolism (TE) in patients taking lenalidomide.

  Barrier methods may be used as the second contraceptive method but must always be supplemented with the use of a spermicide.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 5 months after the last dose of *polatuzumab vedotin, 28 days after the last dose of lenalidomide, and 3 months after the last dose of obinutuzumab or rituximab.* Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 5 months after the last dose of *polatuzumab vedotin, 28 days after the last dose of lenalidomide, and 3 months after the last dose of obinutuzumab or rituximab* to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- *Grade 3b follicular lymphoma*
- *History of transformation of indolent disease to DLBCL*
- Known CD20-negative status at relapse or progression
- Central nervous system lymphoma or leptomeningeal infiltration
- Prior allogeneic stem-cell transplantation (SCT)
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1
- History of resistance to lenalidomide or response duration of <1 year (for patients who had a response to a prior lenalidomide-containing regimen)
- Prior standard or investigational anti-cancer therapy as specified below:

  Lenalidomide, fludarabine, or alemtuzumab within 12 months prior to Day 1 of Cycle1

  Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1

  Monoclonal antibody or antibody-drug conjugate therapy within *5 half-lives or* 4 weeks prior to Day 1 of Cycle 1*, whichever is longer*

  Radiotherapy, chemotherapy, hormonal therapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1
- Clinically significant toxicity (other than alopecia) from prior therapy that has not resolved to Grade ≤ 2 (per NCI CTCAE, Version 4.0) prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medications, including, but not limited to, prednisone, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1

  Treatment with inhaled corticosteroids and mineralocorticoids is permitted.

  If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day of prednisone or equivalent can be given for a maximum of 5 days, but all tumor assessments must be completed prior to initiation of corticosteroid treatment.
- History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies
- Known sensitivity or allergy to murine products or any component of obinutuzumab, *rituximab,* polatuzumab vedotin, or lenalidomide formulations
- History of erythema multiforme, Grade ≥ 3 rash, or desquamation (blistering) following prior treatment with immunomodulatory derivatives such as thalidomide and lenalidomide
- Active bacterial, viral, fungal, or other infection

  Caution should be exercised when considering the use of obinutuzumab *and rituximab* in patients with a history of recurring or chronic infections.
- Positive for hepatitis B surface antigen, total hepatitis B core antibody, or hepatitis C virus antibody at screening
- Known history of HIV positive status

  For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations.
- History of progressive multifocal leukoencephalopathy
- Vaccination with a live virus vaccine within 28 days prior to Day 1 of Cycle 1
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:

  Curatively treated carcinoma in situ of the cervix; good-prognosis ductal carcinoma in situ of the breast; basal- or squamous-cell skin cancer; Stage I melanoma; or low-grade, early-stage localized prostate cancer

Any previously treated malignancy that has been in remission without treatment for ≥ 2 years prior to enrollment

- Contraindication to treatment for TE prophylaxis
- Grade ≥ 2 neuropathy
- Evidence of any significant, uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or intravenous (IV) cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm)
- Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1 or anticipation of a major surgical procedure during the course of the study
- Inadequate hematologic function (unless due to underlying lymphoma), defined as follows:

  Hemoglobin < 9 g/dL

  ANC $< 1.5 \times 10^9$/L

  Platelet count $< 75 \times 10^9$/L
- Any of the following abnormal laboratory values (unless due to underlying lymphoma):

  Calculated creatinine clearance < 50 mL/min (using the Cockcroft-Gault formula)

  AST or ALT $> 2.5 \times$ upper limit of normal (ULN)

  Serum total bilirubin $> 1.5 \times$ ULN (or $> 3 \times$ ULN for patients with Gilbert syndrome)

  INR or PT $> 1.5 \times$ ULN in the absence of therapeutic anticoagulation

  PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant
- Pregnant or lactating, or intending to become pregnant during the study

  Women of childbearing potential must have two negative serum pregnancy test results (minimum sensitivity, 25 mIU/mL) prior to initiating therapy: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1.
- Life expectancy < 3 months
- Unable to comply with the study protocol, in the investigator's judgment

End of Study

The end of this study is defined as the time when both of the following criteria are met:

- All enrolled patients with FL have *been followed for at least 90 days after they have* completed or discontinued study treatment (including induction treatment and maintenance treatment as applicable).
- All enrolled patients with DLBCL have been followed for at least 1 year after they have completed or discontinued study treatment (including induction treatment and consolidation treatment as applicable).

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years.

Investigational Medicinal Products

The investigational medicinal products for this study are obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide.

Dosing Schedule for Patients with Relapsed or Refractory Follicular Lymphoma

Obinutuzumab

Dose-Escalation Phase, Induction

Patients will receive obinutuzumab 1000 mg IV on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle for up to a total of 6 cycles.

Expansion Phase, Induction

Patients will receive obinutuzumab 1000 mg IV on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle for up to a total of 6 cycles.

Post-Induction (Maintenance Treatment)

Patients will receive obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months), starting with Month 1 (i.e., Months 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23) for a maximum of 24 months

Polatuzumab Vedotin

Dose-Escalation Phase, Induction

Patients will receive polatuzumab vedotin 1.4 or 1.8 mg/kg IV on Day 1 of each 28-day cycle for up to 6 cycles.

Expansion Phase, Induction

Patients will receive polatuzumab vedotin RP2D (mg) by mouth (PO) on Day 1 of each 28-day cycle for up to 6 cycles.

Post-Induction (Maintenance)

No polatuzumab vedotin will be administered.

Lenalidomide

Dose-Escalation Phase, Induction

Patients will receive lenalidomide 10, 15, or 20 mg PO once daily on Days 1–21 of each 28-day cycle for up to 6 cycles.

Expansion Phase, Induction

Patients will receive lenalidomide RP2D (mg) PO once daily on Days 1–21 of each 28-day cycle for up to 6 cycles.

Post-Induction

Patients will receive lenalidomide 10 mg PO once daily on Days 1–21 of each month for a maximum of 12 months

Dosing Schedule for Patients with Relapsed or Refractory DLBCL

Rituximab

Dose-Escalation Phase, Induction

Patients will receive rituximab 375 mg/m² IV on Day 1 of each 28-day cycle for up to 6 cycles.

Expansion Phase, Induction

Patients will receive rituximab 375 mg/m² IV on Day 1of every other month (i.e., every 2 months) starting with Month 1 (i.e., Months 1, 3, 5) for up to 6 cycles.

Post-Induction

Patients will receive rituximab 375 mg/m² IV on Day 1 of every other month for (i.e, every 2 months starting with Month 1 (i.e., Months 1, 3, 5) a maximum of 6 months of additional treatment.

Polatuzumab Vedotin

Dose-Escalation Phase, Induction

Patients will receive polatuzumab vedotin 1.8 mg/kg IV on Day 1 of each 28-day cycle for up to 6 cycles.

Expansion Phase, Induction

Patients will receive polatuzumab vedotin 1.8 mg/kg IV on Day 1 of each 28-day cycle for up to 6 cycles.

Post-Induction

No polatuzumab vedotin will be administered.

Lenalidomide

Dose-Escalation Phase, Induction

Patients will receive lenalidomide 10, 15, or 20 mg PO once daily on Days 1–21 of each 28-day cycle for up to 6 cycles.

Expansion Phase, Induction

Patients will receive lenalidomide RP2D (mg) PO once daily on Days 1–21 of each 28-day cycle for up to 6 cycles.

Expansion Phase, Post-Induction

Patients will receive lenalidomide 10 mg PO once daily on Days 1–21 of each month for a maximum of 6 months

Statistical Methods

Primary Analysis

Safety

The safety analyses will include all treated patients (i.e., patients who received any amount of study treatment). Data for patients in the dose-escalation phase will be summarized by cohort *and histology type*, and data for patients in the expansion phase will be summarized by histologic subtype (FL or DLBCL).

Safety will be assessed through summaries of adverse events and changes from baseline in laboratory test results, shift-tables of ECGs findings, and vital signs.

All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE, Version 4.0 grade. All serious adverse events, adverse events of special interest, and selected adverse events will be summarized and listed.

Deaths reported during the treatment period and during post-treatment follow-up will be listed *and summarized*.

Relevant laboratory *results* will be displayed by time, with Grade 3 and 4 values identified as appropriate.

Efficacy

The primary efficacy analysis will be estimation of the proportion of patients achieving a CR at EOI, as determined by the IRC through use of the PET-CT-based Lugano 2014 criteria. Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non responders.

Determination of Sample Size

Limited dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a standard 3+3 algorithm. It is anticipated that enrollment of 5 cohorts of 3–6 patients each, for a total of 18*–30* patients, will be required to establish the RP2D during the dose-escalation phase *for patients with R/R FL. An additional 3 possible cohorts of 3–6 patients each, for a total of 12–18 patients will be required to establish the RP2D during the dose-escalation phase for patients with R/R DLBCL.*

Approximately 80 patients (40 patients with FL and 40 patients with DLBCL) will be enrolled during the expansion phase. Overall, approximately *110–128* patients will be enrolled in the study.

The primary efficacy analysis will be the estimation of the true proportion of patients expected to obtain a PET-CT-defined CR at EOI.

Data from completed and ongoing studies in similar disease settings will be used as historical controls for comparison. Currently available data indicate that the historical CR rate based on PET-CT scans is 40% for R/R FL and DLBCL.

A sample size of 40 patients is deemed sufficient to provide adequate precision for the point estimate and for the lower bound of the two sided 90% CI to rule out a clinically uninteresting probability of response of $<55\%$, assuming an observed PET-CT-defined CR rate of 70%.

Interim Analyses

It is anticipated that at least two interim analyses, one per histology, will be conducted during the expansion phase of the study, when at least 15 patients *in each histology* have been evaluated for PET-CT-defined CR at EOI. Additional analyses may be conducted to guide early stopping of enrollment for safety on the basis of observed toxicities and the ability to maintain chemotherapy dose intensity.

During the expansion phase, a *modified version of the* predictive probability design may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a PET-CT-defined CR at EOI in each indication specific expansion cohort with that in historical controls. Updated estimates for the assumed historical control PET-CT-defined CR rate will be available from currently ongoing studies by the time of the first interim analysis. *The design is based on Lee and Lui 2008, with the modification that the uncertainty in the historical control data is fully taken into account by utilizing a beta posterior on the control response rate. Interim analysis decision rules will be based on the predicative probability that the trial will have a positive outcome if carried out to completion and will use the historical control data available at the time of analysis.*

If, at any time, an interim analysis suggests that the proportion of patients achieving a PET-CT-defined CR for one of the indication specific expansion cohorts is lower than expected, the IMC will review the data and decide whether to recommend an early decision to stop enrollment in that subgroup.

Additional review of safety and/or efficacy data by the IMC may be requested by and carried out at the discretion of the Medical Monitor. Further details regarding the rules and guidelines of data review will be provided to the IMC in an IMC charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	*first line*
ABC	activated (non-germinal) B cell–like (subgroup)
acMMAE	antibody-conjugated MMAE
ADC	antibody-drug conjugate
AML	acute myelogenous leukemia
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC_{inf}	area under the concentration-time curve extrapolated to infinity
BSA	*body surface area*
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone
CHP	cyclophosphamide, doxorubicin, and prednisone or prednisolone
CI	confidence interval
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CR	complete response
CRu	complete response unconfirmed
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DVT	deep vein thrombosis
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EOC	*end of consolidation*
EOI	end of induction
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FDA	United States Food and Drug Administration

FDG	fluorodeoxyglucose
FL	follicular lymphoma
FLIPI, FLIPI2	Follicular Lymphoma International Prognostic Index Follicular Lymphoma International Prognostic Index 2
G	obinutuzumab (GA101)
G-benda	*obinutuzumab plus bendamustine*
G-CHOP	*obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone*
G-CHP	*obinutuzumab plus cyclophosphamide, doxorubicin, and prednisone*
G-CVP	*obinutuzumab in combination with cyclophosphamide, vincristine, and prednisone*
G + Len	*obinutuzumab plus lenalidomide*
G + Pola	*obinutuzumab plus polatuzumab vedotin*
G + Pola + Len	obinutuzumab plus polatuzumab vedotin plus lenalidomide
GCB	germinal center B cell–like (subgroup)
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HACA	*anti-chimeric antibodies*
HAHA	human anti-human antibody
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICH	International Council for Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
iNHL	*indolent non-Hodgkin's lymphoma*
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous
IxRS	interactive voice or web-based response system
Len	lenalidomide
LMWH	low-molecular-weight heparin

MAD	maximum administered dose
MCL	mantle cell lymphoma
MC-VC-PABC	maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl
MDS	myelodysplastic syndrome
MMAE	mono-methyl auristatin E
MOA	mechanism of action
MRD	minimum residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	*not evaluable*
NHL	*non-Hodgkin's lymphoma*
NK	natural killer
OS	overall survival
P	polatuzumab vedotin
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	by mouth
Pola	polatuzumab vedotin
PR	partial response
Q3W	every 3 weeks
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone
R-CHP	rituximab plus cyclophosphamide, doxorubicin, and prednisone or prednisolone
RCR	Roche Clinical Repository
R-DHAP	rituximab plus cisplatin, cytosine arabinoside, and dexamethasone
R-ICE	rituximab plus ifosfamide, carboplatin, and etoposide
R + Len	*rituximab plus lenalidomide*
R + Pola + Len	*rituximab plus polatuzumab vedotin plus lenalidomide*
RP2D	recommended Phase II dose
R/R	*relapsed or refractory*

SCT	stem-cell transplantation
SJS	*Stevens-Johnson syndrome*
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SWFI	Sterile Water for Injection
$t_{½}$	half-life
TAb	total antibody
TE	thromboembolism
TEN	*toxic epidermal necrolysis*
TFR	tumor flare reaction
TLS	tumor lysis syndrome
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state

1. BACKGROUND

1.1 BACKGROUND ON B-CELL LYMPHOMA

B-cell lymphoma is the most common hematologic malignancy in adults. In 2013, there were an estimated 69,740 new cases and 19,020 deaths due to the disease in the United States (Siegel et al. 2013). In Europe, there were an estimated 93,400 new cases and 37,900 deaths in 2012 (Ferlay et al. 2013). Non-Hodgkin's lymphoma is most often of B-cell origin, including a wide range of different subtypes of B-cell lymphoma, broadly divided into indolent and aggressive lymphomas, each with unique characteristics.

1.1.1 Follicular Lymphoma

Indolent B-cell lymphomas are a heterogeneous group of malignant lymphomas and account for approximately one-third of all B-cell lymphomas. Follicular lymphoma (FL) is the most common subtype of indolent B-cell lymphoma, accounting for about 22% of all newly diagnosed cases of B-cell lymphoma (Armitage and Weisenburger 1998). Approximately 90% of the cases have a t(14:18) translocation, which juxtaposes *BCL2* with the IgH locus and results in deregulated expression of Bcl-2.

FL remains an incurable disease with the currently available therapies. The addition of rituximab, an anti-CD20 monoclonal antibody, to commonly used induction chemotherapy, including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone), CVP (cyclophosphamide, vincristine, and prednisone), fludarabine, or bendamustine (Zelenetz et al. 2014; Dreyling et al. 2014), followed by rituximab maintenance therapy led to prolonged remission and improved patient outcomes. Updated results from Study MO18264 confirmed the benefit of 2-year rituximab maintenance in patients responding to first-line immunotherapy, with a 6-year progression-free survival (PFS) of 59.2% compared with 42.7% in the observation arm ($p < 0.0001$) (Salles et al. 2013b).

Despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, most patients will eventually relapse. Relapses are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy. Thus, new treatments are needed to improve the outcome for these patients.

1.1.2 Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive B-cell lymphoma, accounting for approximately 30% of all B-cell lymphomas diagnosed annually (Armitage and Weisenburger 1998). The use of immunochemotherapy, most commonly rituximab + CHOP (R-CHOP), for newly diagnosed DLBCL led to a significant improvement in survival in patients of all age groups. In older patients (> 60 years), R-CHOP was associated with a 2-year event-free survival (EFS) rate of 57% and a 10-year survival rate of 43.5% (Coiffier et al. 2010). In younger patients (18–60 years) with favorable prognostic features, R-CHOP demonstrated a 3-year EFS rate of 79%

and survival rates of 93% and 74.3% at 3 and 6 years, respectively (Pfreundschuh et al. 2011). However, nearly 40% of patients with DLBCL will eventually die of relapsed disease or disease that is refractory to first-line therapy. Patients with a high-risk International Prognostic Index (IPI) have a 5-year PFS rate of only 40% following treatment with R-CHOP (Zhou et al. 2014).

Second-line therapies include high-dose chemotherapy regimens such as R-ICE (rituximab plus ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab plus cisplatin, cytosine arabinoside, and dexamethasone) followed by autologous stem-cell transplantation (SCT). Approximately half of patients do not achieve a complete remission after salvage treatment (Gisselbrecht et al. 2010). Moreover, elderly patients or patients with comorbidities are often deemed ineligible for this aggressive therapy.

Specific molecular subsets of DLBCL are associated with an inferior outcome following R-CHOP therapy. Patients with germinal center B cell–like (GCB) DLBCL had a better prognosis than patients with activated (non-germinal) B cell–like (ABC) DLBCL, with a 3-year survival rate of 84% versus 56%, respectively ($p < 0.001$) (Lenz et al. 2008). Several genetic abnormalities predictive of poor outcome have been identified in DLBCL, including *MYC* rearrangement, *BCL2* and *BCL6* overexpression, and *TP53* mutations. Rearrangement in *MYC* (*MYC*-positive DLBCL) has been reported in 9%–17% of DLBCL cases and often correlates with the GCB DLBCL phenotype (Savage et al. 2009; Barrans et al. 2010). Patients with *MYC*-negative DLBCL who receive R-CHOP have a 5–year survival rate that is markedly worse than patients with *MYC*-positive DLBCL who receive R-CHOP (33% vs. 72%, respectively; Savage et al. 2009). Concurrent *MYC* and *IGH-BCL2* rearrangement ("double-hit" DLBCL), observed in 2%–11% of patients with DLBCL, represents a DLBCL subset with an inferior outcome (5-year PFS of 18%; 5-year survival of 27%) (Savage et al. 2009; Dunleavy et al. 2014). Mutations in *TP53* have been described in approximately 20% of patients with DLBCL (Lossos and Morgensztern 2006) and are strong predictors of poor overall survival (OS; Young et al. 2008; Xu-Monette et al. 2012).

DLBCL remains a high unmet medical need for which novel targeted therapies are needed to move the field beyond R-CHOP.

1.2 BACKGROUND ON OBINUTUZUMAB

Obinutuzumab (also known as GA101) is a novel glycoengineered type II anti-CD20 antibody. Compared with rituximab, obinutuzumab is characterized by more potent direct B-cell death induction and increased affinity for FcγRIII receptors expressed on natural killer (NK) cells, macrophages, and monocytes, resulting in enhanced antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis (Beers et al. 2010; Mössner et al. 2010; Herter et al. 2014). Together, these characteristics confer obinutuzumab with enhanced immune effector functions and B-cell depleting activity compared with rituximab.

Obinutuzumab is approved for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). *Obinutuzumab is also approved for use in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen.*

1.2.1 Nonclinical Studies with Obinutuzumab

In nonclinical studies, obinutuzumab demonstrated superior depletion of normal B cells (measured as CD19+ depletion) from the blood of healthy volunteers (Mössner et al. 2010) as well as malignant B cells from the blood of patients with CLL (Patz et al. 2011). Nonclinical xenograft experiments performed with obinutuzumab as monotherapy and in combination with chemotherapy have consistently showed promising anti-tumor activity of obinutuzumab (Mössner et al. 2010; Dalle et al. 2011) and have demonstrated the superiority of obinutuzumab over rituximab (Herting et al. 2014).

For more detailed nonclinical information on obinutuzumab, please refer to the current version of the Obinutuzumab Investigator's Brochure.

1.2.2 Clinical Studies with Obinutuzumab

As of 4 July 2016, clinical data from Roche-sponsored studies on obinutuzumab are available from *13 clinical studies:* 8 Phase I or II studies (BO20999, BO21003, JO21900, BO21000, GAO4915g, GAO4779g, YP25623, and GAO4768g), *and 5 Phase III studies (GAO4735g, BO21004/CLL11, MO28543, BO21223, and BO21005).* Available efficacy results from the non-Hodgkin's lymphoma (NHL) cohorts in these studies and available safety results from all patients are summarized below

For more detailed clinical information on obinutuzumab, including results in the CLL cohorts of the clinical studies and clinical pharmacology data, please refer to the Obinutuzumab Investigator's Brochure.

1.2.2.1 Clinical Efficacy of Obinutuzumab in Patients with B-Cell Lymphoma

In studies of obinutuzumab monotherapy in patients with relapsed or refractory (R/R) B-cell lymphoma (Studies BO20999, BO21003, and JO21900), the proportion of patients who had a response (complete response [CR] or partial response [PR]) at the end of treatment (as determined on the basis of computed tomography [CT] scans alone) ranged from 28% to 58%. The CR rate ranged from 0% to 19%.

In *early* studies of obinutuzumab in combination with chemotherapy (e.g., CHOP, bendamustine) in patients with previously untreated, or R/R B-cell lymphoma (Studies BO21000, GAO4915g, and GAO4753g), the proportion of patients with a CR or PR at the end of induction (EOI) treatment ranged from 69% to 96%. The CR rate was higher with combination therapy (35%–39% in previously untreated FL, 39%–50% in R/R FL, and 55% in previously untreated DLBCL) than with monotherapy.

Phase III Study GAO4753g investigated obinutuzumab plus bendamustine (G-benda) compared with bendamustine alone in patients with rituximab-refractory indolent NHL (iNHL; n =396). Patients in the G-benda arm who had not experienced disease progression at EOI received obinutuzumab monotherapy every 2 months for up to 2 years. On the basis of positive results from this study, demonstrating significant improvement in PFS in the G-benda arm, with a median investigator-assessed PFS of 29 versus 14 months (hazard ratio [HR]: 0.52; 95% CI: 0.39, 0.70; p<0.0001; Sehn et al. 2015), obinutuzumab was granted approval for use in patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen (see Section 1.2).

Phase III Study BO21223 investigated obinutuzumab plus chemotherapy (G-benda, obinutuzumab plus CVP [G-CVP], obinutuzumab plus CHOP [G-CHOP]) compared with rituximab plus chemotherapy, followed by obinutuzumab or rituximab maintenance in patients with previously untreated iNHL (FL cohort, n =1202). On the basis of positive results that demonstrated significant improvement in PFS in the obinutuzumab chemotherapy arm, the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor at a pre-planned interim analysis (Marcus et al. 2016).

Phase III Study BO21005 investigated G-CHOP compared with rituximab plus CHOP (R-CHOP) in patients with previously untreated DLBCL. The study did not meet its primary endpoint of PFS at final analysis. Based upon the BO21005 efficacy results, this study protocol is amended to cease evaluating obinutuzumab in patients with R/R DLBCL; these patients will receive instead rituximab in combination with polatuzumab vedotin and lenalidomide (Vitolo et al. 2016).

1.2.2.2 Clinical Safety of Obinutuzumab

As of 4 July 2016, an estimated *3636* patients with B-cell lymphoma (including DLBCL, indolent B-cell lymphoma, and CLL) had been treated with obinutuzumab given as monotherapy or in combination with CHOP, bendamustine, fludarabine plus cyclophosphamide, or chlorambucil, at doses ranging from 50 to 2000 mg. Overall, the safety of obinutuzumab monotherapy and obinutuzumab combination therapy was manageable.

The most frequent causes of death were disease progression and adverse events associated with infectious diseases. This is consistent with the study population and the disease under treatment. In Study GAO4768g (obinutuzumab 1000 mg vs. 2000 mg), the incidence of deaths did not increase with increased obinutuzumab dose (7.5% and 2.6%, respectively).

Of particular interest, a high incidence of infusion-related reactions (IRRs) was observed consistently in all obinutuzumab trials. The reported incidence of IRRs varied across studies. In the CLL population, the incidence ranged from 66% in previously untreated

patients receiving obinutuzumab plus chlorambucil (Study BO21004) to 100% in patients with R/R disease who received obinutuzumab monotherapy (pooled data from Studies BO21003 and BO20999, CLL cohorts).

In the B-cell lymphoma population, the incidence of IRRs in studies of obinutuzumab monotherapy was 75.1% (pooled data from Study BO21003 and from high-dose B-cell lymphoma cohorts from Study BO20999). In studies of obinutuzumab in combination with either CHOP (Study GAO4915g) or bendamustine (Study BO21000), the incidence of IRRs, regardless the relationship with obinutuzumab, was 70%–78%.

Other important risks associated or potentially associated with obinutuzumab are tumor lysis syndrome (TLS), thrombocytopenia (including acute thrombocytopenia), neutropenia, prolonged B-cell depletion, infections (including progressive multifocal leukoencephalopathy [PML] and hepatitis B virus [HBV] reactivation), worsening of preexisting cardiac conditions, gastrointestinal (GI) perforation, impaired immunization response, immunogenicity, and second malignancies. The important identified risks associated with obinutuzumab are presented in detail in Section 5.1.1 of this protocol and in the Obinutuzumab Investigator's Brochure.

1.2.2.3 Clinical Pharmacokinetics of Obinutuzumab

A two-compartment pharmacokinetic model composed of a linear clearance pathway and a nonlinear, time-varying clearance pathway adequately described serum obinutuzumab concentration data. Terminal obinutuzumab clearance and half-life are approximately 0.09 L/day and 28.4 days, respectively. The initial clearance of obinutuzumab was approximately 2.8 times higher than the steady-state clearance, consistent with a decrease in the time-varying clearance component, which is high at the start of treatment and declines with repeated cycles of obinutuzumab treatment. The time-varying clearance pathway is consistent with the target-mediated drug disposition such that, at the start of treatment, there is a large quantity of CD20-positive cells that rapidly bind obinutuzumab. Repeated dosing of obinutuzumab saturates the pool of CD20-positive cells, hence reducing this component in clearance. The linear clearance pathway is consistent with the catabolism of IgG antibodies and is therefore independent of CD20-positive cells. Additional details can be found in the Obinutuzumab Investigator's Brochure.

1.3 BACKGROUND ON POLATUZUMAB VEDOTIN

CD79b is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B-cell-derived malignancies, including nearly all B-cell lymphoma and CLL samples tested (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, which makes CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007; Polson et al. 2009).

Polatuzumab vedotin (DCDS4501A) is an antibody–drug conjugate (ADC) that contains a humanized IgG1 anti–human CD79b monoclonal antibody (MCDS4409A) and a potent

anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl.

MMAE has a mode of action that is similar to that of vincristine, which is a component of standard chemotherapy (e.g., R-CHOP used for treatment of lymphoma). Following binding at the cell-surface epitope and internalization of the ADC by the targeted cell, MMAE is released following cleavage of the linker by lysosomal enzymes. MMAE then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth (Doronina et al. 2003). This therapeutic approach takes advantage of the specific targeting capability of the antibody, the cytotoxic activity of MMAE, and the increased potency of MMAE compared with vincristine. It is hypothesized that polatuzumab vedotin in combination with other novel agents will provide enhanced efficacy and safety to patients with B-cell lymphoma.

1.3.1 Nonclinical Studies with Polatuzumab Vedotin

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamics (PD), and toxicology studies were conducted to support the entry of polatuzumab vedotin into clinical trials. Because polatuzumab vedotin specifically recognizes CD79b on B cells of humans—but not on those of the cynomolgus monkey, rat, or mouse—a surrogate ADC (DCDS5017A) that binds to cynomolgus monkey CD79b was generated to assess the antigen-dependent activities in cynomolgus monkeys. The structure, binding epitope, and binding affinity of the surrogate ADC are similar to that of polatuzumab vedotin. Polatuzumab vedotin has demonstrated efficacy in nonclinical murine xenograft models of human CD79b-positive B-cell lymphoma. Additionally, when combined with rituximab plus chemotherapy (rituximab in combination with cyclophosphamide, doxorubicin, and prednisone or prednisolone [CHP] or bendamustine), polatuzumab vedotin demonstrated better anti-tumor activity compared with polatuzumab vedotin as single agent or compared with a current standard-of-care regimen (R-CHOP or rituximab plus bendamustine) in xenograft models of B-cell lymphoma. The pharmacokinetics and safety of polatuzumab vedotin and the surrogate ADC were characterized in repeat-dose toxicity studies in rats and cynomolgus monkeys. Polatuzumab vedotin and the surrogate ADC were well tolerated in both species at the tested doses. The predominant antigen-independent findings associated with polatuzumab vedotin or the surrogate ADC exposure were reversible bone marrow toxicity and associated peripheral blood cell effects in both monkeys and rats. The PK profiles of polatuzumab vedotin and the surrogate ADC suggested that the pharmacokinetics of the ADC were driven mainly by the antibody component (similar serum concentration–time profile between the ADC and total monoclonal antibody).

Refer to the Polatuzumab Vedotin Investigator's Brochure for complete details of the biochemical composition and nonclinical studies.

1.3.2 Clinical Studies with Polatuzumab Vedotin

To date, clinical data on polatuzumab vedotin are available from one completed Phase I/Ib study (DCS4968g) *and the ongoing Phase Ib/II Studies GO27834, GO29044, GO29833, BO29561, and GO29365* in patients with B-cell lymphoma.

DCS4968g evaluated polatuzumab vedotin as a single agent and in combination with rituximab in patients with R/R B-cell lymphoma.

GO27834 is evaluating polatuzumab vedotin in combination with either obinutuzumab or rituximab in patients with R/R FL or DLBCL.

GO29044 is evaluating polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) or obinutuzumab plus cyclophosphamide, doxorubicin, and prednisone (G-CHP) in patients with newly diagnosed or R/R B-cell lymphoma.

GO29365 is evaluating polatuzumab vedotin in combination with bendamustine plus rituximab or obinutuzumab in patients with R/R FL or DLBCL.

Available efficacy and safety results from these studies are summarized in Sections 1.3.2.1 and 1.3.2.2, respectively.

For more detailed clinical information on polatuzumab vedotin, including clinical pharmacology data, refer to the Polatuzumab Vedotin Investigator's Brochure.

1.3.2.1 Clinical Efficacy of Polatuzumab Vedotin in Patients with B-Cell Lymphoma

Polatuzumab vedotin demonstrated clinical activity as a single agent.
In Study DCS4968g, at the 2.4-mg/kg dose, objective responses (CR or PR) were observed in 7 of 16 patients (44%) with R/R indolent B-cell lymphoma (FL, marginal zone lymphoma [MZL], or small lymphocytic lymphoma [SLL]) and 14 of 27 patients (52%) with R/R DLBCL. *At a dose of 1.8 mg/kg, a PR was observed in 2 of 4 patients with DLBCL and in 2 of 2 patients with MCL, and no objective responses were observed in the 5 patients with CLL. The median duration of response was 6.2 months (95% CI: 3.3, 19.3 months) for the 2.4-mg/kg dose and 6.6 months (95% CI: 2.3, 11.4 months) for the 1.8-mg/kg dose. At the 2.4-mg/kg dose, median PFS was 7.9 months (95% CI: 3.0, 11.6 months) for patients with indolent B-cell lymphoma and 5.0 months (95% CI: 2.3, 6.8 months) for patients with DLBCL. Median PFS was 4.6 months (95% CI: 1.4, 13.9 months) for patients with DLBCL treated at the 1.8-mg/kg dose.*

Polatuzumab vedotin also demonstrated clinical activity when administered in combination with rituximab. In Study DCS4968g, at a dose of 2.4 mg/kg, objective responses were observed in 7 of 9 patients with indolent B-cell lymphoma, DLBCL, or MCL (78%); 2 of those 7 patients had CRs. Median duration of response among these patients was 12.3 months (95% CI: 4.3, not estimable [NE]). Median PFS was 12.5 months (95% CI: 6.9, 17.4 months).

Preliminary data show that for patients in Study GO27834 who received polatuzumab vedotin (2.4 mg/kg) in combination with rituximab overall responses were observed in 14 of 20 patients with R/R FL (70%; *9* patients with CRs) and *21* of 39 patients with R/R DLBCL (*54*%;*8* patients with CRs). *For patients who received polatuzumab vedotin (1.8mg/kg) in combination with rituximab, objective responses were observed in 15 of 20 patients with FL (75%; 6 patients with CRs).*

Median duration of response was 12.9 months (95% CI: 6.7, NE) and 13.2 months (95% CI: 7.2, 21.2) for patients who received polatuzumab vedotin 1.8 mg/kg (FL) or 2.4 mg/kg (FL or DLBCL), respectively. At the 2.4 mg/kg dose, median PFS was 15.1 months (95% CI: 11.8, NE) among the 20 patients with FL and 5.6 months (95% CI: 4.2, 12.7 months) among the 39 patients with DLBCL. Among the 20 patients with R/R FL treated with 1.8 mg/kg polatuzumab vedotin in combination with rituximab, the median PFS was 18.1 months (95% CI: 9.9, NE).

For patients in Study GO27834 who received polatuzumab vedotin (1.8 mg/kg) in combination with obinutuzumab, overall responses were observed in 8 of 12 patients with R/R FL (67%; 1 patient with CR) and 3 of 15 patients with R/R DLBCL (20%; 0 patients with CR).

Preliminary data from Study GO29044 in patients treated with polatuzumab vedotin (1.0–1.8 mg/kg) in combination with R-CHP showed overall responses in 29 of 31 patients (94%; 24 patients with CRs). When polatuzumab vedotin (1.4 or 1.8 mg/kg) was combined with G-CHP, overall responses were seen in 10 of 12 patients (83%; 10 patients with CRs).

Preliminary data from GO29365 in FL patients treated with polatuzumab vedotin (1.8 mg/kg) in combination with bendamustine showed overall responses in 7 of 7 patients (100%; 2 patients with CRs) when combined with rituximab and in 3 of 4 patients (75%; 1 patient with CR) when combined with obinutuzumab. Patients with DLBCL treated with polatuzumab vedotin (1.8 mg/kg) in combination with bendamustine showed overall responses in 3 of 7 patients (43%; 2 patients with CRs) when combined with rituximab and in 6 of 8 patients (75%; 2 patient with CR) when combined with obinutuzumab.

1.3.2.2 Clinical Safety of Polatuzumab Vedotin

Clinical safety data are available from *327* patients with B-cell lymphoma or CLL *who received polatuzumab vedotin as a single agent (DCS4968g), in combination with rituximab (DCS4968g and GO27834), in combination with obinutuzumab (GO27834), in combination with G-CHP or R-CHP (GO29044), or in combination with obinutuzumab or rituximab plus bendamustine (GO29365).*

In Study DCS4968g, Grade ≥ 3 adverse events were reported in 74% of patients with R/R B-cell lymphoma who received single–agent polatuzumab vedotin; the most

common (occurring in ≥ 5% of patients) Grade ≥ 3 adverse events were neutropenia (38% of patients), anemia and peripheral sensory neuropathy (9% each), and leukopenia (6%).

In the dose-escalation phase of Study DCS4968g, dose-limiting toxicities (DLTs) of Grade 4 neutropenia occurred in 1 of 10 DLT-evaluable patients treated with 2.4 mg/kg polatuzumab vedotin and 1 of 9 DLT-evaluable patients treated with 2.4 mg/kg polatuzumab vedotin in combination with rituximab. Polatuzumab vedotin at a dose of 2.4 mg/kg given every 3 weeks (Q3W) was chosen as the recommended Phase II dose (RP2D) when administered as a single agent and in combination with rituximab. *Due to additional information about the benefit-risk profile of polatuzumab vedotin at the 2.4 mg/kg dose, the Sponsor is no longer pursuing the clinical development of the 2.4-mg/kg dose of polatuzumab vedotin.*

The overall safety profile of polatuzumab vedotin (1.8- and 2.4-mg/kg doses) in combination with rituximab was comparable to that of single–agent polatuzumab vedotin. In Study GO27834, the most frequent (≥ 5%) Grade ≥ 3 adverse events were neutropenia (19 of 79 patients [24%]), diarrhea (5 of 79 patients [6%]), and febrile neutropenia (4 of 79 patients [5%]). No fatal adverse events were reported for the combination.

Serious adverse events were reported for 37% of all patients treated with polatuzumab vedotin alone or in combination with rituximab in Studies DCS4968g and GO27834 combined. The most frequently reported (≥ 2%) serious adverse events were febrile neutropenia (5%), pyrexia (4%), and diarrhea (2%). In Studies DCS4968g and GO27834 combined, 33% to 41% of patients discontinued polatuzumab vedotin because of an adverse event. The most frequently reported adverse events leading to discontinuation were peripheral sensory neuropathy, peripheral neuropathy, and peripheral motor neuropathy.

In Study GO29044, Grade ≥3 adverse events were reported in 19 of 40 patients (48%) with B-cell lymphoma who received polatuzumab vedotin (1.8 mg/kg) in combination with G-CHP or R-CHP. The most frequent events (≥10% of patients) were fatigue (33%), diarrhea (33%), and nausea (30%). Serious adverse events were reported for 33% of patients in this treatment group.

In Study GO29365, Grade ≥3 adverse events were reported in 11 of 21 patients (52%) with B-cell lymphoma who received polatuzumab vedotin in combination with rituximab plus bendamustine and in 17 of 28 patients (61%) who received polatuzumab vedotin in combination with obinutuzumab plus bendamustine. The most frequent events (≥10% of patients) were nausea (43%), diarrhea (41%), and fatigue (35%). Serious adverse events were reported for 33% of patients receiving polatuzumab vedotin in combination with rituximab plus bendamustine and 39% of patients receiving polatuzumab vedotin in combination with obinutuzumab plus bendamustine.

A total of 44 deaths have been reported: 11 deaths in patients treated with single-agent polatuzumab vedotin and 33 deaths in patients treated with polatuzumab vedotin combined with rituximab or obinutuzumab. The majority of deaths were judged as related to disease progression.

1.3.2.3 Clinical Pharmacokinetics of Polatuzumab Vedotin

The pharmacokinetics of antibody-conjugated MMAE (acMMAE), total antibody (TAb), and unconjugated MMAE appear to be dose-proportional across the dose range of 0.1–2.4 mg/kg of polatuzumab vedotin. At the polatuzumab vedotin dose level of 2.4 mg/kg, mean half-life values range from 5.2 to 6.3 days for acMMAE and from 6.2 to 8.1 days for TAb. The mean clearance values range from 16.2 to 23.8 mL/day/kg for acMMAE and from 11.4 to 28.0 mL/day/kg for TAb, which suggests that the disposition of acMMAE, as characterized by a small steady-state volume of distribution and slow clearance, is largely dominated by its antibody component. Across doses tested (0.1–2.4 mg/kg), the exposure of acMMAE (e.g., C_{max}, AUC_{inf}) is, on average, 100 to 150- and ~50-fold higher than the corresponding unconjugated MMAE exposure. MMAE peak concentrations are reached 2–3 days after dosing. The mean half-life for unconjugated MMAE is 2.9–6.4 days, which is similar to the corresponding value for acMMAE and suggestive of formation rate-limited kinetics of unconjugated MMAE due to the ADC catabolism. Combination with the anti-CD20 antibody rituximab does not appear to affect the PK of acMMAE, TAb, and unconjugated MMAE in the *R/R* BCL patient population.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Progress has been made in the treatment of FL and DLBCL; however, a significant number of patients will relapse or die of progression or treatment-related toxicity. Patients who relapse after receiving several prior treatments may not be able to tolerate more bone marrow toxicity, thereby limiting their treatment options. There is a need for the continued development of safe and effective therapies for patients with disease that relapses and for patients who develop refractory disease during or after first-line therapy. This study will evaluate the activity of a novel triplet combination of obinutuzumab *or rituximab plus* polatuzumab vedotin and lenalidomide.

B-cell lymphomas, including FL and DLBCL, express the CD20 antigen, and anti-CD20 therapy (rituximab) has been demonstrated to provide enhanced anti-tumor activity when given in combination with other agents, leading to increased response rates, PFS, and OS (Coiffier et al. 2002; Coiffier et al. 2007; Coiffier et al. 2010; Feugier et al. 2005; Hiddemann et al. 2005; Habermann et al. 2006; Herold et al. 2007; Marcus et al. 2008; Pfreundschuh et al. 2008; Salles et al. 2008). This has led to the acceptance of rituximab as a standard component in initial therapy.

Obinutuzumab has shown superiority over rituximab in a Phase III study in first-line CLL (Goede et al. 2014). *Obinutuzumab showed clinical benefit compared to rituximab when combined with chemotherapy in a Phase III trial (BO21223) in patients with*

previously untreated indolent B-cell lymphomas, including FL (Marcus et al. 2016). A Phase III study, GAO4753g, evaluated patients with rituximab-refractory indolent B-cell lymphoma, including patients with FL, and showed improvement in PFS with obinutuzumab added to bendamustine followed by obinutuzumab maintenance compared with bendamustine alone (Sehn et al. 2015). Obinutuzumab will be included as the anti-CD20 backbone for patients with R/R FL in this study.

Obinutuzumab did not show superiority compared to rituximab in the Phase III trial (BO21005) comparing R-CHOP to G-CHOP in patients with previously untreated DLBLC (Vitolo et al. 2016). Based upon the BO21005 efficacy results, this study protocol is amended, and patients with R/R DLBCL will receive rituximab as the anti-CD20 backbone in combination with polatuzumab vedotin and lenalidomide.

In addition to the potential for obinutuzumab as the next-generation anti-CD20 therapy to enhance the efficacy of current standard immunochemotherapy regimens in patients with FL, ADCs may have added benefit when combined with standard systemic chemotherapy, or replace these agents, in certain lymphoma combination regimens. Polatuzumab vedotin is an ADC designed for the targeted delivery of MMAE, a potent microtubule inhibitor to lymphoma cells expressing CD79b. MMAE has a mechanism of action similar to that of vincristine and is hypothesized to be a more targeted therapy. To date, Phase Ib/II data suggest that polatuzumab vedotin in combination with rituximab has activity in R/R FL and DLBCL, with a generally acceptable safety and tolerability profile. Additionally, several ongoing Phase Ib/II studies are assessing the safety and clinical activity of the combination of obinutuzumab and polatuzumab vedotin alone and in combination with chemotherapy (see Section 3.3.3.2 for details).

Lenalidomide, a thalidomide analogue, is a potent immunomodulatory agent with activity in lymphoid malignancies occurring primarily through immune modulation and direct anti-tumor effects. Although lenalidomide has not been approved for the treatment of R/R FL and DLBCL, clinical activity has been demonstrated with lenalidomide as a single agent (Wiernik et al. 2008; Witzig et al. 2009, 2011) or in combination with rituximab (Zinzani et al. 2011, 2013; Leonard et al. 2012; Tuscano et al. 2014; Wang et al. 2013). Obinutuzumab in combination with lenalidomide is currently being evaluated in an ongoing Phase Ib/II study sponsored by the Lymphoma Academic Research Organisation (GALEN study) in patients with R/R FL and aggressive lymphoma (DLBCL and mantle cell lymphoma [MCL]). This study evaluated a fixed dose of obinutuzumab in combination with lenalidomide doses of 10–25 mg/day. Preliminary data indicate a manageable safety profile. An increased incidence of Grade 3/4 neutropenia was reported. Of the 19 evaluable patients, 13 (68%) achieved an overall response (see Section 3.3.3.2.2 for details).

On the basis of the distinct mechanisms of action (MOAs) for each molecule and the current available clinical data, there is a strong rationale to expect an improved benefit-risk profile with the triplet combination of obinutuzumab *or rituximab plus*

polatuzumab vedotin and lenalidomide. This novel triplet regimen may have the potential to extend treatment-free remissions and to decrease toxicity by improving upon individual agents used as part of current standard of care, which includes traditional chemotherapy. Early clinical data that evaluated obinutuzumab*, rituximab*, polatuzumab vedotin, and lenalidomide each as single-agents has been associated with neutropenia. Rituximab and polatuzumab vedotin and rituximab and lenalidomide doublet combinations have also been associated with neutropenia. The replacement of rituximab with obinutuzumab (Study GO27834 [obinutuzumab plus polatuzumab vedotin {G+Pola}] and GALEN [obinutuzumab plus lenalidomide {G+Len}]) in these doublets is anticipated to be associated with treatment-related neutropenia. Patients with overlapping toxicities will be closely monitored; such events are expected to be manageable in the clinical setting, and drug-drug interactions (DDIs) are unlikely to occur (see Sections 5.1.5 and 5.1.6).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of induction treatment consisting of obinutuzumab in combination with polatuzumab vedotin and lenalidomide (G+Pola+Len) in patients with R/R FL *and rituximab in combination with polatuzumab vedotin and lenalidomide (R +Pola +Len) in patients with R/R DLBCL*, followed by post-induction treatment with G+Len *(referred to as maintenance)* in patients with FL who achieve a CR, PR, or stable disease at EOI and *post-induction treatment with rituximab plus lenalidomide (R +Len; referred to as consolidation)* in patients with DLBCL who achieve a CR or PR at EOI. Specific objectives and corresponding endpoints for the study are outlined below.

In this study, "study treatment" refers to the protocol-mandated treatments under study (i.e., obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide).

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To determine the RP2D for polatuzumab vedotin and lenalidomide when given in combination with a fixed dose of obinutuzumab *and the RP2D of lenalidomide when given in combination with a fixed dose of polatuzumab vedotin and rituximab* on the basis of the following endpoint:

  Incidence of DLTs during the first cycle of study treatment

- To evaluate the safety and tolerability of G+Pola+Len *and R +Pola +Len* on the basis of the following endpoints *in the respective combinations*:

  Nature, frequency, severity, and timing of adverse events, including DLTs

  Changes in vital signs, ECGs, and clinical laboratory results during and following study treatment administration

2.2 EFFICACY OBJECTIVES

Response will be determined on the basis of positron emission tomography (PET) and computed tomography (CT) scans or CT scans alone, using Revised Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014), hereinafter referred to as the Lugano 2014 criteria. Response will be determined by an Independent Review Committee (IRC) and by the investigator.

2.2.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of induction treatment with G+Pola+Len *in R/R FL and R +Pola +Len in R/R DLBCL* on the basis of the following endpoint:

- CR at EOI, as determined by the IRC on the basis of PET-CT scans

2.2.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of induction treatment with G+Pola+Len *and maintenance treatment with G +Len in R/R FL and of induction treatment with R +Pola +Len and consolidation treatment with R +Len in R/R DLBCL* on the basis of the following endpoints:

- CR at EOI, as determined by the investigator on the basis of PET-CT scans
- CR at EOI, as determined by the *IRC and by the* investigator on the basis of CT scans alone
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator on the basis of PET-CT scans
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator on the basis of CT scans alone
- Best response of CR or PR during the study, as determined by the investigator on the basis of CT scans alone

2.2.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of G+Pola+Len *and R +Pola +Len* on the basis of the following endpoints:

- For patients who have positive PET scans at EOI:
  - CR at 12 months, as determined by the IRC and by the investigator on the basis of PET-CT scans *in FL patients*
  - *CR at end of consolidation (EOC), as determined by the IRC and by the investigator on the basis of PET-CT scans, in DLBCL patients*
- PFS, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by investigator, or death from any cause

- EFS, defined as the time from initiation of study treatment to any treatment failure, including disease progression or relapse, as determined by investigator, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first
- Disease-free survival (DFS), defined, among patients achieving a CR, as the time from the first occurrence of a documented CR to relapse, as determined by the investigator, or death from any cause, whichever occurs first
- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the PK profiles of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide when given in combination on the basis of the following endpoints:

- Observed serum obinutuzumab concentration at specified timepoints
- *Observed serum rituximab concentration at specified timepoints*
- Observed serum and plasma concentrations of polatuzumab vedotin and relevant analytes (TAb, acMMAE, and unconjugated MMAE) at specified timepoints
- Observed plasma lenalidomide concentration at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab*, rituximab,* and to polatuzumab vedotin on the basis of the following endpoints:

- Incidence of human anti-human antibodies (HAHAs) to obinutuzumab during the study relative to the prevalence of HAHAs at baseline
- *Incidence of human anti-chimeric antibodies (HACAs) to rituximab during the study relative to the prevalence of HACAs at baseline*
- Incidence of ATAs to polatuzumab vedotin during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential relationships between HAHAs *or HACAs, and* ATAs on the basis of the following endpoint:

- Correlation between HAHA *or HACA, and* ATA status and *respective* efficacy, safety, or PK endpoints

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify non-inherited biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, can increase the knowledge and understanding of lymphoma biology or study treatment mechanism of action, or can contribute to improvement of diagnostic assays on the basis of the following endpoint:

- Association between non-inherited biomarkers (listed in Section 4.5.6) and efficacy, safety, pharmacokinetics, or immunogenicity endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study

This Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study will evaluate the safety, efficacy, and pharmacokinetics of G+Pola+Len in patients with R/R FL *and R+Pola+Len in patients with R/R* DLBCL.

The study will include an initial dose-escalation phase followed by an expansion phase, during which polatuzumab vedotin and lenalidomide will be given at their RP2Ds (see Sections 3.1.2 and 3.1.2.2).

Approximately *110–128* patients are expected be enrolled in this study, at approximately 20–25 investigative sites worldwide.

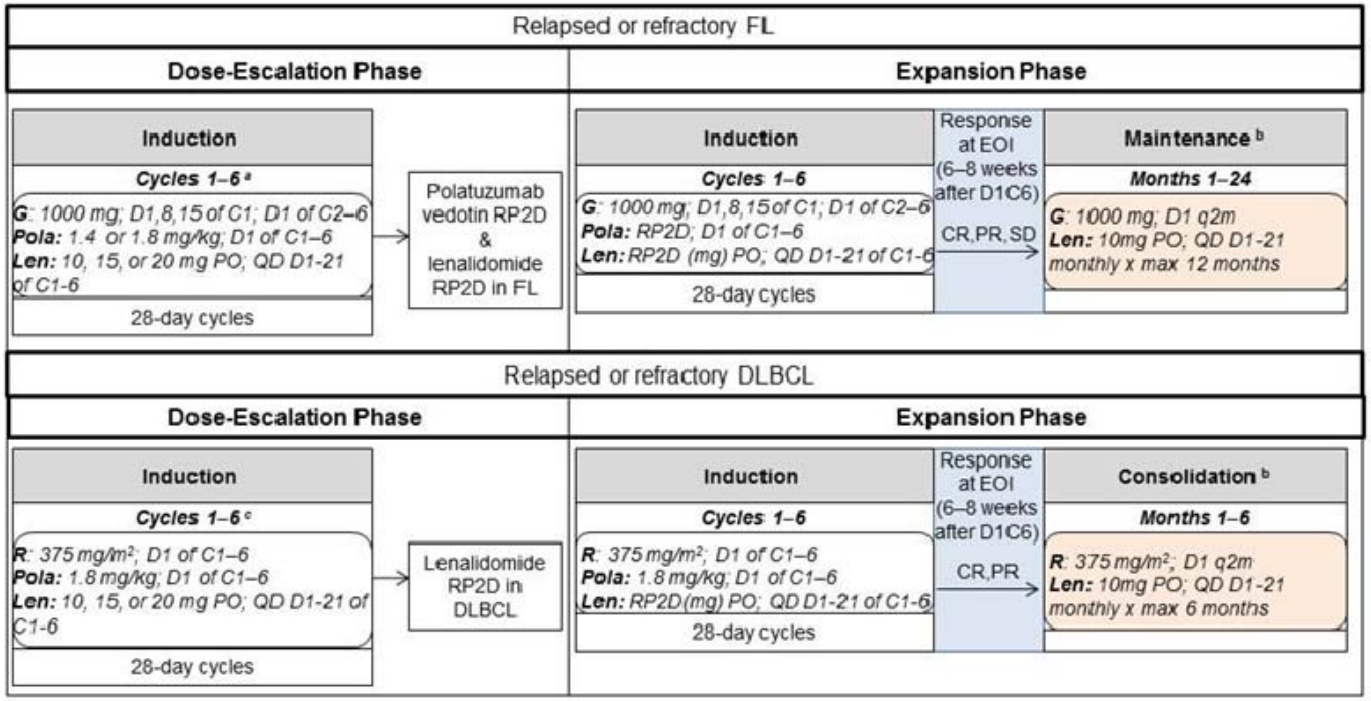
All patients will be closely monitored for adverse events throughout the study and for at least 90 days after the last dose of study treatment (see Section 5.3.1). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. An Internal Monitoring Committee (IMC) will be established to monitor patient safety throughout the study (see Section 3.1.4).

To characterize the PK properties of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide, blood samples will be obtained at various timepoints before and during study treatment administration.

Response will be determined by the IRC (see Section 3.1.5) and the investigator using the Lugano 2014 criteria. The primary efficacy endpoint will be based on IRC assessment of response. Refer to Section 4.5.5 for details on tumor assessments.

Schedules of assessments are provided in Appendix 1, Appendix 2, and Appendix 3. The Lugano Response Criteria are provided in Appendix 5.

Figure 1 *Study Schema*



C = cycle; CR = complete response; D = day; DLBCL = diffuse large B-cell lymphoma; EOI = end of induction; FL = follicular lymphoma; G = obinutuzumab; Len = lenalidomide; PO = by mouth; Pola = polatuzumab vedotin; PR = partial response; QD = every day; *Q2M=every 2 months; R=rituximab;* RP2D = recommended Phase II dose; SD = stable disease.

Notes: Each cycle is 28 days. A month is defined as 28 days.

[a] *FL patients enrolled in the dose-escalation phase who achieve a CR, PR, or SD at EOI may receive maintenance treatment with G + Len following the maintenance schedule outlined for patients with FL during the expansion phase.*

[b] *Maintenance and consolidation treatment should start 8 weeks (± 1 week) after Day 1 of Cycle 6.*

[c] *DLBCL patients enrolled in the dose-escalation phase who achieve a CR or PR at EOI may receive consolidation treatment with R + Len following the maintenance schedule outlined for patients with DLBCL during the expansion phase.*

3.1.2 *Obinutuzumab plus Polatuzumab Vedotin plus Lenalidomide Treatment Group (Patients with Follicular Lymphoma)*

3.1.2.1 Dose-Escalation Phase

The purpose of the *FL* dose-escalation phase is to identify the RP2D for polatuzumab vedotin and the RP2D for lenalidomide when combined with a fixed dose of obinutuzumab as induction treatment. *This* dose-escalation phase will include FL patients only; these patients may receive post-induction treatment if eligible (see Section 3.3.1).

Approximately 18*–30* patients will be enrolled in the *FL* dose-escalation phase. Cohorts of 3–6 patients each will be treated in accordance with the treatment regimens and dose-escalation rules described in Section 3.1.2.1.3.

Patients will be closely monitored for adverse events during the DLT assessment window, defined as the first treatment cycle (from Day 1 of Cycle 1 to Day 1 of Cycle 2). Adverse events meeting the criteria for DLT, as defined below (see Section 3.1.2.1.1), will be reported to the Sponsor within 24 hours (see Section 5.4.2).

Patients experiencing a DLT during the DLT assessment period *may continue receiving study treatment once the event has resolved, if determined by investigator in consultation with Sponsor that it is safe to continue treatment and there is potential for clinical benefit in their judgment.*

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and RP2D assessments and will be replaced by an additional patient at that same dose level. Patients who miss 1 or more doses of polatuzumab vedotin *or obinutuzumab* or 5 consecutive daily doses of lenalidomide during the DLT assessment window for reasons other than a DLT will also be replaced *and considered non-evaluable for dose-escalation decisions.* Patients who receive supportive care during the DLT assessment window that may confound the evaluation of DLTs may be replaced at the discretion of the Medical Monitor.

3.1.2.1.1 Definition of Dose-Limiting Toxicity

In this study, a DLT is defined as any <u>one</u> of the following events occurring during the first cycle of treatment and assessed by the investigator as related to study treatment *that is not attributed to disease progression or another clearly identified cause*:

- *Any adverse* event of any grade that leads to a delay of >14 days in the start of the next treatment cycle
- *Any* Grade 3 or 4 non-hematologic adverse event, <u>with the following exceptions</u>:
  - Grade 3 or 4 IRRs

    Note that IRRs may occur even after a small amount of drug has been administered (i.e., IRRs are not dose dependent).

- Grade 3 diarrhea that responds to therapy within 72 hours
- Grade 3 nausea or vomiting that occurs in the absence of premedication and responds to adequate therapy within 72 hours
- *Grade 3 laboratory TLS without manifestations of clinical TLS (i.e., creatinine ≥1.5× upper limit of normal (ULN) and/or renal dysfunction, cardiac arrhythmias, seizures, or sudden death) that resolves within 7 days (see Appendix 12)*
- *Grade 3 fatigue that resolves to Grade ≤2 within 7 days*
- *Grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator not to be clinically significant*
- *Grade 3 elevation in ALT or AST, provided the following criteria are met:*

  ALT or AST level is no greater than 8× ULN

  ALT or AST elevation resolves to Grade <2 (<5 ULN) within 7 days

  Total and direct bilirubin and other laboratory parameters of liver synthetic function (e.g., prothrombin time) are normal

  No clinical signs or symptoms of hepatic injury

- *Any increase in hepatic transaminase >3 ×baseline AND an increase in direct bilirubin >2 ×ULN, WITHOUT any findings of cholestasis or jaundice or signs of hepatic dysfunction AND in the absence of other contributory factors (e.g., worsening of metastatic disease or concomitant exposure to known hepatotoxic agent or of a documented infectious etiology) is suggestive of potential drug-induced liver injury (according to Hy's Law) and will be considered a DLT.*
- *In patients with Grade 1 ALT or AST elevation at baseline as a result of liver metastases, only a Grade ≥3 elevation that is also ≥3 ×baseline lasting >7 days will be considered a DLT.*
- Hematologic adverse event that meets <u>any</u> of the following criteria:

  Grade 3 or 4 neutropenia in the presence of sustained fever of > 38°C (lasting > 5 days) or a documented infection

  Grade 4 neutropenia lasting > 7 days

  Grade 3 or 4 thrombocytopenia that results in significant bleeding per investigator judgment

  Grade 4 thrombocytopenia lasting > 7 days

Other toxicities occurring during the first cycle that are considered to be clinically relevant and related to study treatment, as determined by the investigator and the Medical Monitor may also be considered DLTs.

3.1.2.1.2 Treatment Regimens for the *Follicular Lymphoma* Dose-Escalation Phase

All patients enrolled in the dose-escalation phase will receive induction treatment, administered in 28-day cycles as shown in Table 1. When study treatments are given on

the same day, they will be administered sequentially in the following order: lenalidomide, obinutuzumab, and polatuzumab vedotin.

Table 1 Induction Treatment for the *Follicular Lymphoma* Dose-Escalation Phase

Cycle	G + Pola + Len (28-Day Cycles)
Cycle 1	• Lenalidomide 10 mg, 15 mg, or 20 mg PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Days 1, 8, and 15 • Polatuzumab vedotin 1.4 mg/kg or 1.8 mg/kg IV on Day 1
Cycles 2–6	• Lenalidomide 10 mg, 15 mg, or 20 mg PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Day 1 • Polatuzumab vedotin 1.4 mg/kg or 1.8 mg/kg IV on Day 1

G + Pola + Len = obinutuzumab in combination with polatuzumab vedotin and lenalidomide; IV = intravenous; PO = by mouth.

Note: Treatments will be administered sequentially in the following order: lenalidomide, obinutuzumab, and polatuzumab vedotin.

Patients who achieve a CR, a PR, or stable disease at EOI will receive maintenance treatment with G + Len, as outlined in Table 2. Polatuzumab vedotin will not be given as maintenance treatment. Maintenance treatment should start 8 weeks (±1 week) after Day 1 of Cycle 6 and will continue until disease progression or unacceptable toxicity for up to 24 months.

Table 2 Maintenance Treatment for the *Follicular Lymphoma* Dose-Escalation Phase

Patient Population	Regimen
Patients with FL	Maintenance treatment consisting of the following, administered for approximately 24 months (from Months 1–24): • Lenalidomide 10 mg PO once daily on Days 1–21 of each month for a maximum of 12 months • Obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months) for a maximum of 24 months

FL = follicular lymphoma; IV = intravenous; PO = by mouth.

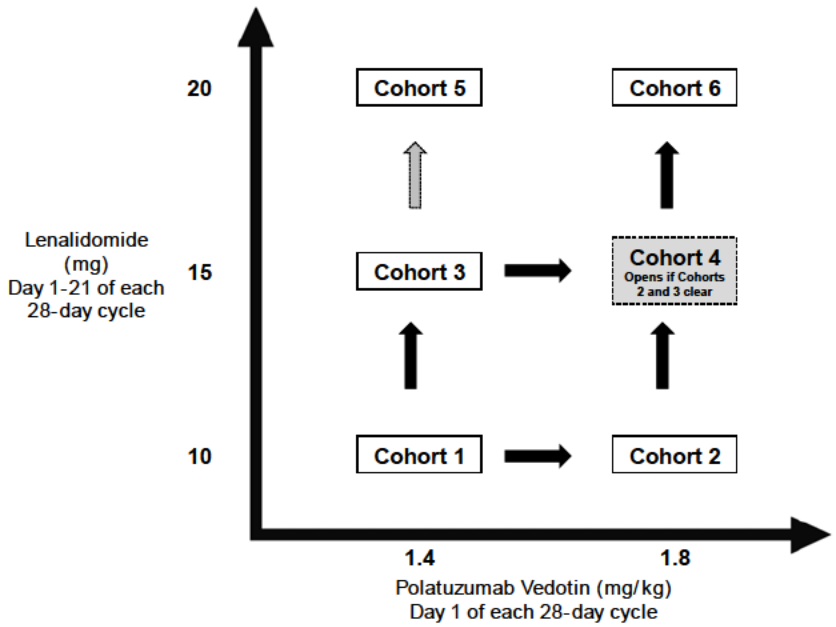
Notes: A month is defined as 28 days. Treatments will be administered sequentially in the following order: lenalidomide followed by obinutuzumab.

3.1.2.1.3 Dose-Escalation Rules

A standard 3 + 3 dose-escalation schema will be used. The obinutuzumab dose will remain fixed at 1000 mg during the dose-escalation phase. The starting doses in Cohort 1 are 1.4 mg/kg for polatuzumab vedotin and 10 mg for lenalidomide. In Cohorts 2–6, dose escalation of polatuzumab vedotin and lenalidomide will proceed in

increments that parallel the magnitude of dose increases tested in ongoing Phase Ib studies (see Sections 3.3.3.2 and 3.3.3.2.2). For polatuzumab vedotin, there are two possible dose levels: 1.4 or 1.8 mg/kg. For lenalidomide, there are three possible dose levels (10, 15, or 20 mg). Intrapatient dose escalation is not allowed. The *FL* dose-escalation plan is depicted in Figure 2, and the doses for each cohort are summarized in Table 3.

Figure 2 *Follicular Lymphoma* **Dose-Escalation Plan**



If Cohort 1 doses are deemed safe and tolerable, escalation will continue with simultaneous enrollment of Cohort 2 (only the polatuzumab vedotin dose will increase) and Cohort 3 (only the lenalidomide dose will increase).

Escalation to Cohort 4 may occur only if Cohort 2 doses and Cohort 3 doses are deemed safe and tolerable.

If Cohort 4 doses are not tolerable, escalation may continue with Cohort 5 (based on tolerated Cohort 3 dose combination, in which only the lenalidomide dose will increase).

If the Cohort 4 doses are safe and tolerable, further escalation will occur with enrollment of Cohort 6 (only the lenalidomide dose will increase).

Table 3 *Follicular Lymphoma* **Dose-Escalation Cohorts**

Cohort	Obinutuzumab [a]	Polatuzumab Vedotin [b]	Lenalidomide [c]
1	1000 mg	1.4 mg/kg	10 mg
2	1000 mg	1.8 mg/kg	10 mg
3	1000 mg	1.4 mg/kg	15 mg
4	1000 mg	1.8 mg/kg	15 mg
5	1000 mg	1.4 mg/kg	20 mg
6	1000 mg	1.8 mg/kg	20 mg

[a] Obinutuzumab will be administered intravenously at a fixed dose of 1000 mg. During Cycle 1, obinutuzumab will be administered on Days 1, 8, and 15. During Cycles 2–6, obinutuzumab will be administered on Day 1 only.

[b] Polatuzumab vedotin will be administered intravenously on Day 1 of each 28-day cycle.

[c] Lenalidomide will be administered orally on Days 1–21 of each 28-day cycle.

Dose escalation will occur in accordance with the rules listed below.

- A minimum of 3 patients will initially be enrolled in each cohort. *The first 3 patients in each cohort will be sequentially enrolled and dosed at least 48 hours apart.*
- If none of the first 3 DLT-evaluable patients experiences a DLT, the doses in that cohort will be deemed safe and tolerable and escalation may continue per the dose-escalation plan described above.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, the doses in that cohort will be deemed safe and tolerable and escalation may continue per the dose-escalation plan described above.
- If a DLT is observed in $\geq$ 33% of patients (e.g., 2 or more of up to 6 DLT-evaluable patients), the dose combination at which this occurs will be considered intolerable and the MTD will have been exceeded for polatuzumab vedotin and/or lenalidomide in the G+Pola+Len treatment combination. However, enrollment may continue in alternative cohorts according to the dose-escalation plan described above.
- If the MTD is exceeded in any cohort, the highest dose combination at which $<$33% of patients (e.g., 2 of 6 DLT-evaluable patients) experience a DLT will be declared the combination MTD (i.e., the MTDs for polatuzumab vedotin and lenalidomide in the G+Pola+Len treatment combination).
- If the MTD is not exceeded at any dose level, the highest dose combination administered in this study will be declared the maximum administered dose for polatuzumab vedotin and lenalidomide in the G+Pola+Len treatment combination.

If the MTD is exceeded in any cohort, de-escalation of the polatuzumab vedotin dose and/or the lenalidomide dose and adjustment of treatment schedules (e.g., lenalidomide treatment on Days 1–10) may occur. It is possible that more than one combination MTD (i.e., potential RP2Ds) will be identified, which may consist of different dose or schedule

combinations for polatuzumab vedotin and lenalidomide that are deemed safe and tolerable when combined with a fixed dose of obinutuzumab. If this occurs, it is possible that more than one expansion cohort will be enrolled to gather additional safety, PK, and PD data at these RP2Ds and schedules. Additional patients may be enrolled in a given cohort in the absence of DLTs to acquire additional safety data for the appropriate dose levels in the expansion phase of the study.

On the basis of a review of real-time safety data and available preliminary PK data, dose escalation may be halted or modified by the Sponsor as deemed appropriate.

Relevant demographic, adverse event, laboratory, dose administration/intensity, and PK (if available) data will be reviewed *throughout the study by the Clinical Study Team and* prior to dose-escalation decisions, which will be made by the *Medical Monitor* in consultation with the Principal Investigator *and participating investigators.*

Although the DLT assessment window is defined as the first treatment cycle, cumulative *or late* toxicities occurring beyond the first cycle may be considered when determining the RP2Ds. *Prior to opening the R/R FL expansion phase, the Clinical Study Team and the Medical Monitor will review the cumulative data, recommend the RP2D, and review this with the IMC for approval.*

3.1.2.2 *Follicular Lymphoma* Expansion Phase

The expansion phase is designed to further assess the safety and efficacy of polatuzumab vedotin and lenalidomide at their respective RP2Ds when combined with a fixed dose of obinutuzumab *in FL patients*.

Approximately 40 patients with FL will be enrolled during the expansion phase and treated as described below.

All patients enrolled in the expansion phase will receive induction treatment as outlined in Table 4. When study treatments are given on the same day, they will be administered sequentially in the following order: lenalidomide, obinutuzumab, and polatuzumab vedotin.

Table 4 Induction Treatment for the *Follicular Lymphoma* Expansion Phase

Cycle	G + Pola + Len (28-Day Cycles)
Cycle 1	• Lenalidomide at the RP2D (mg) PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Days 1, 8, and 15 • Polatuzumab vedotin at the RP2D (mg/kg) IV on Day 1
Cycles 2–6	• Lenalidomide at the RP2D (mg) PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Day 1 • Polatuzumab vedotin at the RP2D (mg/kg) IV on Day 1

G + Pola + Len = obinutuzumab in combination with polatuzumab vedotin and lenalidomide; IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

Note: Treatments will be administered sequentially in the following order: lenalidomide, obinutuzumab, and polatuzumab vedotin.

*P*atients with FL who achieve a CR, PR, or stable disease at EOI will receive post-induction treatment (referred to as maintenance) with obinutuzumab and lenalidomide, as outlined in Table 5. Polatuzumab vedotin will not be given during the post-induction phase. Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity, for up to 24 months for maintenance treatment.

Table 5 Post-Induction Treatment for the *Follicular Lymphoma* Expansion Phase

Patient Population	Regimen
Patients with FL	Maintenance treatment consisting of the following, administered for approximately 24 months (from Months 1–24): • Lenalidomide 10 mg PO once daily on Days 1–21 of each month for a maximum of 12 months • Obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months), starting with Month 1 (i.e., Months 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23) for a maximum of 24 months

FL = follicular lymphoma; IV = intravenous; PO = by mouth.

Notes: A month is defined as 28 days. Treatments will be administered sequentially in the following order: lenalidomide followed by obinutuzumab.

3.1.3 *Rituximab plus Polatuzumab Vedotin plus Lenalidomide Treatment Group (Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma)*

Based on the safety and efficacy results from the Phase III BO21005 study in patients with DLBCL, the protocol has been amended to explore dose-finding of lenalidomide in

combination with fixed doses of polatuzumab vedotin and rituximab instead of obinutuzumab for patients with R/R DLBCL.

3.1.3.1 *Dose-Escalation Phase*

The DLBCL dose-escalation phase will open with the purpose of identifying the RP2D for lenalidomide when combined with polatuzumab vedotin at 1.8 mg/kg and rituximab at 375 mg/m² as induction treatment in patients with R/R DLBCL. The dose escalation will initiate at the lenalidomide 10-mg dose level and increase through Cohorts A, B, and C (see Figure 3).

Approximately 12–18 patients will be enrolled in the R/R DLBCL dose-escalation phase. Cohorts of 3–6 patients each will be treated in accordance with the treatment regimens and dose-escalation rules described below.

Patients will be closely monitored for adverse events during the DLT assessment window, defined as the first treatment cycle (from Day 1 of Cycle 1 to Day 1 of Cycle 2). Adverse events meeting the criteria for DLT, as defined below (see Section 3.1.2.1.1), will be reported to the Sponsor within 24 hours (see Section 5.4.2).

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and RP2D assessments and will be replaced by an additional patient at that same dose level. Patients who miss one or more doses of polatuzumab vedotin or rituximab or five consecutive daily doses of lenalidomide during the DLT assessment window for reasons other than a DLT will also be replaced and considered non-evaluable for dose-escalation decisions. Patients who receive supportive care during the DLT assessment window that may confound the evaluation of DLTs may be replaced at the discretion of the Medical Monitor.

Patients will receive induction treatment with R +Pola +Len for a total of six cycles. Patients achieving a CR or PR at EOI will be eligible to receive consolidation treatment with R +Len. A study schema is provided in Figure 1 .

Treatment Regimens for DLBCL Dose-Escalation Phase

Patients enrolled in the DLBCL-dose-escalation phase will receive induction treatment, administered in 28-day cycles as shown in Table 6. When study treatments are given on the same day, they will be administered sequentially in the following order: lenalidomide, rituximab, and polatuzumab vedotin.

Table 6 *Induction Treatment for the DLBCL Dose-Escalation Phase*

Cycle	*R + Pola + Len (28-Day Cycles)*
Cycles 1–6	• *Lenalidomide 10 mg, 15 mg, or 20 mg PO once daily on Days 1–21* • *Rituximab 375 mg/m² IV on Day 1* • *Polatuzumab vedotin 1.8 mg/kg IV on Day 1*

IV = intravenous; PO = by mouth; R + Pola + Len = rituximab in combination with polatuzumab vedotin and lenalidomide.
Note: Treatments will be administered sequentially in the following order: lenalidomide, rituximab, and polatuzumab vedotin.

Patients who achieve a CR or PR at EOI will receive consolidation treatment with R +Len, as outlined in Table 7. Polatuzumab vedotin will not be given as maintenance treatment. Consolidation treatment should start 8 weeks (±1 week) after Day 1 of Cycle 6 and will continue for 6 months until disease progression or unacceptable toxicity.

Table 7 *Consolidation Treatment for the Dose-Escalation Phase*

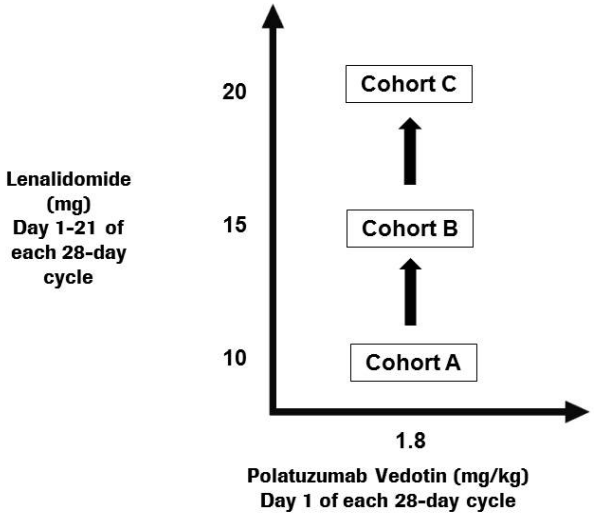
Patient Population	*Regimen*
Patients with DLBCL	*Consolidation treatment consisting of the following, administered for approximately 6 months (from Months 1–6):* • *Lenalidomide 10 mg PO once daily on Days 1–21 of each month for a maximum of 6 months* • *Rituximab 375 mg/m² IV on Day 1 of every other month (i.e, every 2 months starting with Month 1 (i.e., Months 1, 3, 5)*

DLBCL = diffuse large B-cell lymphoma; IV = intravenous; PO = by mouth.
Notes: A month is defined as 28 days. Treatments will be administered sequentially in the following order: lenalidomide followed by rituximab.

Dose-Escalation Rules

A standard 3 +3 dose-escalation schema will be used. The rituximab and polatuzumab dose levels will remain fixed during the dose-escalation phase, and only the lenalidomide will be dose escalated. The polatuzumab dose of 1.8 mg/kg is based on ongoing Phase II trials (see Sections 1.3.2 and 3.3.3.3). Intrapatient dose escalation is not allowed. The overall DLBCL dose-escalation plan is depicted in Figure 3.

Figure 3 *DLBCL Dose-Escalation Plan*



If Cohort A doses are deemed safe and tolerable, escalation will continue with enrollment of Cohort B.

If Cohort B doses are deemed safe and tolerable, escalation will continue with enrollment of Cohort C.

Table 8 *DLBCL Dose-Escalation Cohorts*

Cohort	*Rituximab* [a]	*Polatuzumab Vedotin* [b]	*Lenalidomide* [c]
A	*375 mg/m²*	*1.8 mg/kg*	*10 mg*
B	*375 mg/m²*	*1.8 mg/kg*	*15 mg*
C	*375 mg/m²*	*1.8 mg/kg*	*20 mg*

DLBCL = diffuse large B-cell lymphoma; IV = intravenous; PO = by mouth.

[a] *Rituximab will be administered at a dose of 375 mg/m² IV on Day 1 of each 28-day cycle of induction.*

[b] *Polatuzumab vedotin will be administered at a dose of 1.8 mg/kg IV on Day 1 of each 28-day cycle of induction.*

[c] *Lenalidomide will be administered at doses of 10 mg, 15 mg, or 20 mg PO once daily on Days 1–21 of each 28-day cycle.*

Dose escalation will occur in accordance with the rules listed below.

- *A minimum of 3 patients will initially be enrolled in each cohort. The first 3 patients in each cohort will be sequentially enrolled and dosed at least 48 hours apart.*
- *If none of the first 3 DLT-evaluable patients experiences a DLT, the doses in that cohort will be deemed safe and tolerable, and escalation may continue per the dose-escalation plan described above.*

- *If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, the doses in that cohort will be deemed safe and tolerable, and escalation may continue per the dose-escalation plan described above.*
- *If a DLT is observed in ≥33% of patients (e.g., 2 or more of up to 6 DLT-evaluable patients), the dose combination at which this occurs will be considered intolerable and the MTD will have been exceeded for lenalidomide in the R +Pola +Len treatment combination.*
- *If the MTD is exceeded in any cohort, the highest dose combination at which <33% of patients (e.g., 2 of 6 DLT-evaluable patients) experience a DLT will be declared the combination MTD (i.e., the MTDs lenalidomide in the R +Pola +Len treatment combination).*
- *If the MTD is not exceeded at any dose level, the highest dose combination administered in this study will be declared the maximum administered dose for polatuzumab vedotin and lenalidomide in the R +Pola +Len treatment combination.*

If the MTD is exceeded in any cohort, de-escalation of the lenalidomide dose and/or polatuzumab vedotin dose, and/or adjustment of treatment schedules (e.g., lenalidomide treatment on Days 1–10) may occur. Additional patients may be enrolled in a given cohort in the absence of DLTs to acquire additional safety data for the appropriate dose levels in the expansion phase of the study.

On the basis of a review of real-time safety data and available preliminary PK data, dose escalation may be halted or modified by the Sponsor as deemed appropriate.

Relevant demographic, adverse event, laboratory, dose administration/intensity, and PK (if available) data will be reviewed prior to dose-escalation decisions, which will be objectively reviewed throughout the study by the Clinical Study Team and prior to dose-escalation decisions, which will be made by the Medical Monitor in consultation with the Principal Investigator and participating investigators.

Although the DLT assessment window is defined as the first treatment cycle, cumulative or late toxicities occurring beyond the first cycle may be considered when determining the RP2Ds. Prior to opening the R/R DLBCL expansion phase, the Clinical Study Team and the Medical Monitor will review the cumulative data, determine the RP2D, and review this with the IMC for approval.

3.1.3.2 *DLBCL Expansion Phase*

The expansion phase is designed to further assess the safety and efficacy of lenalidomide when combined with a fixed dose of rituximab and polatuzumab vedotin in DLBCL patients.

Approximately 40 patients with DLBCL will be enrolled during the expansion phase and treated as described below.

All patients enrolled in the expansion phase will receive induction treatment as outlined in Table 9. When study treatments are given on the same day, they will be administered sequentially in the following order: lenalidomide, rituximab, and polatuzumab vedotin.

Table 9 ***Induction Treatment for the DLBCL Expansion Phase***

Cycle	*R + Pola + Len (28-Day Cycles)*
Cycles 1–6	*Lenalidomide 10 mg, 15 mg, or 20 mg PO once daily on Days 1–21* *Rituximab 375 mg/m² IV on Day 1* *Polatuzumab vedotin 1.8 mg/kg IV on Day 1*

DLBCL = diffuse large B-cell lymphoma; IV = intravenous; PO = by mouth; R + Pola + Len = rituximab in combination with polatuzumab vedotin and lenalidomide.
Note: Treatments will be administered sequentially in the following order: lenalidomide, rituximab, and polatuzumab vedotin.

Patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with rituximab and lenalidomide as outlined in Table 10. Polatuzumab vedotin will not be given during the post-induction phase. Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity, for up to 6 months for consolidation treatment.

Table 10 ***Post-Induction Treatment for the DLBCL Expansion Phase***

Patient Population	*Regimen*
Patients with DLBCL	*Consolidation treatment consisting of the following, administered for approximately 6 months (Months 1–6):* • *Lenalidomide 10 mg PO once daily on Days 1–21 of each month, for a maximum of 6 months* • *Rituximab 375mg/m² IV on Day 1 of every other month (i.e., every 2 months) starting with Month 1 (i.e., Months 1, 3, 5)*

DLBCL = diffuse large B-cell lymphoma; IV = intravenous; PO = by mouth.
Notes: A month is defined as 28 days. Treatments will be administered sequentially in the following order: lenalidomide followed by rituximab.

3.1.4 Internal Monitoring Committee

An IMC will monitor patient safety throughout the study. The IMC will include, but will not be limited to, Roche representatives from Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis. In addition to the ongoing assessment of the incidence and nature of adverse events (particularly Grade ≥ 3 events), serious adverse

events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, additional analyses should be performed, or enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any potential new safety signals. Specific operational details such as the committee's composition, frequency and timing of meetings, members' roles and responsibilities, and data to be reviewed will be detailed in an IMC charter.

3.1.5 Independent Review Committee

An IRC will assess all patients for response on the basis of imaging results and bone marrow biopsy results. The IRC will consist of radiologists, nuclear medicine experts, and a board-certified oncologist with experience in malignant lymphoma. Specific methodological and operational details will be specified in an IRC charter.

3.1.6 Post-Treatment and Survival Follow-Up

Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments every 3 months during the post-treatment follow-up period, which will continue until disease progression, the start of new anti-lymphoma treatment, or the end of the study (as defined below), whichever occurs first. Patients who experience disease progression will be evaluated for survival status and initiation of new anti-lymphoma treatment every 3 months until the end of the study. Details are provided in the schedules of assessments (see Appendix 1 and Appendix 2).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the time when both of the following criteria are met:

- All enrolled patients with FL have *been followed for at least 90 days after they have* completed or discontinued study treatment (including induction treatment and maintenance treatment as applicable).
- All enrolled patients with DLBCL have been followed for at least 1 year after they have completed or discontinued study treatment (including induction treatment and consolidation treatment as applicable).

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

As discussed in Section 1.1.1, despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, FL remains essentially an incurable disease. Patients invariably relapse, and subsequent active and well-tolerated agents are needed. DLBCL can be cured in > 50% of cases; however, up to one-third of patients have refractory disease of relapse after treatment. Success rates with salvage therapy and autologous transplantation are poor, highlighting the urgent need for novel therapeutic approaches for these patients.

On the basis of a compelling biologic and clinical rationale, as presented in Section 1.4, the addition of polatuzumab vedotin to obinutuzumab *or rituximab* and lenalidomide is a promising approach to expand the number of patients with R/R FL and DLBCL who achieve remission and to prolong response duration in these patients.

The study will include an initial dose-escalation phase followed by an expansion phase. The objective of the dose-escalation phase is to define the RP2D for lenalidomide and the RP2D dose for polatuzumab vedotin when given with obinutuzumab *in patients with R/R FL and the RP2D for lenalidomide when given in combination with polatuzumab at 1.8 mg/kg and rituximab at 375 mg/m² in patients with R/R DLBCL.* Although the DLT assessment window is the first cycle of treatment, long-term or cumulative toxicities will also be assessed and considered for the dose definition.

3.3.2 Rationale for the Triplet Combination

This study combines treatments with different MOA that have demonstrated clinical activity against B-cell lymphoma. Refer to Appendix 11 for descriptions of clinical studies that use the study drugs as single or doublet treatment.

As discussed in Section 1.4, there is a strong MOA and clinical rationale to expect an improved benefit-risk profile with the triplet combination of obinutuzumab *or rituximab*, polatuzumab vedotin, and lenalidomide over standard immunochemotherapy regimens. The hypothesis is that this novel triplet regimen may have the potential to extend treatment-free remissions and decrease toxicity by improving upon individual agents in the current standard of care. Overlapping toxicities are anticipated and expected to be manageable in the clinical setting (see Section 5.1.5).

As discussed in Section 1.4, the development of obinutuzumab in B-cell malignancies is based on the hypothesis that obinutuzumab will be a superior anti-CD20 agent compared to rituximab *in patients with FL.* This has been demonstrated in CLL (Goede et al. 2014) and *has been studied in* two additional Phase III studies in DLBCL and FL.

Study BO21223 investigated obinutuzumab plus chemotherapy (G-benda, G-CVP, G-CHOP) compared with rituximab plus chemotherapy, followed by obinutuzumab or

rituximab maintenance in patients with previously untreated iNHL (FL cohort, n =1202) and demonstrated positive results, showing a significant improvement in PFS in the obinutuzumab chemotherapy arm.

Study BO21005, investigated G-CHOP compared with R-CHOP in patients with previously untreated DLBCL and this study did not meet its primary endpoint of PFS at final analysis.

On the basis of the results of these Phase III studies evaluating obinutuzumab in combination with chemotherapy in both FL and DLBCL, patients with R/R FL in this current protocol amendment will continue to receive obinutuzumab in combination with polatuzumab vedotin and lenalidomide, while patients with R/R DLBCL will instead receive rituximab in combination with polatuzumab vedotin and lenalidomide.

In the following sections, data generated for rituximab in combination with either polatuzumab vedotin or lenalidomide are also provided to further support the combination of an anti-CD20 antibody with polatuzumab vedotin and lenalidomide.

3.3.2.1 Rituximab and Polatuzumab Vedotin Combination

During its early development, polatuzumab vedotin treatment has been investigated as a single agent and in combination with rituximab. On the basis of available Phase I and II data (see Section 3.3.3.2 and Appendix 11), polatuzumab vedotin as a single agent and combined with rituximab has shown clinical activity in heavily pretreated patients with R/R B-cell lymphoma (Palanca-Wessels et al. 2012; Morschhauser et al. 2014a). In both studies, patients received rituximab 375 mg/m^2 and polatuzumab vedotin up to 2.4 mg/kg Q3W for up to 1 year, progression, or unacceptable toxicity. *The ongoing Study GO27834 has also shown preliminary safety and efficacy results evaluating the combination of rituximab and polatuzumab vedotin 1.8 mg/kg.*

3.3.2.2 Obinutuzumab and Polatuzumab Vedotin Combination

The combination of obinutuzumab with polatuzumab vedotin is being evaluated in several ongoing studies (see Table 11), including two Phase Ib/II trials in patients with R/R FL. *Preliminary results from these studies show safety and efficacy at the polatuzumab vedotin 1.8-mg/kg dose level when combined with obinutuzumab, every 3 weeks for 6–8 cycles as described in Section 1.3.2.*

3.3.2.3 Rituximab and Lenalidomide Combination

The thalidomide analogue lenalidomide is currently approved for the treatment of multiple myeloma, deletion 5q myelodysplastic syndromes, and MCL as Revlimid. Nonclinical studies demonstrated that T-cell immune synapse dysfunction in FL can be restored with lenalidomide (Ramsay et al. 2009). In addition, lenalidomide has been shown to reduce T regulatory cells and activate CD8 T cells (Kater et al. 2014). E3 ligase protein cereblon (encoded by the *CRBN* gene) is the molecular target of lenalidomide. Lenalidomide binding to CRBN mediated its direct anti-tumor effects and

is also required for T-cell production of interleukin-2 and tumor necrosis factor α (Lopez-Girona et al. 2012).

In nonclinical studies, lenalidomide combined with rituximab resulted in anti-tumor effects via increased NK-cell function, enhanced antibody-dependent cell-mediated cytotoxicity, and improved NK cell–mediated synapse formation (Wu et al. 2008; Zhang et al. 2009).

Although lenalidomide has not been approved for the treatment of R/R FL and DLBCL, clinical activity has been demonstrated in the treatment of both R/R indolent and aggressive B-cell lymphoma with lenalidomide as a single agent (Wiernik et al. 2008; Witzig et al. 2009, 2011) or in combination with rituximab (Zinzani et al. 2011, 2013; Leonard et al. 2012; Tuscano et al. 2014; Wang et al. 2013) or obinutuzumab (Morschhauser et al. 2014b) (see Appendix 11).

3.3.2.4 Obinutuzumab and Lenalidomide Combination

Because the combination of lenalidomide and rituximab has been shown to be synergistic in nonclinical models and in patients with relapsed and first-line FL, replacing rituximab with obinutuzumab in combination with lenalidomide might be even more efficient than the lenalidomide and rituximab combination.

The combination of obinutuzumab with lenalidomide has been evaluated in nonclinical studies using the MCL Z138 xenograft model in SCID-beige mice. Results from these studies demonstrated greater anti-tumor efficacy than either single agent and superior activity to the combination of lenalidomide with rituximab (data available upon request [RDR 1064289]).

The combination of obinutuzumab with lenalidomide is currently being investigated in an ongoing Phase Ib/II study sponsored by the Lymphoma Academic Research Organisation (GALEN study) as induction and maintenance treatment in patients with R/R FL and aggressive lymphoma (DLBCL and MCL). The recommended dose of lenalidomide was established at 20 mg/day on the basis of an increased incidence of Grade 3 or 4 neutropenia between Cycles 2 and 6 at the next higher dose of 25 mg/day (Morschhauser et al. 2014). The most common adverse events observed during the dose-escalation phase (all grades, $\geq$20% patients) were neutropenia (10/19; 53%), constipation (10/19; 53%) asthenia (7/19; 37%), upper respiratory tract infection (7/19; 37%), rash/cutaneous eruption (5/19; 26%), cough (5/19; 26%), diarrhea (4/19; 21%), and fever (4/19, 21%). Grade 3/4 adverse events occurring in $\geq$2 patients only consisted of neutropenia (8/19; 42%). IRRs occurred in 3 patients and did not exceed Grade 2. Preliminary efficacy data available from the dose-escalation phase of the study are encouraging, with an overall response according to Cheson et al. 1999 criteria of 68% (13 of 19 evaluable patients), including 7 patients with a CR; 3 patients with a CR, unconfirmed; and 3 patients with a PR (Morschhauser et al. 2014). Enrollment in the expansion phase at 20 mg/day (Phase II part) is in progress. Available preliminary

unpublished data (cutoff date: 30 September 2014) for 45 patients evaluable for safety during the induction period (Cycles 1–6) show a median of 5 induction cycles (range: 2–6 cycles) received. The following hematologic adverse events (all grades) were reported: neutropenia (17/45; 37.8%), febrile neutropenia (3/45; 6.7%), anemia (8/45; 17.8%), and thrombocytopenia (5/45; 11.1%). The most common (occurring in >10% of patients) non-hematologic adverse events (all grades) were constipation (9/45; 20%); rash (7/45; 15.6%); cough (7/45; 15.6%); asthenia (6/45; 13.3%); and fatigue, diarrhea, and pruritus (5/45; 11.1% each).

As mentioned in Section 1.4, there is a strong rationale for enhanced activity with combination therapy as well as apparent limited additional toxicity that argues that exploration of the G+Pola+Len combination is appropriate. This novel triplet regimen may have the potential to extend treatment-free remissions and decrease toxicity by improving upon individual agents in current standard of care and incorporating a targeted chemotherapy regimen.

3.3.3 Rationale for Dose and Schedule

3.3.3.1 Rationale for Obinutuzumab Dose and Schedule *in Patients with Follicular Lymphoma*

The dose and schedule for obinutuzumab in this study will be fixed for the induction and the maintenance components of the study, and obinutuzumab will not be dose-escalated. This is based on the recommended dose and schedule (6–8 cycles depending on the trial) of obinutuzumab *from the* Phase III program in patients with B-cell lymphoma.

The dose and schedule of obinutuzumab in the induction regimen will be 1000 mg IV on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle (Cycles 2–6). For this protocol, patients will be treated for 6 cycles during the induction phase.

The dose and schedule of obinutuzumab in the maintenance regimen (FL) will be 1000 mg IV administered every 2 months for 2 years. This dosing administration is based on the obinutuzumab maintenance regimen that was administered in the Phase III Study GAO4753g (Sehn et al. 2015). Study GAO4753g showed that bendamustine and obinutuzumab followed by obinutuzumab maintenance was associated with superior PFS compared with bendamustine alone (median PFS had not been reached in the obinutuzumab and bendamustine followed by obinutuzumab maintenance arm vs. 14.9 months in the bendamustine arm; stratified hazard ratio [HR]=0.55; 95% CI: 0.40, 0.74; p=0.0001, by log-rank test).

3.3.3.2 Rationale for Polatuzumab Vedotin Dosing Regimen

3.3.3.2.1 *Rationale for Polatuzumab Vedotin Dose in Patients with Folllicular Lymphoma*

For this study, dose escalation of polatuzumab vedotin *for patients with R/R FL* will begin at a dose level of 1.4 mg/kg (one dose level below the highest polatuzumab vedotin dose *currently under development*) and will escalate to a final dose of 1.8 mg/kg, if tolerated. The *initial* polatuzumab vedotin dose and schedule for this study were based on the experience from the Phase I study (DCS4968g) with single-agent polatuzumab vedotin and the Phase II study (GO27834) with polatuzumab vedotin in combination with rituximab in patients with relapsed and refractory B-cell lymphoma, the majority of which had FL or DLBCL. Most evidence of anti-tumor activity was observed at doses ≥1.8 mg/kg alone or in combination with rituximab.

Evidence from Study DCS4968g indicated that duration of study treatment might be limited by tolerability to polatuzumab vedotin at a dose of 2.4 mg/kg. Specifically, peripheral neuropathy (sensory and/or motor) has been identified as a known risk (see Section 5.1.3.1). Because of the chronic course and incurability of indolent B-cell lymphoma, treatment paradigms are increasingly emphasizing tolerability to treatment in addition to efficacy. As polatuzumab vedotin has shown single-agent activity at the 1.8-mg/kg dose level (Palanca-Wessels et al. 2012), an additional cohort was opened with the purpose of determining whether lower doses of polatuzumab vedotin (1.8 mg/kg) in combination with standard doses of rituximab result in improved tolerability while maintaining efficacy in FL.

An analysis comparing the 2.4- and 1.8-mg/kg polatuzumab vedotin dose levels in combination with rituximab was reported (Advani et al. 2015). A high objective response rate was observed at both doses (76% at 2.4 mg/kg and 75% at 1.8 mg/kg), with a higher rate of CRs at 2.4 mg/kg (44% at 2.4 mg/kg and 10% at 1.8 mg/kg). Adverse events and discontinuation rates were reduced at both doses if only the first 8 cycles are considered versus through study completion. Therefore, to minimize the risk for the potential development of peripheral neuropathy (sensory and/or motor), treatment with polatuzumab vedotin was limited to a maximum of 6-month duration, corresponding to 6–8 cycles as defined per the protocol. Further, in all current studies, the maximum dose of polatuzumab vedotin was limited to 1.8 mg/kg per the dose defined in the protocol.

The combination of obinutuzumab with polatuzumab vedotin is being evaluated in several ongoing studies (see Table 11), including two Phase Ib/II trials in patients with R/R FL.

Table 11 Polatuzumab Vedotin plus Obinutuzumab–Containing Regimens for the Treatment of *Follicular* Lymphoma

	Study		
	GO27834 [a]	GO29365 [b]	GO29044 [c]
Patient population	R/R FL (n = 46)	R/R FL (n = 26)	R/R *FL* (Ph Ib; n = 2) [d]
Obinutuzumab dose	1000 mg	1000 mg	1000 mg
Polatuzumab vedotin dose	1.8 mg/kg	1.8 mg/kg	1.4 and 1.8 mg/kg
Chemotherapy	—	Bendamustine	CHP

CHP = cyclophosphamide, doxorubicin, prednisone; FL = follicular lymphoma; Ph = phase; R/R = relapsed or refractory.

[a] Study GO27834: polatuzumab vedotin and obinutuzumab administered every 21 days for 8 cycles.

[b] Study GO29365: polatuzumab vedotin, bendamustine, and obinutuzumab administered every 21 days (FL) for 6 cycles.

[c] Study GO29044: polatuzumab vedotin plus obinutuzumab plus CHP administered every 21 days for 6–8 cycles.

[d] In the Phase Ib portion of the study, *1 patient with R/R FL was treated with* polatuzumab vedotin at 1.4 mg/kg *and 1 patient with R/R FL was treated with polatuzumab vedotin at 1.8 mg/kg (Forero-Torres et al. 2016).*

In Study GO29044, the starting dose of polatuzumab vedotin *was* 1.4 mg/kg and *was* escalated to 1.8 mg/kg, *in combination* with G-CHP. In Study GO29365, the starting dose of polatuzumab vedotin is 1.8 mg/kg when combined with obinutuzumab and bendamustine. Since polatuzumab vedotin is being combined with obinutuzumab and chemotherapy (CHP or bendamustine) at 1.4 or 1.8 mg/kg, *for patients with R/R FL in this study,* dose escalation of polatuzumab vedotin will begin at a dose level of 1.4 mg/kg (one dose level below the highest polatuzumab vedotin dose *level in clinical development*) and will escalate to a final dose of 1.8 mg/kg, if tolerated. This novel triplet, G + Pola + Len, substitutes out the standard chemotherapy components with lenalidomide, which in this combination may have the potential to extend treatment-free remissions and decrease toxicity, compared to combinations with standard chemotherapy components.

3.3.3.2.2 *Rationale for Polatuzumab Vedotin Dose in Patients with DLBCL*

On the basis of the preliminary data from the patients with DLBCL treated in Studies GO29044 and GO29365, the dose level of polatuzumab vedotin at 1.8 mg/kg has been shown to be safe and tolerable in combination with rituximab and chemotherapy.

Due to the aggressive nature of DLBCL and the evidence that anti-tumor activity was observed at doses ≥1.8 mg/kg alone or in combination with rituximab, the higher dose

level of polatuzumab vedotin is preferred to maximize clinical benefit for the R/R DLBCL population, which has no standard of care.

The safety profile of rituximab differs slightly in comparison with obinutuzumab and is expected to be tolerated when combined with polatuzumab vedotin at 1.8 mg/kg and lenalidomide; hence, in this amendment, the R/R DLBCL dose-escalation phase will start at the dose level of 1.8 mg/kg and only the lenalidomide dose will be escalated to determine an RP2D in this population.

3.3.3.2.3 *Rationale for Polatuzumab Vedotin Dosing Schedule in Patients with Follicular Lymphoma and DLBCL*

The number of induction cycles (six *28*-day cycles) *is in line with other anti-CD20 plus polatuzumab vedotin regimens studied in R/R NHL.*

Polatuzumab vedotin will not be administered as post-induction treatment (consolidation for DLBCL or maintenance for FL) owing to the risk of peripheral neuropathy with cumulative dosing.

3.3.3.3 Rationale for Lenalidomide Dose and Schedule

For the induction phase of the dose-escalation study, the lenalidomide starting dose will be 10 mg (two dose levels below the recommended expansion dose in combination with obinutuzumab in Phase Ib study) and will escalate to 15 mg and then to a final dose of 20 mg, if tolerated. Patients enrolled in the expansion study will receive lenalidomide at the RP2D during induction. The lenalidomide dose and schedule for this study were primarily based on the experience from the Phase Ib study (GALEN) that evaluated the combination of lenalidomide with obinutuzumab (Morschhauser et al. 2014b). The MTD of lenalidomide was not reached; however, the recommended dose of lenalidomide established was 20 mg when combined with obinutuzumab for R/R FL or DLBCL on the basis of the increased incidence of Grade 3/4 neutropenia between Cycles 2 and 6 at 25 mg (see Section 3.3.2.4 for details).

The optimal use of lenalidomide in maintenance/consolidation therapy is under active investigation. In combination with rituximab, the most common schedule of lenalidomide has been 20 mg administered on Days 1–21 of each 28-day cycle in R/R B-cell lymphoma (Leonard et al. 2012; Wang et al. 2013; Zinzani et al. 2013).

For the post-induction phase of this study, the lenalidomide dose will be 10 mg administered on Days 1–21 of each month for a maximum of 12 months (additional 1 year of treatment) for patients with R/R FL and for a maximum of 6 months (total of 1 year of treatment inclusive of induction phase) for patients with R/R DLBCL. This schedule is based on the post-induction schedule administered in the GALEN study.

3.3.3.4 Rationale for Treatment Duration

In this study, patients with R/R FL or DLBCL will receive 6 cycles of induction treatment followed by post-induction treatment, with the objective to improve the response to

induction therapy, either by converting a PR to a CR or by eradicating minimal residual disease (MRD) to achieve a molecular response in patients with a clinical CR after induction treatment, thus reducing the relapse risk for responders. In this study, MRD levels will be measured during the post-induction period as an additional means of evaluating the benefits of the triple combination as post-induction treatment (see Section 3.3.5.3).

Despite recent improvements in therapy for FL, including demonstrated benefit from 2-year rituximab maintenance in patients who responded to first-line immunochemotherapy (Study MO18264), FL is still not considered curable, with a 6-year PFS of 59.2% (Salles et al. 2013b). A Phase III study, GAO4753g, investigated obinutuzumab plus bendamustine (GB) compared with bendamustine alone in patients with rituximab-refractory indolent B-cell lymphoma (n = 396). Patients in the GB group who had not experienced disease progression at EOI received obinutuzumab monotherapy every 2 months for up to 2 years. On the basis of positive results from this study, demonstrating significant improvement in PFS in the GB arm, with a median PFS of 29 versus 14 months (HR = 0.52; 95% CI: 0.39, 0.70; p > 0.0001) (Sehn et al. 2015), the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor. These data support further investigation of obinutuzumab in combination with new targeted drugs in the setting of induction and maintenance treatment for patients with FL.

The combination of obinutuzumab with lenalidomide is currently being investigated in an ongoing Phase Ib/II study (GALEN) as induction and maintenance treatment in patients with R/R FL. In the GALEN study, maintenance treatment consists of obinutuzumab administered every 2 months for 2 years and lenalidomide administered on Days 1–21 of each 28-day cycle for 1 year, and the same obinutuzumab and lenalidomide dosing schedule will be employed in this study.

Patients with R/R DLBCL who are not suitable for or do not benefit from consolidative autologous transplantation exhibit a poor prognosis. Responses obtained with different rituximab treatment regimens tested in clinical trials (e.g., rituximab in combination with bendamustine, with gemcitabine plus oxaliplatin, or with lenalidomide) have been of short duration, with the longest reported median PFS of approximately 7 months observed in one study of BR (Ohmachi et al. 2013). Thus, 6 months of consolidation treatment, for a total treatment duration of approximately 12 months, is considered to be a reasonable exploratory therapeutic approach in patients with R/R DLBCL with an anticipated positive benefit-risk ratio. On the basis of the complementary mechanism of action between all three study drugs and considering the aggressiveness of R/R DLBCL, the study was designed to investigate the safety and efficacy of the triple combination in the consolidation setting.

3.3.4 Rationale for PET-CT-Defined Complete Response as the Primary Efficacy Endpoint

In DLBCL, the prognostic value of the post-treatment fluorodeoxyglucose (FDG) PET-CT scan has been well documented (Thomas et al. 2010; Vitolo et al. 2010). PET-CT scans have been implemented in the Lugano 2014 criteria (Cheson et al. 2014) and are commonly used to assess efficacy in medical practice and clinical trials of lymphoma. More recently, the value of post-induction PET-CT status has been investigated as a prognostic marker for long-term outcome in patients with FL. In the first-line setting, results from a pooled analysis of 246 patients enrolled in three studies and having PET-CT scans available at the end of chemoimmunotherapy showed, with a median follow-up of 55 months, a 4-year PFS in PET-CT–positive and PET-CT–negative patients of 23.2% (95% CI: 11.1%, 37.9%) versus 63.4% (95% CI: 55.9%, 70.0%; $p < 0.001$), respectively, and a 4-year survival of 87.2% (95% CI: 71.9%, 94.5%) versus 97.1% (95% CI: 93.2%, 98.8%; $p < 0.0001$), respectively (Trotman et al. 2014). In the relapsed FL setting, results from a preliminary analysis of Phase II study (BO21003) comparing obinutuzumab versus rituximab monotherapy demonstrated that the post-induction PET-CT status is strongly prognostic of PFS. With a median follow-up of 32.1 months, the risk of disease progression was significantly reduced in PET-CT–negative patients compared with PET-CT–positive patients, regardless of the assessment criteria, either International Harmonization Project criteria (HR = 0.25; 95% CI: 0.191, 0.807; $p = 0.0083$) or European Organization for Research and Treatment of Cancer (EORTC) criteria (HR = 0.39; 95% CI: 0.191, 0.807; $p = 0.0083$) (Kostakoglu et al. 2014).

In response to developments involving PET-CT status, the 11th International Conference of Malignant Lymphoma imaging group provided an updated guidance for the use of PET-CT scan results for lymphoma staging and response assessment (see Appendix 5; Cheson et al. 2014).

3.3.5 Rationale for Biomarker Assessments

3.3.5.1 Rationale for Analysis of DLBCL Subtype, *BCL2*, and *MYC*

DLBCL cell-of-origin prognostic subgroups (ABC and GCB), defined using gene expression profiling, have been associated with different clinical outcomes in patients receiving R-CHOP for DLBCL, with GCB subgroups demonstrating an improved prognosis than ABC groups (3-year survival rate of 84% vs. 56%, respectively; $p < 0.001$) (Lenz et al. 2008). Moreover, non-GCB patients preferentially respond to lenalidomide (Hernandez-Ilizaliturri et al. 2011).

Similarly, Bcl-2 overexpression has been associated with inferior outcomes in DLBCL with standard treatment (Iqbal et al. 2006). Next-generation sequencing studies have shown that *BCL2* is the most mutated gene in patients with GCB DLBCL, observed in up to 35% of cases (Schuetz et al. 2012). Approximately 9%–17% of patients with newly diagnosed DLBCL harbor an underlying *MYC* rearrangement, and these patients are at

high risk of treatment failure with R-CHOP (Savage et al. 2009). A subset of patients with *MYC*-positive DLBCL also harbors an additional *BCL2* rearrangement. These "double-hit" lymphomas are associated with a very poor outcome (Dunleavy et al. 2014; Savage et al. 2009). Overexpression of Bcl-2 and Myc in DLBCL has also been observed in the absence of translocation. This "double-positive" DLBCL status is also associated with worse prognosis (Green et al. 2012; Hu et al. 2013; Johnson et al. 2012).

Identification of these molecularly defined prognostic subtypes in DLBCL is critical for interpretation of correlative investigations aimed to understand mechanisms of both sensitivity and resistance to study treatment.

3.3.5.2 Rationale for Assessment of Therapeutic Target Expression

CD79b is a signal-transducing subunit of the B-cell receptor that is rapidly internalized upon antigen binding (Jang et al. 2010). The activity of ADCs like polatuzumab depends on the presence of the target, internalization, and sensitivity to the payload drug (Zheng et al. 2009). To ascertain the expression of CD79b in this study, CD79b expression will be measured in the mandatory archival tissue.

3.3.5.3 Rationale for Assessment of Minimal Residual Disease

MRD measurement is an increasingly recognized tool for response assessment in B-cell malignancies. Circulating lymphoma cells and circulating tumor DNA can be detected and quantified at low levels as MRD to assess depth of response and monitor patients for possible disease recurrence. However, there is no scientific proof that MRD is a reliable measure of clinical outcome in NHL, and technical validation of novel technologies for MRD assessment that have clinical utility is still pending.

In FL, MRD at end of treatment is likely to be prognostic (Ladetto et al. 2013). In DLBCL, serum MRD was shown to predict early and late progression after first-line treatment (Roschewski et al. 2014). In addition, MRD assessment may complement the response assessment, particularly in immune treatment–based regimens, and mitigate potential false-positive PET-CT results caused by infiltration of metabolically active immune cells into the tumor (Kurtz et al. 2014). For these reasons, initial MRD analysis will be performed in patients with FL, and subsequent analysis in patients with DLBCL may be performed.

In this study, MRD will be quantified by circulating lymphoma cells and circulating tumor DNA as an exploratory endpoint. The lymphoma clone will be identified in DNA from the lymphoma tissue specimen. MRD levels will be determined in blood samples collected prior to dosing and during treatment to explore a pharmacodynamic (PD) relationship. MRD assessments will be performed at EOI to allow for an evaluation of the depth of response, and during and after post-induction treatment to allow for an evaluation of long-term response or possible disease recurrence.

3.3.5.4 Rationale for Assessment of Lymphoma-Related Genetic Changes and Gene Expression

Measurement of relevant protein, RNA, and DNA from tissue specimens will be assessed for biomarkers associated with disease biology (immune gene expression profiles and disease subtype gene expression patterns and associated mutations, i.e., MYD88 and CD79b), mechanism of action of study drugs (i.e., including but not limited to regulated substrates of lenalidomide, i.e., CRBN, MYC, IRF4, or immune repertoire signatures), mechanisms of resistance, and improvement of diagnostic assays.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll patients with FL or DLBCL who meet the eligibility criteria presented below.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2 (see Appendix 6)
- *For G+Pola+Len treatment group:* *R/R* FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator
- *For R+Pola+Len treatment group:* R/R DLBCL after treatment with at least one prior chemoimmunotherapy regimen *that included an anti-CD20 monoclonal antibody* in patients who are not eligible for autologous stem-cell transplantation or who have experienced disease progression following treatment with high-dose chemotherapy plus autologous stem-cell transplantation
- Histologically documented CD20-positive B-cell lymphoma as determined by the local laboratory
- FDG-avid lymphoma (i.e., PET-positive lymphoma)
- At least one bi-dimensionally measurable lesion (>1.5 cm in its largest dimension by CT scan or magnetic resonance imaging [MRI])
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL

  If the archival tissue is unavailable or unacceptable, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

If the patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, a repeat core-needle biopsy is strongly recommended.

Further details are provided in Section 4.5.6.

- Agreement to abstain from donating blood during the treatment period (including periods of treatment interruption) and for 28 days after the last dose of study treatment
- Agreement not to share study medication with another person
- Agreement to comply with all local requirements of the lenalidomide risk minimization plan

  In every country where lenalidomide has been approved, a risk minimization plan, which includes a pregnancy prevention program, is in place. The risk minimization plan should be followed by patients using lenalidomide.

  US sites only: *Per standard Revlimid REMS™ requirements, all physicians who prescribe lenalidomide for research subjects enrolled in this study and all research subjects enrolled in this study must be registered in and must comply with all requirements of the Revlimid REMS™ program.*

  For Ex-US sites only: *Subjects will be counseled on pregnancy prevention prior to medication being dispensed to ensure that the subject has complied with all requirements, including use of birth control and pregnancy testing, and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Education and Counseling Guidance Document (refer to Lenalidomide Pregnancy Prevention Risk Management Plans), and no drug will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (refer to Lenalidomide Pregnancy Prevention Risk Management Plans) will be supplied with each medication dispensed. All requirements must be followed by each site as noted within the Lenalidomide Pregnancy Prevention Risk Management Plans.*

  In addition, because lenalidomide will be administered in combination with obinutuzumab, *rituximab,* and polatuzumab vedotin, patients must comply with contraceptive measures designed to ensure safe administration of all study treatments as outlined below.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use <u>two</u> adequate methods of contraception, including at least one method with a failure rate of $<1\%$ per year, for at least 28 days prior to Day 1 of Cycle 1, during the treatment period (including periods of treatment interruption), and for at least *12 months after the last dose of polatuzumab vedotin, 28 days after the last dose of lenalidomide, 12 months after the last dose of rituximab, and* 18 months after the last dose of *obinutuzumab*

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 24 continuous months of

amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of progestogen-only hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Combined oral contraceptives are not recommended because of the increased risk of venous and arterial thromboembolism (TE) in patients taking lenalidomide.

Barrier methods may be used as the second contraceptive method but must always be supplemented with the use of a spermicide.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 5 months after the last dose of *polatuzumab vedotin, 28 days after the last dose of lenalidomide, and 3 months after the last dose of obinutuzumab or rituximab.* Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 5 months after the last dose of *polatuzumab vedotin, 28 days after the last dose of lenalidomide, and 3 months after the last dose of obinutuzumab or rituximab* to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- *Grade 3b follicular lymphoma*
- *History of transformation of indolent disease to DLBCL*
- Known CD20-negative status at relapse or progression
- Central nervous system lymphoma or leptomeningeal infiltration
- Prior allogeneic SCT
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1

- History of resistance to lenalidomide or response duration of <1 year (for patients who had a response to a prior lenalidomide-containing regimen)
- Prior standard or investigational anti-cancer therapy as specified below:

  Lenalidomide, fludarabine, or alemtuzumab within 12 months prior to Day 1 of Cycle1

  Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1

  Monoclonal antibody or ADC therapy within *5 half-lives or* 4 weeks prior to Day 1 of Cycle 1*, whichever is longer*

  Radiotherapy, chemotherapy, hormonal therapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1
- Clinically significant toxicity (other than alopecia) from prior therapy that has not resolved to Grade ≤ 2 (per NCI CTCAE, Version 4.0) prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medications, including, but not limited to, prednisone, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1

  Treatment with inhaled corticosteroids and mineralocorticoids is permitted.

  If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day of prednisone or equivalent can be given for a maximum of 5 days, but all tumor assessments must be completed prior to initiation of corticosteroid treatment.
- History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies
- Known sensitivity or allergy to murine products or any component of obinutuzumab, *rituximab,* polatuzumab vedotin, or lenalidomide formulations
- History of erythema multiforme, Grade ≥ 3 rash, or desquamation (blistering) following prior treatment with immunomodulatory derivatives such as thalidomide and lenalidomide
- Active bacterial, viral, fungal, or other infection

  Caution should be exercised when considering the use of obinutuzumab *and rituximab* in patients with a history of recurring or chronic infections.
- Positive for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at screening
- Known history of HIV positive status

  For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations.
- History of progressive multifocal leukoencephalopathy
- Vaccination with a live virus vaccine within 28 days prior to Day 1 of Cycle 1
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:

Curatively treated carcinoma in situ of the cervix; good-prognosis ductal carcinoma in situ of the breast; basal- or squamous-cell skin cancer; Stage I melanoma; or low-grade, early-stage localized prostate cancer

Any previously treated malignancy that has been in remission without treatment for $\geq$ 2 years prior to enrollment

- Contraindication to treatment for TE prophylaxis (see Section 4.3.2.5)
- Grade $\geq$ 2 neuropathy
- Evidence of any significant, uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm)
- Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1 or anticipation of a major surgical procedure during the course of the study
- Inadequate hematologic function (unless due to underlying lymphoma), defined as follows:

  Hemoglobin $<$ 9 g/dL

  ANC $<1.5\times10^9$/L

  Platelet count $<75\times10^9$/L
- Any of the following abnormal laboratory values (unless due to underlying lymphoma):

  Calculated creatinine clearance <50 mL/min (using the Cockcroft-Gault formula; see Appendix 7)

  AST or ALT $>2.5\times$ ULN

  Serum total bilirubin $>1.5\times$ ULN (or $>3\times$ ULN for patients with Gilbert syndrome)

  INR or PT $>1.5\times$ ULN in the absence of therapeutic anticoagulation

  PTT or aPTT $>1.5\times$ ULN in the absence of a lupus anticoagulant
- Pregnant or lactating, or intending to become pregnant during the study

  Women of childbearing potential must have two negative serum pregnancy test results (minimum sensitivity, 25 mIU/mL) prior to initiating therapy: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1.
- Life expectancy $<$ 3 months
- Unable to comply with the study protocol, in the investigator's judgment

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study of G+Pola+Len in patients with R/R FL *and R+Pola+Len in patients with R/R* DLBCL.

During the dose-escalation phase, patients will be assigned to cohorts with varying polatuzumab vedotin *(R/R FL dose-finding only)* and lenalidomide dose combinations, through use of an interactive voice or web-based response system (IxRS). During the *FL* expansion phase, patients *with R/R FL* will receive obinutuzumab in combination with lenalidomide at the *FL* RP2D and polatuzumab vedotin at the RP2D as induction treatment. *During the DLBCL expansion phase, patients with R/R DLBCL will receive rituximab and polatuzumab in combination with lenalidomide at the DLBCL RP2D.* Post-induction treatment (for eligible patients only) will depend on lymphoma histology. Patients with FL will receive maintenance treatment with obinutuzumab and lenalidomide, and patients with DLBCL will receive consolidation treatment with *rituximab* and lenalidomide (see Section 3.1.1 for details).

Enrollment tracking will be performed through use of the IxRS. Prior to initiating screening, the study site should confirm via the IxRS that slots are available for enrollment. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the patient number will be assigned and the patient will be enrolled via the IxRS. The Sponsor will communicate to the sites impending closure of screening.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Obinutuzumab

Obinutuzumab will be provided as a single-dose, sterile liquid formulation in a 50-mL glass vial containing 1000 mg/40 mL of obinutuzumab. In addition to the drug substance, the liquid is also composed of histidine, trehalose, and poloxamer 188. For information on the formulation and handling of obinutuzumab, see the pharmacy manual and the Obinutuzumab Investigator's Brochure (oncology) and local prescribing information.

4.3.1.2 Rituximab

Rituximab will be supplied by the Sponsor as an IMP. Rituximab is packaged in 10-mL (100-mg) and 50-mL (500-mg) single-dose, pharmaceutical-grade glass vials at a concentration of 10 mg/mL of protein. The antibody is formulated for IV injection as a sterile product in a solution of sodium chloride (pH 6.5) containing polysorbate 80 and sodium citrate. For information on the formulation and handling of rituximab, see the pharmacy manual and the Rituximab Investigator's Brochure.

4.3.1.3 Polatuzumab Vedotin

Polatuzumab vedotin will be supplied by the Sponsor as a sterile, white to off-white, preservative-free lyophilisate in single-use vials. For information on the formulation and

handling of polatuzumab vedotin, see the pharmacy manual and the Polatuzumab Vedotin Investigator's Brochure.

4.3.1.4 Lenalidomide

Lenalidomide will be supplied by the Sponsor as 5-, 10-, 15-, and 20-mg capsules.

Female caretakers of patients taking lenalidomide who are of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves. Lenalidomide should be stored at room temperature away from direct sunlight and should be protected from excessive heat and cold.

For information on the formulation and handling of lenalidomide, see the local prescribing information for lenalidomide.

4.3.2 Dosage, Administration, and Compliance

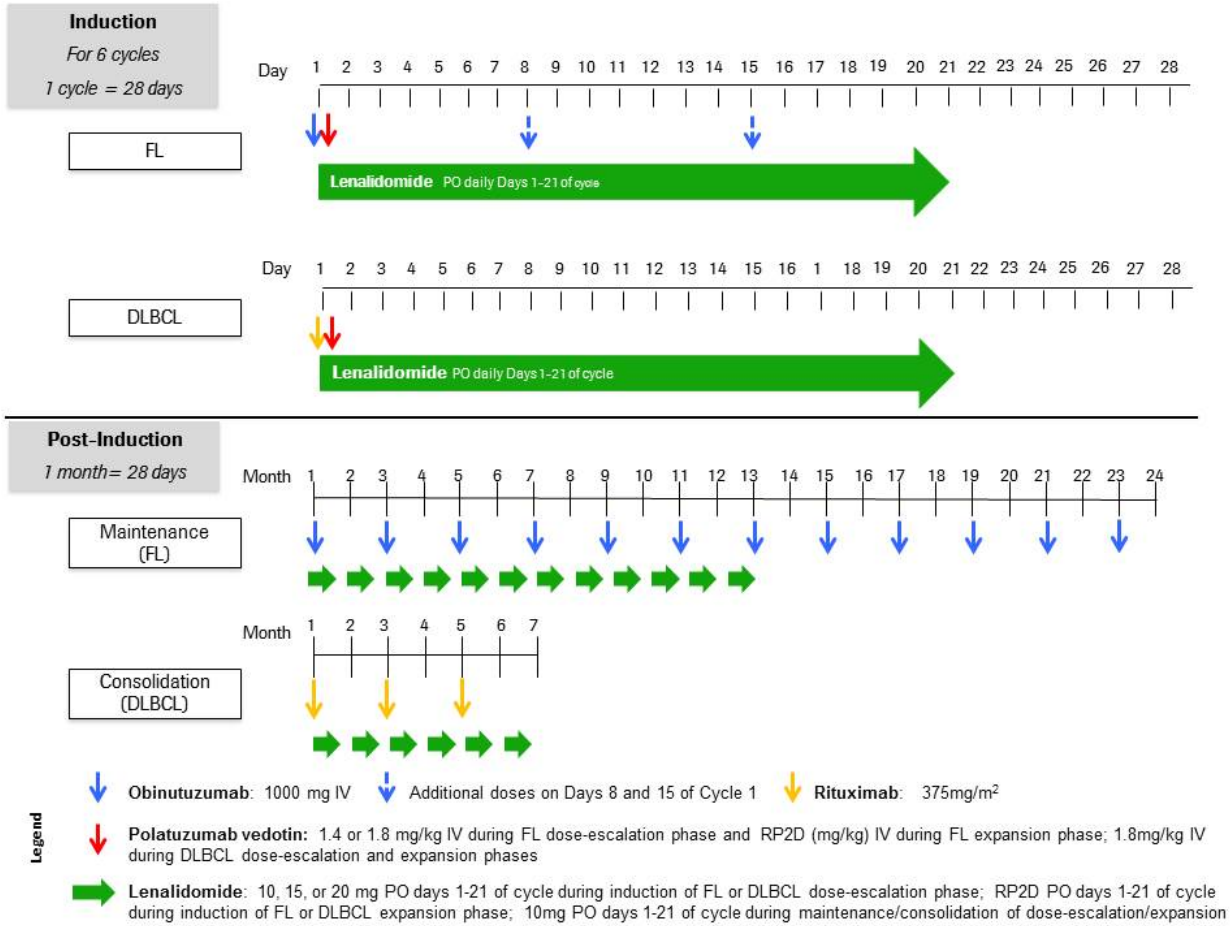
Patients enrolled in the dose-escalation phase or the expansion phase will receive six 28-day cycles of induction treatment with obinutuzumab *or rituximab*, polatuzumab vedotin, and lenalidomide. When study treatments are given on the same day, they will be administered sequentially in the following order: lenalidomide, *obinutuzumab or rituximab*, and polatuzumab vedotin.

Patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with lenalidomide and *rituximab*, and patients with FL who achieve a CR, PR, or SD at EOI will receive post-induction treatment (referred to as maintenance) with lenalidomide and obinutuzumab. When study treatments are given on the same day, lenalidomide will be administered prior to obinutuzumab *or rituximab*.

Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity for up to 2 years for maintenance treatment or *6 months* for consolidation treatment.

Treatment regimens are summarized in Table 1, Table 2, Table 4, and Table 5 *for R/R FL patients and Table 6, Table 7, Table 9, and Table 10 for R/R DLBCL patients* (see Section 3.1) and depicted in Figure 4. All eligible patients in both dose-escalation and expansion phases should receive induction and post-induction (if indicated) therapy.

Figure 4 Induction and Post-Induction Treatment Regimen



DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

Notes: During induction, treatments will be administered sequentially in the following order: lenalidomide, obinutuzumab *or rituximab*, and polatuzumab vedotin. During post-induction, treatment will be administered in the following order: lenalidomide followed by obinutuzumab *or rituximab*.

Premedication and treatment for TE prophylaxis should be administered as described in Section 4.3.2.5.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

4.3.2.1 Obinutuzumab

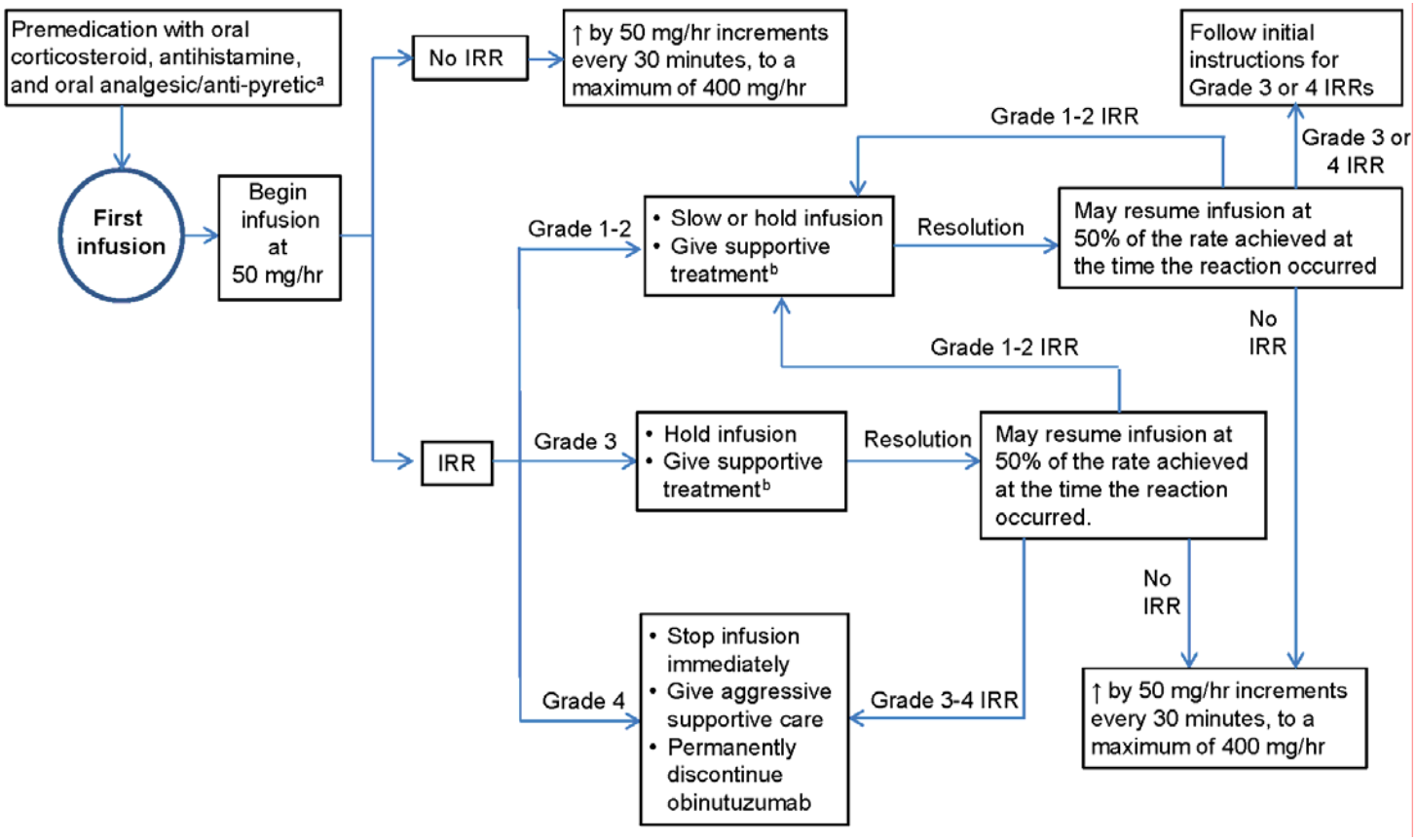
Obinutuzumab will be administered by IV infusion at an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of the first cycle and on Day 1 of each subsequent cycle during induction treatment, and on Day 1 of every other month (i.e., every 2 months) during maintenance treatment (eligible patients with FL only). A month is defined as 28 days.

Obinutuzumab should be administered as an IV infusion through a dedicated line in an environment in which full resuscitation facilities are immediately available and under the close supervision of an experienced physician. Obinutuzumab infusions will be administered according to the instructions outlined in **Figure 5** and Figure 6.
For patients with bulky lymphadenopathy, the infusion may be given slowly over a longer period of time, or the dose may be split and given over more than 1 day.

No dose modification for obinutuzumab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.7.

Premedication with a corticosteroid, antihistamine, and analgesic/antipyretic, as outlined in Section 4.3.2.5, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 8.

Figure 5 Guidelines for Obinutuzumab Infusions: First Infusion

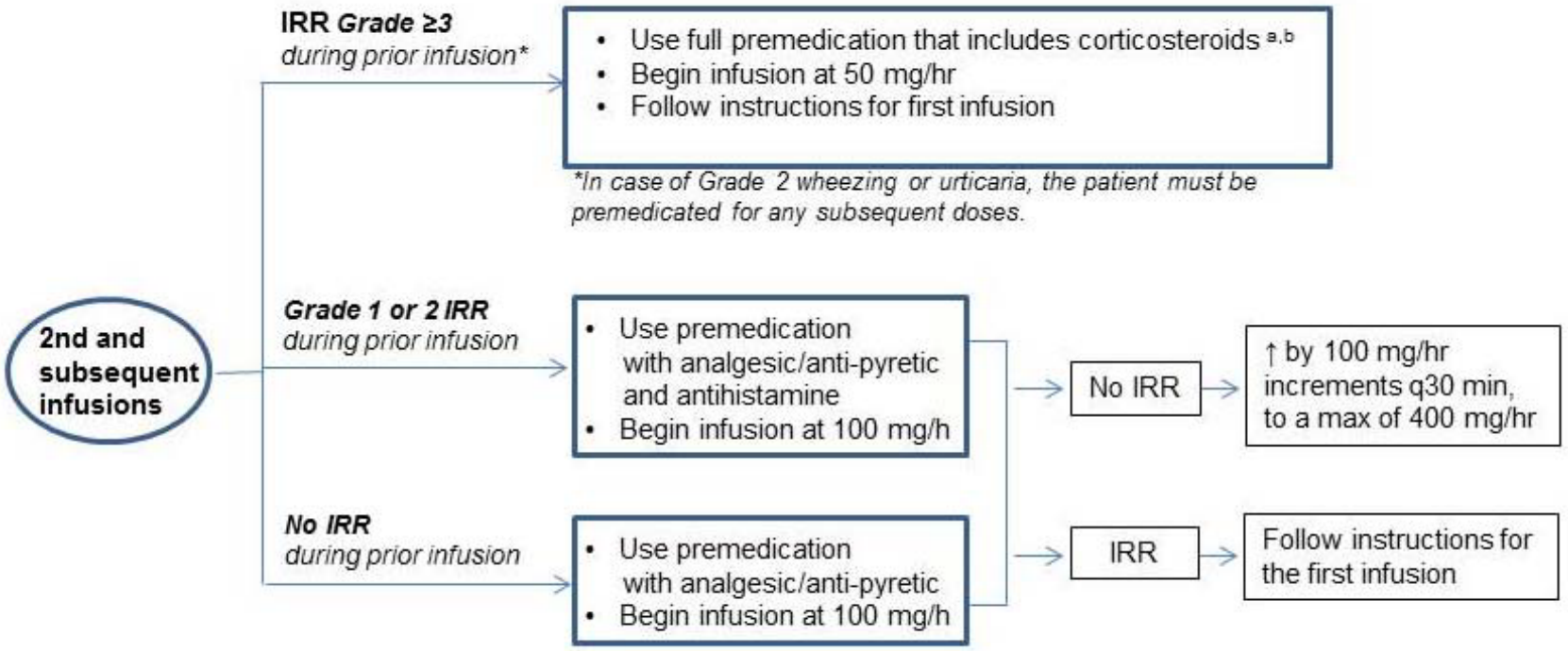


IRR = infusion-related reaction.

[a] All patients should receive full premedication with an oral corticosteroid, antihistamine, and oral analgesic/antipyretic prior to the first obinutuzumab infusion. Refer to Section 4.3.2.5 for details.

[b] Supportive treatment should include acetaminophen/paracetamol and an antihistamine such as diphenhydramine, if not administered within the previous 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg oral prednisone or equivalent), and/or bronchodilators. For anaphylaxis precautions, see Appendix 8.

Figure 6 *Guidelines for Obinutuzumab Infusions: Second and Subsequent Infusions*



IRR =infusion-related reaction; q30 =every 30.

[a] *Patients should receive full premedication with an oral corticosteroid, antihistamine, and oral analgesic/antipyretic prior to the obinutuzumab infusion. In the case of a recurrent Grade 3 IRR, obinutuzumab may be discontinued at the discretion of the investigator, following an individual benefit–risk assessment.*

[b] *Patients who experience wheezing, urticaria, or other symptoms of anaphylaxis must receive full premedication prior to all subsequent doses.*

4.3.2.2 *Rituximab*

Rituximab will be administered by IV infusion at the dose of 375 mg/m² on Day 1 of Cycles 1−6 during induction treatment and on Day 1 of every other month (i.e., every 2 months) during consolidation treatment for patients with R/R DLBCL.

Body surface area (BSA) will be determined at screening and should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by >10% from screening, in which case BSA should be recalculated and used for subsequent dosing. In obese patients (defined as body mass index ≥30 kg/m²), there is no BSA cap and actual body weight, not adjusted weight, is recommended. Empiric dose adjustment for obese patients may be implemented per institutional guidelines.

The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden or high peripheral lymphocyte count). Administration of rituximab may be continued on the following day, if needed, for patients who experience an adverse event during the rituximab infusion.

If a dose of rituximab is split over 2 days, both infusions must occur with appropriate premedication (see Section 4.3.2.5) and at the first infusion rate (see Table 12).

Rituximab infusions will be administered according to the instructions in Table 12. During the treatment period, rituximab must be administered to patients in a setting where full emergency resuscitation facilities are immediately available. Patients should be under close supervision of the investigator at all times.

Rituximab should be administered as a slow IV infusion through a dedicated line. After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥2 hours in order to administer IV drugs, if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

Table 12 ***Administration of First and Subsequent Infusions of Rituximab***

First Infusion (Day 1 of Cycle 1)	*Subsequent Infusions*
• *Begin infusion at an initial rate of 50 mg/hr.* • *If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes to a maximum of 400 mg/hr.* • *If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If the reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time when the reaction occurred).*	• *If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication, including 100 mg of prednisone/prednisolone or 80 mg of methylprednisolone or equivalent (until no further IRR occurs); begin infusion at an initial rate of 50 mg/hr; and follow instructions for first infusion.* • *If the patient tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of ≥ 100 mg/hr), begin infusion at a rate of 100 mg/hr.* • *If no reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes to a maximum of 400 mg/hr.* • *If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If the reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time when the reaction occurred).*

No dose modification for rituximab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.6.

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.5, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 8.

4.3.2.3 Polatuzumab Vedotin

For R/R FL, during the dose-escalation phase, the dose of polatuzumab vedotin for each patient will depend on dose assignment (1.4 or 1.8 mg/kg). During the expansion phase, the dose of polatuzumab vedotin for each patient will depend on the RP2D established during the dose-escalation phase. *For R/R DLBCL, during the dose-escalation phase and the expansion phase, the dose of polatuzumab vedotin will be fixed at 1.8 mg/kg.* Polatuzumab vedotin will be administered by IV infusion on Day 1 of each cycle, during induction treatment only.

The patient's weight obtained during screening (Days −28 to −1) should be used for dose determination for all treatment cycles. If the patient's weight within 96 hours prior to Day 1 of a given treatment cycle is >10% from the weight obtained during screening, the new weight should be used to calculate the dose. The weight that triggered a dose

adjustment will be taken as the new reference weight for future dose adjustments. All subsequent doses should be modified accordingly.

After reconstitution with Sterile Water for Injection (SWFI) and dilution into IV bags containing isotonic sodium chloride solution (0.9% NaCl), polatuzumab vedotin will be administered by IV infusion using dedicated standard administration sets with 0.2- or 0.22-µm in-line filters at a final polatuzumab vedotin concentration determined by the patient-specific dose. Compatibility of polatuzumab vedotin with IV bags, infusion lines, filters, and other infusion aids has been established with items made of specific materials of construction. Please consult the pharmacy manual and the Polatuzumab Vedotin Investigator's Brochure for a list of compatible materials and specific dose preparation instructions.

The initial dose will be administered to patients who are well hydrated over 90 (±10) minutes. Premedication (e.g., 500–1000 mg of oral acetaminophen or paracetamol and 50–100 mg diphenhydramine as per institutional standard practice) may be administered to an individual patient before administration of polatuzumab vedotin. Administration of corticosteroids is permitted at the discretion of the treating physician. If IRRs are observed with the first infusion in the absence of premedication, premedication must be administered before subsequent doses.

The polatuzumab vedotin infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the initial dose, patients will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If prior infusions have been well tolerated, subsequent doses of polatuzumab vedotin may be administered over 30 (±10) minutes, followed by a 30-minute observation period after the infusion.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.7.

4.3.2.4 Lenalidomide

Lenalidomide will be administered orally once daily on Days 1–21 of Cycles 1–6 (28-day cycles) during induction treatment and on Days 1–21 of each month during consolidation or first 12 months of maintenance treatment. During the dose-escalation phase, lenalidomide will be administered at a dose of 10, 15, or 20 mg (dose may be de-escalated to 5 mg). During the expansion phase, lenalidomide will be administered at the RP2D during induction treatment and at 10 mg during consolidation or maintenance treatment.

Lenalidomide capsules should be swallowed whole with water and should not be broken, chewed, or opened. The capsules may be taken with or without food, except on lenalidomide PK sampling days (see Appendix 3), where the patient should fast (water

allowed) at least 2 hours before and at least 1 hour after the lenalidomide dose. On lenalidomide PK sampling visits, lenalidomide dose will be taken in the clinic.

Lenalidomide should be administered at approximately the same time each day. If a dose of lenalidomide is missed and it has been <12 hours since the time of the scheduled dose, the patient may take the missed dose. If it has been >12 hours, the dose should be skipped and the next dose should be taken at the regularly scheduled time. Two doses should not be taken at the same time. If a dose had been vomited, the dose should not be re-taken.

At each cycle, each patient will be supplied with only enough lenalidomide for that cycle. A drug diary will be provided to the patient to record oral administration of doses, including the date and time. Patients will be instructed to return empty bottles or unused capsules. The investigator is responsible for monitoring patient compliance by monitoring the patient diary and counting unused capsules.

4.3.2.5 Premedication and Other Required Medication

Lenalidomide increases the risk of thromboembolism. All patients will be required to take daily aspirin ($75-$100 mg) for TE prophylaxis during lenalidomide treatment and until 28 days after the last dose of lenalidomide. Patients who are unable to tolerate aspirin, patients with a history of TE, and patients at high risk of TE should receive warfarin or low-molecular-weight heparin (LMWH).

Patients should receive premedication as outlined in Table 13.

Table 13 Premedication

Timepoint	Patients Requiring Premedication	Premedication	Administration
Cycle 1, Day 1	• All patients	• Oral corticosteroid [a]	Complete ≥ 1 hour prior to obinutuzumab *or rituximab* infusion
	• All patients	• Antihistamine drug [b] • Oral analgesic/antipyretic [c]	Administer ≥ 30 minutes prior to obinutuzumab *or rituximab* infusion
	• Patients at risk for TLS (e.g., because of bulky disease or renal impairment [creatinine clearance < 70 mL/min])	• Allopurinol or suitable alternative, such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab *or rituximab* infusion
Cycle 1, Days 8 and 15 Cycles 2 and Beyond, Day 1	• *Patients with no IRR during the previous infusion*	• *Oral analgesic/anti-pyretic [c]*	*Administer at least 30 minutes prior to obinutuzumab infusion. For patients receiving rituximab, premedication may be omitted at the investigator's discretion.*
	• *Patients with Grade 1 or 2 IRR during the previous infusion*	• *Antihistamine drug [b]* • *Oral analgesic/antipyretic [c]*	*Administer ≥ 30 minutes prior to obinutuzumab or rituximab infusion*
	• Patients with Grade 3 IRR*, wheezing, urticarial, or other symptoms of anaphylaxis* during the previous infusion • Patients with bulky disease	• Oral corticosteroid [a]	Complete ≥ 1 hour prior to obinutuzumab *or rituximab* infusion
		• Antihistamine drug [b] • Oral analgesic/antipyretic [c]	Administer ≥ 30 minutes prior to obinutuzumab *or rituximab* infusion
	• Patients still at risk for TLS	• Allopurinol or suitable alternative, such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab *or rituximab* infusion

IRR = infusion-related reaction; TLS = tumor lysis syndrome.

[a] Treat with 100 mg of prednisone or prednisolone, 20 mg of dexamethasone, or 80 mg of methylprednisolone. Hydrocortisone should not be used, as it has not been effective in reducing rates of IRR.

[b] For example, 50 mg of diphenhydramine.

[c] For example, 1000 mg of acetaminophen/paracetamol.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. *Lenalidomide will be dispensed to sites in the United States via the Celgene REMS™ system. For sites outside the United States, lenalidomide will be dispensed to sites through the study IxRS. Sites will be trained on lenalidomide specific requirements by their study monitors.*

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Obinutuzumab, *Rituximab,* Polatuzumab Vedotin, and Lenalidomide

Currently, the Sponsor does not have any plans to provide obinutuzumab*, rituximab,* polatuzumab vedotin, or any other study treatments or interventions to patients who have completed the study. The Sponsor will evaluate whether to continue providing obinutuzumab*, rituximab, or* polatuzumab vedotin in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from *7* days prior to the screening period to the visit at EOI or at the end of post-induction treatment, whichever occurs later. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

TE prophylaxis treatment and premedication should be administered as described in Section 4.3.2.5.

Hematopoietic growth factors are allowed if clinically indicated and used in accordance with the prescribing information. G-CSF may be administered in each cycle of therapy as primary prophylaxis for neutropenia, per American Society of Clinical Oncology

(ASCO), EORTC, and European Society for Medical Oncology (ESMO) guidelines (Smith et al. 2006) or per each site's institutional standards.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. However, it must be noted that erythropoietic agents or other agents that may increase the risk of thrombosis, such as estrogen-containing therapies (e.g., oral contraceptives), should be used with caution, because of the increased risk of TE in patients taking lenalidomide. Suitable methods of contraception are presented in Section 4.1.1.

Patients using concomitant medication that could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding. When possible, replace prior vitamin K antagonist therapy with LMWH prior to Day 1 of Cycle 1.

Patients who are receiving digoxin should undergo periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice, because of potential drug interactions with lenalidomide.

Drug-drug interactions between warfarin and lenalidomide have been excluded. However, a close monitoring of PT and INR is recommended in patients receiving warfarin.

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

On the basis of simulations, unconjugated MMAE exposure following polatuzumab vedotin administration with CYP3A4 inhibitors or inducers is unlikely to be altered by more than 50%. Furthermore, MMAE is unlikely a perpetrator of drug interactions. The patients who receive strong CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors in combination with polatuzumab vedotin will be closely monitored for adverse reactions if any.

Prophylactic treatment with antibiotics should be administered as per standard practice.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards.

4.4.2 Prohibited Therapy

Use of the following therapies (excluding protocol-specified treatments) is prohibited during the study:

- Any anti-cancer therapy, approved or investigational, other than intrathecal central nervous system prophylaxis
- Hormonal therapy other than contraceptives, stable hormone-replacement therapy, or megestrol acetate
- Biologic agents other than hematopoietic growth factors (as described in Section 4.4.1)
- *Vaccination with live vaccines is not recommended during treatment with obinutuzumab or rituximab and until B-cell recovery*

4.5 STUDY ASSESSMENTS

See Appendix 1, Appendix 2, and Appendix 3 for the schedules of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed by the investigator to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent, and within the defined window, may be used as screening and baseline assessments (see Appendix 1 and Appendix 2); such tests do not need to be repeated for screening purposes (e.g., screening tumor assessment).

Study treatment should be initiated within 28 days after the Informed Consent Form has been signed.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and alcohol and drug abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening period will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

The following clinical parameters relative to disease history, diagnosis, and prognostic indices will be recorded at screening:

- Date of initial diagnosis
- ECOG Performance Status (see Appendix 6)
- Ann Arbor staging (see Appendix 9)
- For patients with FL: Follicular Lymphoma International Prognostic Index (FLIPI) and Follicular Lymphoma International Prognostic Index 2 (FLIPI2) (see Appendix 10)
- For patients with DLBCL: IPI (see Appendix 10)
- B symptoms (unexplained fever $>$38°C, night sweats, and unexplained weight loss $>$10% of body weight over 6 months)
- Previous lines of anti-lymphoma treatment and response to prior therapy, date of disease progression in relation to start date of prior therapy, and date of last dose of prior therapy

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Height and weight will be recorded.

As part of tumor assessment, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate Tumor Assessment eCRF.

At subsequent visits (or as clinically indicated), targeted (limited, symptom-directed) physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline) (see Section 4.5.5).

Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. Vital sign measurements will be performed as outlined in the schedules of assessments

(see Appendix 1 and Appendix 2), but the associated data, other than the data collected at screening, do not need to be recorded on the eCRF (except in the case of an adverse event).

4.5.5 Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the IRC and the investigator on the basis of PET and CT scans, using the Lugano 2014 criteria*, taking into account results of bone marrow examinations for patients with bone marrow involvement at screening.*

In this study, the Lugano 2014 criteria for a PET-CT–based CR have been slightly modified to require normal bone marrow for patients with bone marrow involvement at screening. *Additionally, designation of PET-CT-based PR requires that CT-based response criteria for a CR or PR be met in addition to the PET-CT-based response criteria for a PR* (see Appendix 5).

4.5.5.1 Radiographic Assessments

PET scans should include the base of the skull to mid-thigh region. Full body PET scans should be performed when clinically appropriate.

CT scans with oral and IV contrast should include chest, abdomen, and pelvic scans. CT scans of the neck should be included if clinically indicated (i.e., if evidence of disease upon physical examination) and must be repeated throughout the study if there is disease involvement at baseline.

PET-CT scans and diagnostic CT scans should be acquired according to a standardized imaging manual, which will be provided to all sites.

If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. If MRI scans cannot be obtained, CT scans without contrast are permitted as long as this allows consistent and precise measurement of the targeted lesions during the study treatment period.

The same radiographic assessment modality must be used for all response evaluations to ensure consistency across different timepoints (including unscheduled assessments).

A full tumor assessment, including radiographic assessment, must be performed any time disease progression or relapse is suspected.

Additional details regarding imaging procedures will be provided in the Imaging Manual.

4.5.5.2 Bone Marrow Assessments

Bone marrow examinations are required at screening for staging purposes in all patients and should be performed within approximately 3 months prior to Day 1 of Cycle 1.

If bone marrow infiltration is present at screening, a bone marrow biopsy is required at the EOI response assessment for all patients who may have achieved a CR. In patients with a PR and continued bone marrow involvement, a subsequent bone marrow examination may be required to confirm a CR at a later timepoint.

Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Local Laboratory Assessments

Samples for the following laboratory tests will be analyzed at the study site's local laboratory for analysis:

- Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, uric acid, glycosylated hemoglobin (HbA_{1c}), amylase, and lipase (amylase and lipase only during induction). HbA_{1c} will be measured only at Screening and can be obtained in a non-fasting state.
- *Thyroid-stimulating hormone, triiodothyronine, thyroxine*
- β_2 microglobulin
- Coagulation: INR, aPTT (or PTT), and PT
- Pregnancy test

  All women of childbearing potential must have two negative serum pregnancy test results (minimum sensitivity, 25 mIU/mL) prior to initiating therapy: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1. Urine pregnancy tests will be performed at specified subsequent visits (see Appendix 1 and Appendix 2). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Viral serology

  Hepatitis B testing includes HBsAg and total HBcAb

  Hepatitis C testing includes HCV antibody

  HIV testing (if required per local regulatory requirements)
- Quantitative immunoglobulins: IgA, IgG, and IgM

Central Laboratory Assessments

The following samples will be sent to one or several Sponsor-designated central laboratories or to the Sponsor for analysis:

- Serum samples for obinutuzumab PK analysis using a validated assay
- *Serum samples for rituximab PK analysis using a validated assay*
- Serum and plasma samples for polatuzumab vedotin PK analysis using a validated assay
- Plasma samples for lenalidomide PK analysis using a validated assay
- Serum samples for assessment of obinutuzumab HAHAs using a validated assay
- *Serum samples for assessment of rituximab HACAs using a validated assay*
- Serum samples for assessment of polatuzumab vedotin ATAs using a validated assay
- Tumor tissue samples (obtained within 6 months prior to the initiation of study treatment for DLBCL or within 12 months prior to the initiation of study treatment for FL) and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL and for exploratory research on candidate biomarkers (see Table 14)

    The specimen must contain adequate evaluable tumor cells (≥ 20% for excisional biopsy and ≥ 50% for core biopsy).

    Formalin-fixed paraffin-embedded tissue blocks are preferred over slides. Tissue blocks that are not formalin fixed will be accepted in countries that use a fixative other than paraformaldehyde, but information on the type of fixative should be included. If a tissue block is not available, a minimum of 20 serial, freshly cut, unstained slides accompanied by a tumor block punch may be sent. A tumor block or tumor block punch is required for construction of a tissue microarray.

    If archival tissue is unavailable or unacceptable according to above criteria, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

    If the available biopsy was performed more than 12 months prior to Day 1 of Cycle 1, or the patient received anti-lymphoma treatment between the time of the most recent available biopsy and Day 1 of Cycle 1, a core-needle biopsy is strongly recommended.

    The sample should be shipped according to instructions provided in the laboratory manual. The remainder of the archival tissue blocks will be returned to the local pathology laboratory, according to country-specific procedures after the clinical study report has been published or upon request.
- Tumor biopsy samples obtained at the time of progression (unless no adequate tumor site is accessible) for exploratory research on candidate biomarkers (see Table 14)
- Plasma samples for exploratory research on candidate biomarkers (see Table 14)

- Whole blood samples for exploratory research on candidate biomarkers (see Table 14)
- Whole blood for lymphocyte immunophenotyping (see Table 14)

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 14.

Table 14 Proposed Non-Inherited Biomarkers

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Archival or fresh pretreatment and progression tumor tissue	Prior to study (archival) or baseline (fresh) and at disease progression	• For DLBCL patients only: DLBCL cell-of-origin subtype (ABC vs. GCB), *BCL2*, *MYC* • For both DLBCL and FL patients: target expression BCL2 and CD79b, immune infiltrate, cereblon (and surrogates) • Lymphoma-related genetic changes (DNA) and gene expression (mRNA) or protein expression (IHC associated with response or potential resistance) • Lymphoma index clone in MRD
Plasma isolated from whole blood	Baseline and subsequent timepoints during treatment (patients who enroll in the expansion phase only)	• Circulating lymphoma cells and/or cell-free circulating tumor DNA (detection of minimal residual disease)
Whole blood	Baseline and subsequent timepoints during and after treatment	• Lymphocyte immunophenotyping, including B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK-cell counts (CD16 and CD56)
Plasma	Baseline (predose and postdose) and subsequent timepoints (predose) during treatment	• Cytokines characteristic of T-cell activation and lenalidomide activity (e.g., IL-8 and IFNγ)

ABC = activated B cell–like; DBLCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; GCB = germinal-center B cell–like; IFNγ = interferon γ; IHC = immunohistochemistry; IL-8 = interleukin 8; NK-cell = natural killer cell.

Note: Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in this table.

Samples collected for PK and immunogenicity analyses may be used for assay development purposes and additional safety and immunogenicity assessments, as appropriate.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research, biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception(s):

- *Serum [or plasma] samples collected for PK and immunogenicity (ATA) analysis may be needed for additional PK and ATA assay development and validation, and additional immunogenicity characterization; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed* (see Section 4.5.8).

4.5.7 Electrocardiograms

Single, resting, 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedules of assessments (see Appendix 1 and Appendix 2) and may be obtained at unscheduled timepoints as clinically indicated. ECGs for each patient should be obtained using the same machine wherever possible. Interpretation of the ECG should be performed by the investigator.

4.5.8 Samples for Roche Clinical Repository

4.5.8.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.8.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board (IRB) or Ethics Committee (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted

approval for RCR sampling, this section of the protocol (Section 4.5.8) will not be applicable at that site.

4.5.8.3 Sample Collection

The following samples and derivatives thereof (e.g., DNA, RNA, proteins, peptides) will be collected for research purposes, including, but not limited to, research on dynamic (non-inherited) and genetic (inherited) biomarkers related to obinutuzumab, *rituximab,* polatuzumab vedotin, lenalidomide, B-cell lymphoma, or other types of cancer:

- Peripheral blood (i.e., whole blood)
- Remaining tumor tissue from lymph node biopsy (archival and/or fresh biopsy)
- Remaining peripheral blood (e.g., whole blood, plasma, and serum)

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.8.4 Confidentiality

Confidentiality for All RCR Specimens

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities and Roche monitors, representatives, and collaborators, as appropriate.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Additional Confidentiality for Specimens Used for Genetic Research

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens collected for genetic research. Upon receipt by the RCR, specimens for genetic research are "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

4.5.8.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.8.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO29834 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GO29834.

4.5.8.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice (GCP) by a quality-controlled, auditable, and appropriately validated laboratory information

management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines that it is in the best interest of the patient
- Patient non-compliance (e.g., consistent failure to show up for scheduled visits)

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

If a patient withdraws consent, this request must be documented in the source documents and signed by the investigator. Study personnel may use a public information source (e.g., county records) to obtain information about survival status.

4.6.2 Study Treatment Discontinuation

Study treatment should be permanently discontinued in patients who experience any of the following:

- Anaphylaxis, acute respiratory distress, or Grade 4 IRR

  If a Grade 3 IRR is recurrent during the second or subsequent cycles, study treatment may be discontinued at the discretion of the investigator, following an individual benefit-risk assessment.
- Any adverse event that meets criteria for permanent discontinuation per guidelines provided in Section 5.1
- Pregnancy
- Disease progression

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients who discontinue study treatment will not be replaced, except as outlined below:

- During the dose-escalation phase, patients who discontinue study treatment prior to completing the DLT assessment window for reasons other than a DLT will be replaced by an additional patient at that same dose level.
- *P*atients who discontinue prior to receiving at least one dose of each component of the combination will be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigators if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Polatuzumab vedotin is not a marketed product, and *lenalidomide is* not approved for the treatment of patients with R/R FL. *Obinutuzumab is only approved in combination with bendamustine for the treatment of R/R FL. Rituximab and lenalidomide are not approved for the treatment of patients with R/R DLBCL*. Clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide in completed and ongoing studies. The anticipated important safety risks of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide are outlined below. Please refer to the Obinutuzumab, *Rituximab,* and Polatuzumab Vedotin Investigator's Brochures and the

lenalidomide Summary of Product Characteristics (SmPC) for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1). Patients will undergo adequate safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events, as described in this section and in Section 4.5. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment delays or discontinuation, have been provided (see Section 5.1.7).

5.1.1 Risks Associated with Obinutuzumab

To date, the following adverse events are considered to be important *identified* risks associated with obinutuzumab: IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), infections (including PML and HBV reactivation), prolonged B-cell depletion, impaired immunization response, worsening of preexisting cardiac conditions, and gastrointestinal perforation.

5.1.1.1 Infusion-Related Reactions

IRRs have been reported predominantly during the first infusion of obinutuzumab. The incidence and severity of IRRs decreased substantially with the second and subsequent infusions. In the majority of patients, IRRs were mild or moderate and resolved with the slowing or interruption of the infusion and supportive care. The commonly experienced IRRs have been characterized by hypotension, fever, chills, flushing, nausea, vomiting, hypertension, fatigue, and other symptoms.

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions; anaphylaxis has been reported in patients treated with obinutuzumab.

Hypotension may occur during obinutuzumab IV infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their antihypertensive medication.

Patients who have preexisting cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period.

Guidelines for medical management of IRRs and anaphylaxis are provided in Section 4.3.2.1 and Appendix 8.

5.1.1.2 Tumor Lysis Syndrome

TLS, including fatal events, has been reported with obinutuzumab administration. Patients at risk for TLS (e.g., because of bulky disease or renal insufficiency) should receive adequate hydration and premedication with allopurinol or an alternative uricostatic agent as indicated in Section 4.3.2.5 (see Table 13). Additional guidelines for management of TLS in this study are provided in Section 5.1.7.3 (see Table 19).

5.1.1.3 Neutropenia

Grade 3 or 4 neutropenia, including febrile neutropenia, has been reported with obinutuzumab administration. Neutropenia resolved spontaneously or with use of hematopoietic growth factors. Patients who experience Grade 3 or 4 neutropenia should be closely monitored until neutrophil values return to at least Grade 2. Cases of late-onset neutropenia (ANC $<$ 1000 cells/μL occurring $\geq$ 28 days after obinutuzumab treatment has been completed or stopped) or prolonged neutropenia (ANC $<$ 1000 cells/μL that does not resolve after 28 days without obinutuzumab treatment) have also been reported. The use of G-CSF is allowed for treatment of neutropenia in this study. Prophylactic treatment with antibiotics should be administered as per standard practice. Guidelines for primary prophylaxis with G-CSF are provided in Section 4.4.1.

5.1.1.4 Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. In patients with CLL exposed to obinutuzumab, fatal hemorrhagic events have also been reported in Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients receiving concomitant medication that could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding. When possible, replace prior vitamin K antagonist therapy with LMWH prior to Day 1 of Cycle 1. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. For patients who experience thrombocytopenia, regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) may be performed at the discretion of the treating physician, according to institutional practice.

5.1.1.5 Infections

On the basis of its mechanism of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Obinutuzumab should not be administered to patients with active infection, and caution should be exercised when including patients with a history of recurrent or chronic infections.

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported.

Reactivation of hepatitis B in patients with chronic hepatitis (HbsAg positive) with evidence of prior hepatitis B exposure, or in patients who are carriers (HbsAg negative and anti-HBc positive) has been reported with other anti-CD20 antibodies. The risk is increased particularly when anti-CD20 antibodies are administered with immunosuppressive therapies, such as steroids or chemotherapy. Patients positive for HbsAg or HbcAb are not eligible for this study.

JC viral infection resulting in PML has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs or symptoms regarded as "cortical" (e.g., aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA). Additional guidelines for medical management of PML in this study are provided in Section 5.1.7.

5.1.1.6 Immunizations

The safety of immunization with live *or attenuated viral* vaccines following obinutuzumab therapy has not been studied *and* vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

5.1.1.7 Worsening of Preexisting Cardiac Condition

In patients with underlying cardiac disease and treated with obinutuzumab, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure, and arrhythmias, including atrial fibrillation and tachyarrhythmia, have been observed. These events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution to prevent a potential fluid overload.

5.1.1.8 Gastrointestinal Perforation

GI perforation has been reported in patients with B-cell lymphoma treated with obinutuzumab, including fatal events. Patients with GI involvement should be monitored for signs of GI perforation.

5.1.2 *Risks Associated with Rituximab*

The following adverse events are considered to be important risks associated or potentially associated with rituximab: IRRs, infections (including severe infections), PML, hepatitis B reactivation, neutropenia (including prolonged neutropenia), TLS, impaired immunization response, severe skin reactions (Stevens-Johnson syndrome [SJS]/toxic epidermal necrolysis [TEN]), and GI perforation. Details for these risks are provided below; refer to the Rituximab Investigator's Brochure for full information.

5.1.2.1 *Infusion-Related Reactions*

Acute IRRs are very common in patients receiving rituximab (occurring in ≥10% of patients) based on clinical trial experience. However, serious IRRs are uncommonly reported (occurring in ≥1 of 1,000 and <1 of 100 patients) and are rarely fatal (occurring in ≥1 of 10,000 and <1 of 1,000 patients). Most IRRs occur with the first administration of rituximab. Most IRRs are mild to moderate in severity (Grades 1 or 2) and can be managed by slowing or stopping the rituximab infusion. IRRs can be severe and, in rare cases, can result in death. Rituximab-induced IRRs consist of a cluster of symptoms and signs occurring during or within 24 hours of a rituximab infusion that may be related to cytokine release and/or other chemical mediators, and these acute IRRs overlap with "cytokine release syndrome." Anaphylactic and other hypersensitivity reactions have been reported following rituximab administration, and clinical manifestations of these reactions are similar to cytokine release syndrome. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the rituximab infusion.

5.1.2.2 *Infections (Including Serious Infections)*

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy.

5.1.2.3 *Hepatitis B Reactivation*

Reactivation of hepatitis B ranges from asymptomatic reactivations (detected by changes in laboratory parameters only) to fulminant liver failure and death. Patients with chronic hepatitis B (HBsAg positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and anti-HBcAb positive) are at a lower risk for reactivation. Patients who demonstrate evidence of reactivation while receiving an appropriate anti-viral therapy will be discontinued from study treatment.

5.1.2.4 *Progressive Multifocal Leukoencephalopathy*

Rare cases of PML have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson and Bennett 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is rare, but it should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic SCT. Most cases of PML were diagnosed within 12 months of the patients' last infusion of rituximab.

5.1.2.5 *Neutropenia (Including Prolonged Neutropenia)*

Neutropenia is very common in patients receiving rituximab (occurring in ≥ 10% of patients) based on clinical trial experience. However, delayed onset neutropenia is very rare (occurring in < 1 of 10,000 patients), and the incidence of prolonged neutropenia is unknown. Neutropenia may lead to serious or overwhelming infection, especially if profound (Grades 3–4), prolonged, associated with breaches in natural mucosal barriers (e.g., diarrhea and/or mucositis), and/or other immunological defects (e.g., lymphopenia, hypogammaglobulinemia, and acquired immunodeficiency syndrome). Despite an increase in incidence of neutropenia and Grade 3–4 neutropenia associated with rituximab, most studies have not reported a significant increase in serious neutropenic infections.

5.1.2.6 *Tumor Lysis Syndrome*

Patients treated with rituximab may be at risk for TLS. Severe tumor TLS is very rare in patients receiving rituximab (occurring in < 1 of 10,000 patients), based on postmarketing experience. Signs and symptoms (e.g., hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated LDH) that are consistent with TLS have been reported to occur after the first rituximab IV infusion in patients with high numbers of circulating malignant lymphocytes. A high number of circulating malignant cells (≥ 25,000/mm^3) or high tumor burden confers a greater risk of TLS. For patients with evidence of TLS, rituximab should be discontinued, and the patient should be treated as clinically indicated.

5.1.2.7 *Impaired Immunization Response*

B-cell depletion is expected (and desired) during rituximab therapy and is directly related to its mechanism of action. In theory, peripheral B-cell depletion may reduce the effectiveness of immunization, as patients may not be able to mount an effective humoral immune response to foreign antigens.

5.1.2.8 *Severe Skin Reactions: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis*

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. The onset of these reactions in patients treated with rituximab has varied from 1to 13 weeks following rituximab exposure. The majority of the SJS/TEN cases reported with rituximab were associated with additional risk factors. Fatal outcome also appeared to increase in patients who were exposed to multiple risk factors for SJS/TEN.

5.1.2.9 *Gastrointestinal Perforation*

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy.
In postmarketing reports of rituximab, the mean time to documented GI perforation was 6 days (range: 1–77 days) in patients with NHL.

5.1.3 Risks Associated with Polatuzumab Vedotin

The clinical safety profile of polatuzumab vedotin based on clinical data obtained in the ongoing Phase I and II studies is summarized in Section 1.3. On the basis of clinical data to date, the following known and suspected risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.7. Refer also to the current Polatuzumab Vedotin Investigator's Brochure for complete and updated details.

5.1.3.1 *Identified Risks*

On the basis of clinical experience with polatuzumab vedotin in patients treated in the current Phase I and II studies, neutropenia and peripheral neuropathy are identified risks of polatuzumab vedotin.

Neutropenia

Neutropenia and neutropenia-associated events resulted in protocol-mandated dose reductions and/or delays. Serious neutropenia including febrile neutropenia has been reported during treatment with polatuzumab vedotin. Patients with inadequate hematologic function will be excluded from this study (see Section 4.1.2). Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Treatment may be delayed for hematologic toxicities as described in Section 5.1.7.3. The use of G-CSF for neutropenia is described in Section 4.4.1.

Peripheral Neuropathy

Patients receiving polatuzumab vedotin may develop or experience worsening of peripheral neuropathy. Patients in clinical trials with polatuzumab vedotin should be monitored for symptoms of neuropathy (sensory and/or motor), including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require a dose delay, change in dose, or discontinuation of treatment and should be managed according to the protocol. Study treatment dose and schedule modifications for peripheral neuropathy are described in Section 5.1.7.3.

5.1.3.2 Potential Risks

Infections

Neutropenia is a known risk for polatuzumab vedotin. Reports in the literature state that granulocytopenia is a major predisposing factor to infections in patients with B-cell lymphoma. Patients receiving chemotherapy for B-cell lymphoma with a granulocyte count of $<$500 cells/μL experienced a higher incidence of infections than those with a count of $>$500 cells/μL.

Progressive Multifocal Leukoencephalopathy

One case of PML was reported in an [redacted]-year-old female with R/R FL after receiving one cycle of polatuzumab vedotin in combination with obinutuzumab and bendamustine.

MRI showed changes suggestive of PML. Cerebrospinal fluid test for JC virus by PCR was negative. Confounders included previous lines of anti-CD20 therapies and concurrent use of obinutuzumab. Additional details of the case can be found in the Polatuzumab Vedotin Investigator's Brochure.

Infusion-Related Events

Because of the potential for infusion reactions, administration of polatuzumab vedotin will be performed in a setting with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies. All patients will be monitored for infusion reactions during the infusion and immediately afterward. Precautions for suspected anaphylactic reaction during study drug infusions are provided in Section 4.3.2.3. The initial dose of polatuzumab vedotin may be administered with premedication with acetaminophen, antihistamines, or corticosteroids per institutional standard practice at the discretion of the Investigator. Premedication should be instituted for subsequent doses if IRRs are observed in patients who receive their first dose of polatuzumab vedotin without premedications (see Section 4.3.2.3). Significant issues with polatuzumab vedotin IRRs have not been observed.

Similar considerations regarding infusion reactions are applicable for obinutuzumab. Refer to Section 4.3.2.1 for additional information.

Tumor Lysis Syndrome

There is the *potential* risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, tumor lysis prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/L or bulky lymphadenopathy) and who are considered to be at risk for tumor lysis by the investigator will receive tumor lysis prophylaxis (e.g., allopurinol $\geq$ 300 mg/day orally or a suitable alternative treatment [according to institutional practice] starting 12–24 hours before study treatment) and must be well hydrated before the initiation of study treatment on Day 1 of Cycle 1. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration before each subsequent infusion, as deemed appropriate by the investigator.

One case of TLS attributed to polatuzumab vedotin has been reported (Study GO27834); however, the laboratory elevations did not meet the Howard criteria for TLS (see Appendix 12). The suspected TLS event resolved after 3 days of supportive care. One case of Grade 3 Laboratory TLS was reported in the ongoing Phase Ib/II Study GO29833 combining polatuzumab vedotin, obinutuzumab, and venetolax. The patient was at high risk for TLS due to bulky disease and decreased renal function. Potassium and phosphorous levels were elevated, while serum creatinine levels remained normal and the patient was asymptomatic. The TLS event was considered related to all three study treatments and resolved in 4 days with supportive care (see Polatuzumab Vedotin Investigator's Brochure for case details.

Bone Marrow Toxicity

Patients with inadequate hematologic function will be excluded from this study (see Section 4.1.2). Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Treatment may be delayed for hematologic toxicities as described in Section 5.1.7.3.

Transfusion support for anemia and thrombocytopenia is also permitted at the discretion of the treating physician.

Immunogenicity

As with any recombinant antibody, polatuzumab vedotin may elicit an immune response, and patients may develop antibodies against polatuzumab vedotin. Patients will be closely monitored for any potential immune response to polatuzumab vedotin. Appropriate screening, confirmatory, and characterization assays will be employed to assess ATAs before, during, and after the treatment with polatuzumab vedotin.

Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of polatuzumab vedotin given the mechanism of action of MMAE. Standard exclusion criteria are used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods.

Specific Gastrointestinal Toxicity

Diarrhea, constipation, anorexia, nausea, and vomiting have been reported frequently as treatment-emergent adverse events in Studies DCS4968g and GO27834 with polatuzumab vedotin. Diarrhea has been responsible for study drug modification and discontinuations.

Hyperglycemia

Hyperglycemia has been observed in patients treated with polatuzumab vedotin as well as with other ADCs that use the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications.

Hepatotoxicity

Hepatotoxicity has been observed in patients treated with polatuzumab vedotin in both the Phase I and II trials. Although the relationship between hepatotoxicity and polatuzumab vedotin has not been definitively determined, transient, dose-related increases in hepatic enzymes were noted in nonclinical rat studies. No hepatotoxicity was noted following administration of the surrogate ADC in cynomolgus monkeys.

Elevations of transaminases have been reported in patients receiving polatuzumab vedotin and have ranged in intensity from Grades 1-3. These have been reversible with and without dose modification.

5.1.4 Risks Associated with Lenalidomide

5.1.4.1 Embryo-Fetal Toxicity

Lenalidomide, a thalidomide analogue, is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects. In a developmental study in monkeys, lenalidomide caused limb abnormalities similar to birth defects caused by thalidomide in humans. If taken during pregnancy, lenalidomide is expected to have a teratogenic effect in humans.

Lenalidomide must not be taken by patients who are pregnant. In every country where lenalidomide has been approved, a risk minimization plan, which includes a pregnancy prevention program, is in place. Investigators must ensure that all specific local requirements that are applicable to the safe and effective use of lenalidomide are fulfilled prior to administration to patients. The risk minimization plan should be followed by prescribers and by patients using lenalidomide, with one exception: Because lenalidomide will be administered in combination with polatuzumab vedotin and obinutuzumab *or rituximab*, patients must comply with contraceptive measures designed to ensure safe administration of all *four* study treatments, as outlined in Section 4.1.1. Pregnancy testing and counseling should be performed if a patient misses her period or has unusual*/irregular* menstrual bleeding. Treatment with lenalidomide must be discontinued until it is confirmed that the patient is not pregnant.

5.1.4.2 Hematologic Toxicity

Lenalidomide can cause significant neutropenia and thrombocytopenia. Patients should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter.

5.1.4.3 Venous and Arterial Thromboembolism

Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients treated with lenalidomide. Prophylactic anti-thrombotic medicines are recommended, especially in patients with additional thrombotic risk factors. The decision to take prophylactic measures should be made after a careful assessment of a patient's underlying risk factors. Thromboprophylaxis is presented in Section 4.3.2.5.

Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis (such as hormone replacement therapy), should be used with caution. A hemoglobin concentration of $>$ 12 g/dL should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

5.1.4.4 Tumor Flare Reaction

Tumor flare reaction (TFR) has occurred during investigational use of lenalidomide for treatment of CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain, and rash. Monitoring and evaluation for TFR are recommended in patients taking lenalidomide. TFR may mimic disease progression. Guidelines for the management of TFR are presented in Table 19.

5.1.4.5 Severe Skin Reactions

Angioedema and serious dermatologic reactions including SJS and TEN have been reported during treatment with lenalidomide. These events can be fatal. Guidelines for the management of severe skin reactions are presented in Table 19. Patients with a history of erythema multiforme, Grade ≥ 3 rash, or blistering following prior treatment with immunomodulatory derivatives (such as thalidomide and lenalidomide) will not be enrolled in the study.

5.1.4.6 Tumor Lysis Syndrome

Fatal instances of TLS have been reported during treatment with lenalidomide. Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely, and appropriate precautions should be taken.

5.1.4.7 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. The mechanism of drug-induced hepatotoxicity is unknown. Preexisting viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Liver enzymes are to be monitored periodically. Guidelines for the management of hepatotoxicity are presented in Table 19.

5.1.4.8 Renal Impairment

Lenalidomide is substantially excreted by the kidney. Patients with renal impairment (i.e., calculated creatinine clearance <50 mL/min) will not be enrolled in this study. Renal function will be monitored during the study, and the lenalidomide dose may be adjusted as outlined in Section 5.1.7.2 (see Table 19).

5.1.4.9 Thyroid Disorders

Cases of hypothyroidism and cases of hyperthyroidism have been reported during treatment with lenalidomide. Optimal control of co-morbid conditions influencing thyroid function is recommended before initiating lenalidomide treatment. .

5.1.4.10 Peripheral Neuropathy

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with

the long-term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

5.1.4.11 Second Primary Malignancies

Patients with multiple myeloma treated with lenalidomide in studies that included melphalan and SCT had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia and Hodgkin's lymphoma. Patients are to be monitored for the development of second malignancies.

5.1.4.12 *Cardiovascular Reactions*

Cases of serious adverse cardiovascular events, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in patients with CLL treated with lenalidomide compared to single agent chlorambucil. Patients will be monitored for the development of cardiac toxicities.

5.1.4.13 *Impaired Stem Cell Mobilization*

Patients have been reported to show a decrease in the number of CD34+ cells collected after treatment with lenalidomide. Early referral to a transplant center is recommended in patients who are autologous SCT candidates.

5.1.5 Risk of Overlapping Toxicities

The anticipated toxicities from the combined administration of obinutuzumab *or rituximab with* polatuzumab vedotin and lenalidomide are expected to be manageable in the clinical setting and will be closely monitored throughout the study.

Rituximab was safely combined with polatuzumab vedotin in patients with R/R FL or DLBCL. Grade 3 or 4 neutropenia (21%) appeared to be the most important hematologic adverse event associated with this combination. When given as monotherapy for the treatment of patients with R/R B-cell lymphoma, obinutuzumab was associated with 5% Grade 3 or 4 neutropenia. Because obinutuzumab is expected to have an incidence of neutropenia that is higher that with rituximab monotherapy, there is a risk of increase incidence of neutropenia. Obinutuzumab and polatuzumab vedotin for the treatment of patients with R/R FL or DLBCL is currently being assessed in Study GO27834. As these new data emerge, they will be assessed and applied to update this study if required.

Lenalidomide has also been associated with hematologic adverse events, including neutropenia. When lenalidomide was combined with obinutuzumab, the incidence of Grade 3 or 4 neutropenia was reported to be 33.3% (Morschhauser et al. 2014b). Therefore, the combination of G+Pola+Len is anticipated to result in overlapping hematologic toxicity, for which patients will be closely monitored. Guidelines for the management of patients who develop hematologic toxicities are provided in Sections 5.1.7.3 and 5.1.7.4. In addition to the standard hematologic monitoring, patients enrolled in this study will be closely monitored for evidence of infections.

Because both polatuzumab vedotin and lenalidomide have been associated with a risk of peripheral sensory neuropathy, it is unknown whether this risk may be increased when they are combined. Therefore, peripheral neuropathy will be closely monitored, and guidelines for management for patients who develop neurotoxicity (i.e., peripheral neuropathy, sensory and/or motor) are provided in Sections 5.1.3.1 and 5.1.4.10, and in Table 19.

There is an identified risk of TLS if treated with obinutuzumab, *rituximab,* or lenalidomide and a theoretical risk if treated with polatuzumab vedotin because these agents can result in the rapid destruction of a large number of tumor cells. Therefore, overlapping toxicity in regard to TLS cannot be excluded. Guidelines for management of patients who develop TLS are provided in Table 19.

Both rituximab and lenalidomide have been associated with dermatologic reactions such as SJS and TEN, and the risk of overlapping toxicities will be monitored. Guidelines for management of patients who develop dermatologic toxicities are provided in Table 19.

5.1.6 Risk of Drug-Drug Interactions

The risk for clinically relevant PK DDIs between study treatments is low. First, obinutuzumab, *rituximab,* and polatuzumab vedotin are not anticipated to interact directly with CYP isoforms or other drug–metabolizing enzymes or drug transporters. Cytokine modulation may be considered as an indirect mechanism through which a monoclonal antibody could alter CYP expression. However, treatment with obinutuzumab results in only transient increases in cytokine levels after the first infusion, and no increases are observed after subsequent infusions. In vitro (human PBMCs) and in vivo (cynomolgus monkeys) treatment with anti-CD79 antibodies (i.e., the same antigen target as polatuzumab vedotin) showed a low risk for release of systemic pro-inflammatory cytokines. Taken together, these results suggest that both obinutuzumab and polatuzumab vedotin are unlikely to precipitate DDIs via indirect effects on cytokines.

Second, lenalidomide is primarily excreted in the urine. Lenalidomide is not a substrate, inhibitor, or inducer of the CYP group of enzymes (Kumar et al. 2009). In vitro, the MMAE component of polatuzumab vedotin is mainly metabolized by CYP3A4, and it is mainly eliminated by biliary secretion in vivo. Both lenalidomide and MMAE are substrates but not inhibitors of P-gp. Owing to the different elimination pathways for lenalidomide and MMAE, the risk of CYP-mediated and transporter-mediated DDI risk is low when polatuzumab vedotin is combined with lenalidomide.

In addition, simulation results suggest that unconjugated MMAE exposure is likely to be altered by $<$50% when polatuzumab vedotin is co-administered with strong CYP3A inhibitors or inducers. Therefore, patients who receive concomitant medications that are strong CYP3A or P-gp inhibitors should be closely monitored for adverse reactions.

In summary, clinically relevant PK DDIs are unlikely to occur between lenalidomide, obinutuzumab, *rituximab,* and polatuzumab vedotin.

5.1.7 Management of Specific Adverse Events

Study treatment may be delayed for toxicity for a maximum amount of time, as specified in Table 17, Table 18, and Table 19 . If study treatment is delayed for longer than the specified maximum amount of time, study treatment will be permanently discontinued. When a treatment cycle is delayed because of toxicity resulting from any component of the regimen, all study treatment should be held and resumed together to remain synchronized. If one drug is discontinued, treatment with the other two drugs may be continued for patients experiencing clinical benefit as determined by the investigator after discussing with the Medical Monitor.

Treatment delays apply to all toxicities described below; dose modifications apply only to toxicities that are considered to be related to lenalidomide or polatuzumab vedotin (only for peripheral neuropathy). There will be no dose reductions of obinutuzumab *or rituximab. For patients receiving obinutuzumab, if toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses of obinutuzumab will not be skipped but given after resolution of toxicity.*

5.1.7.1 Polatuzumab Vedotin Dose-Reduction Steps

The dose of polatuzumab vedotin may be reduced *due to neurotoxicity only* according to the following dose reduction steps based on the starting dose (see Table 15 and Table 19).

Table 15 Polatuzumab Vedotin Dose-Reduction Steps

Starting Dose	Dose Reduction	
	Step 1	Step 2
1.8 mg/kg	1.4 mg/kg	none
1.4 mg/kg	none	none

5.1.7.2 Lenalidomide Dose-Reduction Steps

The dose of lenalidomide may be reduced in 5-mg increments one or two times *during induction or post-induction*, depending on the starting dose, as outlined in Table 16. There will be no more than one dose reduction per treatment cycle. *If the lenalidomide dose is reduced to 5 mg during induction, the maintenance or consolidation dose may be escalated to start at 10 mg in post-induction if considered safe per investigator judgment in consultation with the Sponsor. In all other cases, i*f the lenalidomide dose is reduced, re-escalation is not permitted.

Table 16 Lenalidomide Dose-Reduction Steps

Starting Dose	Dose Reduction	
	Step 1	Step 2
20 mg	15 mg	10 mg
15 mg	10 mg	5 mg
10 mg	5 mg	none

If a lenalidomide-related toxicity occurs during lenalidomide treatment (i.e., before Day 21 of the cycle), lenalidomide must be withheld until criteria for recovery have been met (i.e., improves to Grade $\leq$2 or baseline values).

If recovery is observed prior or on Day 15 of the cycle, lenalidomide may be resumed at the same dose for the remainder of the cycle (through Day 21; missed doses will not be made up) at the discretion of the investigator. If the investigator considers that resuming lenalidomide at the same dose within the cycle represents an unacceptable risk for the patient, lenalidomide shall be resumed at reduced dose or withheld for the remainder of the cycle. For subsequent cycles, lenalidomide will be resumed at reduced doses.

If recovery is observed after Day 15 of the cycle, lenalidomide will not be resumed for the current cycle. For subsequent cycles, lenalidomide will be resumed at reduced doses.

Guidelines for management of toxicities occurring during induction and post-induction treatment are provided in Sections 5.1.7.3 and 5.1.7.4, respectively.

5.1.7.3 Hematologic Toxicities during Induction Treatment

Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia is not considered a hematologic toxicity, but rather an expected outcome of therapy. Table 16 provides guidelines for management of hematologic toxicities that occur during induction treatment, with the exception of Days 8 and 15 of Cycle 1 *for patients receiving obinutuzumab.* Table 17 provides guidelines for management of hematologic toxicities that occur at Days 8 and 15 of Cycle 1, when patients are to receive treatment with obinutuzumab only.

Table 17 Guidelines for Management of Hematologic Toxicities That Occur during Induction Treatment (Except Days 8 and 15 of Cycle 1 *for Patients Receiving Obinutuzumab*)

Event	Action to Be Taken
Grade 3 or 4 hematologic toxicity [a,b]	**For patients on a lenalidomide dose ≥10 mg who have had one or no prior lenalidomide dose reductions:** • Withhold study treatment.[a] • Administer RBCs or platelets as required. • If patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles. • For patients who develop platelet count of <20,000/μL while receiving LMWH, reduce the dose of LMWH. For patients who develop platelet count of <20,000/μL while receiving platelet inhibitors, consider temporarily withholding platelet inhibitors. • Permanently discontinue study treatment if any of the following events occur: – Grade 3 or 4 thrombocytopenia that results in significant bleeding per investigator judgment – Recurrent Grade 3 or 4 neutropenia associated with fever > 38°C lasting >5 days or documented infection despite use of G-CSF and after one lenalidomide dose reduction – Recurrent Grade 4 neutropenia or thrombocytopenia lasting > 7 days despite use of G-CSF (for neutropenia) and after one lenalidomide dose reduction • If improvement to Grade ≤2 or baseline ≤14 days after the scheduled date for the next cycle, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume lenalidomide at current dose. • If improvement to Grade ≤2 or baseline 15–21 days after the scheduled date for the next cycle, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume lenalidomide at a reduced dose per guidelines in Section 5.1.7 [a,b] for current and subsequent cycles. • If study treatment is withheld for >21 days, permanently discontinue study treatment. **For patients who have had two prior dose reductions:** • Permanently discontinue study treatment.

G=obinutuzumab; G-CSF=granulocyte colony-stimulating factor; LMWH=low-molecular-weight heparin.

[a] Treatment delays apply to all toxicities; dose modifications apply only to toxicities that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications.

[b] If cytopenia is thought to be caused mainly by B-cell lymphoma infiltration of the bone marrow, the investigator may decide not to reduce the lenalidomide dose.

Table 18 Guidelines for Management of Hematologic Toxicities That Occur on Days 8 and 15 of Cycle 1 *for Patients Receiving Obinutuzumab*

Event	Action to Be Taken
Febrile neutropenia or neutropenia with documented infection	• Withhold obinutuzumab and lenalidomide until resolution of fever and infection (as applicable). • If the event is ongoing at Day 1 of Cycle 2, follow instructions in Table 17. Note: Obinutuzumab and lenalidomide should not be withheld for asymptomatic neutropenia.
Severe thrombocytopenia [a] or bleeding	• Withhold obinutuzumab and lenalidomide until platelet count is ≥50,000/μL and there is resolution of bleeding. • If receiving LMWH, reduce the dose. • If receiving platelet inhibitors, consider temporarily withholding platelet inhibitors. • If the event is ongoing at Day 1 of Cycle 2, follow instructions in Table 17.

LMWH = low-molecular-weight heparin.

[a] Severe thrombocytopenia is defined as a platelet count < 10,000/μL for patients who are not receiving concomitant anticoagulants or platelet inhibitors and < 20,000/μL for patients who are receiving concomitant anticoagulants or platelet inhibitors.

Non-Hematologic Toxicities during Induction Treatment

Table 19 provides guidelines for management of non-hematologic toxicities that occur during induction treatment.

Table 19 Guidelines for Management of Non-Hematologic Toxicities *During Induction*

Event		Action to Be Taken
General guidance for treatment delays and discontinuation		– If study treatment is withheld for >21 days because of a toxicity that is attributable to study treatment, permanently discontinue study treatment. – When a treatment cycle is delayed because of toxicity resulting from any component of the regimen, all study treatment should be held and resumed together to remain synchronized. – If one drug is discontinued, treatment with the other two drugs may be continued for patients experiencing clinical benefit as determined by the investigator after discussion with the Medical Monitor.
IRRs and anaphylaxis		– Guidelines for the management of IRRs are provided in Section 4.3.2.1 for obinutuzumab, Section 4.3.2.2 *for rituximab,* and Section 4.3.2.3 for polatuzumab vedotin. – In case of anaphylaxis, study treatment should be permanently discontinued.
Renal toxicity		– Adjust the dose of lenalidomide [a] as outlined below: • If creatinine clearance is ≥ 30 but < 50 mL/min, lenalidomide should be given at a dose of 10 mg/day. • If creatinine clearance is < 30 mL/min and dialysis is not required, lenalidomide should be given at a dose of 10 mg every other day. • If creatinine clearance is < 30 mL/min and dialysis is required, lenalidomide should be given at a dose of 5 mg/day. On dialysis days, the dose should be administered after dialysis.
TLS	Clinical TLS [b]	– Withhold study treatment. – Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. Rasburicase therapy (if approved by the local health authority) may be administered as needed to reduce hyperuricemia. – If symptoms resolve completely, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.7.2 for current and subsequent cycles. – Perform chemistry panel every other day for the first week after re-initiation of lenalidomide.
	Laboratory TLS [b]	– Withhold study treatment. – Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care as clinically indicated. – If laboratory abnormalities have resolved completely, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.7.2 for current and subsequent cycles.

Table 19 Guidelines for Management of Non-Hematologic Toxicities *During Induction* (cont.)

Event		Action to Be Taken
New-onset neurologic manifestations suggestive of PML		– Withhold study treatment.[a] – Consult with a neurologist if PML is suspected (refer to Section 5.1.1.5 for guidance on investigations). – If PML is ruled out, resume obinutuzumab *or rituximab* at full dose and resume polatuzumab vedotin and lenalidomide at current dose. – If PML is confirmed, permanently discontinue study treatment.
AST, ALT, or bilirubin increase: Grade ≥ 3 (or ≥10× ULN for patients with liver involvement)		– Withhold study treatment and monitor liver enzymes at least every 7 days. – Investigate etiology. – If improvement to Grade ≤ 1, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.7.2 for current and subsequent cycles. – Permanently discontinue study treatment for life-threatening liver toxicity.
Tumor flare reaction	Grade 3–4 [c]	– Withhold study treatment. – Administer corticosteroids, NSAIDs, and/or narcotic analgesics at investigator's discretion. – If improvement to Grade ≤ 1, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.7.2 for current and subsequent cycles.
	Grade 1–2 [c]	– Continue study treatment. – Administer corticosteroids, NSAIDs, and/or narcotic analgesics at investigator's discretion.

Table 19 Guidelines for Management of Non-Hematologic Toxicities *During Induction* (cont.)

Event		Action to Be Taken
Neurotoxicity	Grade 4	– Permanently discontinue polatuzumab vedotin and all other study treatments.
	Grade 2 or 3	– Withhold study treatment.[a] – If improvement to Grade ≤ 1 within 21 days, resume study treatments for current and subsequent cycles as follows (see guidelines in Section 5.1.7): – Resume obinutuzumab *or rituximab* at full dose. – For patients who started at 1.8 mg/kg, resume polatuzumab vedotin at a reduced dose of 1.4 mg/kg per guidelines in Section 5.1.7.1; for patients who started at 1.4 mg/kg, permanently discontinue polatuzumab vedotin. [a] – Resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.7.2.
Dermatologic toxicity: Grade ≥ 2	Grade 3 with blistering or Grade 4	– Permanently discontinue study treatment.
	Grade 2 or Grade 3 without blistering	**First occurrence:** – Withhold study treatment and evaluate patient at least every 7 days. – Investigate etiology. Consult with a dermatologist. – Topical or parenteral corticosteroids may be required. – If improvement to Grade ≤ 1, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and *consider resuming* lenalidomide at a reduced dose [a] per guidelines in Section 5.1.7.2 *or continue current dose* for current and subsequent cycles. – *Permanently discontinue all drugs in the event of angioedema, exfoliative or bullous rash, or if SJS or TEN is suspected.* **Second occurrence:** – Permanently discontinue study treatment.
Venous thrombosis or embolism		– Withhold lenalidomide. – Start anticoagulation treatment. – After patient has been stabilized on anticoagulants and any complications of the thromboembolic event have been managed, lenalidomide may be resumed at current dose at investigator's discretion, dependent upon a benefit-risk assessment. – Anticoagulants should be continued during the course of lenalidomide treatment.

Table 19 Guidelines for Management of Non-Hematologic Toxicities *During Induction* (cont.)

Event		Action to Be Taken
Other non-hematologic toxicities (i.e., not described above), excluding alopecia, nausea, and vomiting	Grade 3 or 4	Grade 4 events – Permanently discontinue study treatment. Grade 3 events – Withhold study treatment. – If improvement to Grade ≤1 or baseline, resume obinutuzumab *or rituximab* at full dose and, if the event is considered related to lenalidomide, *resume lenalidomide accordingly at a reduced dose as per guidelines in Section 5.1.7.2 for current and subsequent cycles.* – No more than two dose reductions of lenalidomide are allowed.
	Grade 2	– Withhold study treatment. – If improvement to Grade ≤1 or baseline, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and *consider resuming* lenalidomide at a reduced dose [a] per guidelines in Section 5.1.7.2 *or continue current dose* for current and subsequent cycles.

CT = computed tomography; DBLCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LMWH = low-molecular-weight heparin; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug; PML = progressive multifocal leukoencephalopathy; *SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis;* TLS = tumor lysis syndrome; ULN = upper limit of normal.

[a] Dose modifications apply only to events that are considered to be related to lenalidomide.

[b] According to Cairo-Bishop classification system.

[c] Graded according to NCI CTCAE, Version 3.0.

5.1.7.4 Toxicities during Consolidation or Maintenance Treatment

Table 20 provides guidelines for management of toxicities that occur during consolidation or maintenance treatment.

Table 20 Guidelines for Management of Toxicities that Occur during Consolidation or Maintenance Treatment

Event	Action to Be Taken
Hematologic toxicity: Grade 3 or 4	– Withhold obinutuzumab *or rituximab* and lenalidomide. – Administer G-CSF for neutropenia per institutional guidelines. – Administer RBCs or platelets as required. – If improvement to Grade ≤ 2, resume obinutuzumab *or rituximab* and lenalidomide at same dose. *Lenalidomide dose may be reduced by one dose level per investigator judgment following discussion with the medical monitor.* – If study treatment is withheld for > 42 days, permanently discontinue study treatment.
Non-hematologic toxicity: Grade ≥ 2	– Withhold obinutuzumab *or rituximab* and lenalidomide. – If improvement to Grade ≤ 1 or baseline, administer study treatment at full dose. *Lenalidomide dose may be reduced by one dose level per investigator judgment following discussion with the medical monitor.* – If study treatment is withheld for > 42 days, permanently discontinue study treatment.

G-CSF = granulocyte colony-stimulating factor.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

During the DLT assessment window, adverse events identified as DLTs, as defined in Section 3.1.2.1.1, are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.5 Selected Adverse Events

Selected adverse events in this study are defined as adverse events for which additional data collection or analyses will be performed. Selected adverse events do not require immediate reporting if they are not serious (except for TLS).

The following adverse events are considered selected adverse events:

- Thrombocytopenia, including acute thrombocytopenia (events occurring during and within 24 hours following obinutuzumab infusion)
- Hepatitis B reactivation
- Cardiac events
- TLS
- IRRs
- All infections, including PML

- Neutropenia, including prolonged neutropenia (neutropenia $<$1000 cells/μL that does not resolve after 28 days without obinutuzumab treatment) and late-onset neutropenia (neutropenia $<$1000 cells/μL occurring $\geq$28 days after obinutuzumab treatment has been completed or stopped)
- Peripheral neuropathy (motor and/or sensory)
- Gastrointestinal perforation

Events for which additional data collection will be required are PML *and* hepatitis B reactivation.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. After this period, the investigator should report any serious adverse events that are believed to be related to prior study treatment *and events of second malignancies for patients who received obinutuzumab* (see Section 5.6).

An exception is *for the FL patients, where* Grade 3 and 4 infections (both related and unrelated) should be reported until up to 2 years after the last dose of *obinutuzumab.*

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (Version 4.0) will be used for assessing adverse event severity. Table 21 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 21 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (Version 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to any of the study treatment

components, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, considering especially the effects of study treatment modifications or discontinuation, or reintroduction of study treatment (as applicable)
- Known association of the event with the study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

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

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after the end of study treatment infusion and are judged to be related to infusion of any of the study treatment components should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events that Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increase or decrease in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An IMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should

be replaced by the established cause of death. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should **not** be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the Lugano 2014 criteria (see Appendix 5). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or insertion of access device for study treatment administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstance is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Treatment Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No experience with overdosage is available from human clinical trials. In clinical trials with obinutuzumab, doses ranging from 50 mg up to and including 2000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose-dependent.

Patients who experience overdose should have immediate interruption or reduction of their infusion and should be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B-cell depleted.

No safety data related to overdosing of polatuzumab vedotin or lenalidomide are available.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to any of the study treatments:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- *Dose-limiting toxicities (see Section 5.4.2 for further details)*
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor/Roche Medical Responsible:	[redacted], Pharm.D. (primary)
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Medical Monitor/Roche Medical Responsible:	[redacted], Pharm.D (secondary)
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events, Adverse Events of Special Interest, and Dose-Limiting Toxicities

5.4.2.1 Events that Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events that Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment. *After this period, the investigator should report any serious adverse events that are believed to be related to prior study treatment (see Section 5.6).* DLTs will be reported during the DLT assessment window. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting *events after the* adverse events *reporting period* are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 18 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the

pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Exposure of Pregnant Female to Lenalidomide

If a pregnant female not enrolled in the study (e.g., caregiver or pharmacist) is exposed to lenalidomide, the Adverse Event Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the exposure), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. The woman should be referred to an obstetrician or gynecologist, preferably one who is experienced in reproductive toxicity, for further evaluation and counseling.

5.4.3.4 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.5 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of study treatment), if the event is believed to be related to prior study treatment. *The sponsor should also be notified of events of second malignancies after the end of the adverse event reporting period for patients who received obinutuzumab.*

An exception is *for patients receiving obinutuzumab, where* Grade 3–4 infections (both related and unrelated) should be reported until up to 2 years after the last dose of study treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting *Form* using the fax number or email address provided to investigators.

During survival follow-up, deaths attributed to progression of lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Obinutuzumab Investigator's Brochure (Oncology)
- *Rituximab Investigator's Brochure (Oncology)*
- Polatuzumab Vedotin Investigator's Brochure
- Lenalidomide SmPC

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This Phase Ib/II, open-label, multicenter, non-randomized study will evaluate the safety, efficacy, and pharmacokinetics of G+Pola+Len in patients with R/R FL *and R+Pola+Len in patients with R/R* DLBCL.

The study will include an initial dose-escalation phase followed by an expansion phase. The dose-escalation phase *in* FL patients is designed to determine the RP2Ds for both polatuzumab vedotin and lenalidomide when combined with fixed doses of obinutuzumab. *The dose-escalation phase in DLBCL patients is designed to determine the RP2D of lenalidomide when combined with fixed doses of polatuzumab vedotin (1.8 mg/kg) and rituximab (375 mg/m²).* During the expansion phase, additional patients with R/R FL or DLBCL will undergo treatment with polatuzumab vedotin and lenalidomide at their respective RP2Ds in combination with obinutuzumab *or rituximab*.

Study data will be summarized separately for each phase. Data from the dose-escalation phase will be summarized by cohort (assigned dose level). Data from the expansion phase will be summarized by histologic subtype (i.e., FL or DLBCL). Data will be summarized as warranted, and listings will be used in place of tables when the sample sizes are small.

6.1 DETERMINATION OF SAMPLE SIZE

Limited dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a standard 3+3 algorithm, as outlined in Section 3.1. It is anticipated that enrollment of 5 cohorts of 3–6 patients each, for a total of 18–*30* patients, will be required to establish the RP2D during the dose-escalation phase *for patients with R/R FL. An additional 3 possible cohorts of 3–6 patients each, for a total of 12–18 patients will be required to establish the RP2D during the dose-escalation phase for patients with R/R DLBCL.*

Approximately 80 patients (40 patients with FL and 40 patients with DLBCL) will be enrolled during the expansion phase. Overall, approximately *110–128* patients will be enrolled in the study.

The primary efficacy analysis will be the estimation of the true proportion of patients expected to obtain a PET-CT–defined CR at EOI.

Data from completed and ongoing studies in similar disease settings will be used as historical controls for comparison. Currently available data indicate that the historical CR rate based on PET-CT scans is 40% for R/R FL and DLBCL.

A sample size of 40 patients is deemed sufficient to provide adequate precision for the point estimate and for the lower bound of the two-sided 90% CI to rule out a clinically uninteresting probability of response of $<$55%, assuming an observed PET-CT–defined CR rate of 70%.

Table 22 lists the two-sided 90% Clopper-Pearson exact CIs for the true probability of achieving a PET-CT–defined CR at EOI for a range of observed proportions based on a sample of 40 patients.

Table 22 Potential 90% CI for the True Probability of Achieving a PET-CT–Defined Complete Response at End of Induction

Observed Proportion of Patients Who Achieve a PET-CT–Defined CR at EOI	Two-Sided 90% Clopper-Pearson CI [a] for True Population PET-CT–Defined CR
0.50	(0.36, 0.64)
0.55	(0.40. 0.68)
0.60	(0.46, 0.73)
0.65	(0.51, 0.77)
0.70	(0.56, 0.82)
0.72	(0.58, 0.83)
0.75	(0.61, 0.86)
0.80	(0.66, 0.89)
0.85	(0.72, 0.93)

CI = confidence interval; CR = complete response; CT = computed tomography; EOI = end of induction; PET = positron emission tomography.

[a] Note that the lower limit of a two-sided 90% CI is equivalent to a one-sided 95% CI.

6.2 *DEFINITION OF ANALYSIS POPULATIONS*

The following populations are defined:

- *The primary safety and efficacy populations will include patients who received at least one dose of any component of the combination.*
- *The intent-to-treat population will include all patients enrolled in the study.*

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations, and discontinuations from the study will be listed. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated.

Data related to administration of study treatment components will be listed, and any dose modifications will be flagged. The number of doses, treatment cycles, average dose received, and relative dose intensity for each treatment component will be summarized using descriptive statistics (mean, standard deviation, median, and range).

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, such as age, sex, race, and duration of malignancy, will be summarized using descriptive statistics (mean, standard deviation, median, and range) for continuous variables and frequencies and percentages for categorical variables.

6.5 SAFETY ANALYSES

The safety analyses will include all treated patients (i.e., patients who received any amount of study treatment). Data for patients in the dose-escalation phase will be summarized by cohort *and histology type*, and data for patients in the expansion phase will be summarized by histologic subtype (FL or DLBCL).

Safety will be assessed through summaries of adverse events and changes from baseline in laboratory test results, shift-tables of ECGs findings, and vital signs.

All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE, Version 4.0 grade. All serious adverse events, adverse events of special interest, and selected adverse events will be summarized and listed.

Deaths reported during the treatment period and during post-treatment follow-up will be listed *and summarized*.

Relevant laboratory *results* will be displayed by time, with Grade 3 and 4 values identified as appropriate.

6.6 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include *the primary efficacy population and the intent-to-treat population for* patients enrolled in the expansion phase, with patients grouped according to histologic subtype*, and will be performed by treatment group. In addition, patients with FL and DLBCL who received polatuzumab vedotin and lenalidomide at the RP2D during the dose-escalation phases will be pooled for analysis by histology with patients treated in the expansion phase at the same dose levels.*

Response will be determined on the basis of PET-CT scans or CT scans alone, using the Lugano 2014 criteria (see Appendix 5).

6.6.1 Primary Efficacy Endpoint

The primary efficacy analysis will be estimation of the proportion of patients achieving a CR at EOI, as determined by the IRC through use of the PET-CT–based Lugano 2014 criteria. Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non-responders.

6.6.2 Secondary Efficacy Endpoints

The secondary efficacy analyses will be estimation of the proportion of patients achieving each of the following endpoints:

- CR at EOI, as determined by the investigator on the basis of PET-CT scans

- CR at EOI, as determined by the *IRC and* investigator on the basis of CT scans alone
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator on the basis of PET-CT scans
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator on the basis of CT scans alone
- Best response of CR or PR during the study, as determined by the investigator on the basis of CT scans alone

Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non-responders.

6.6.3 Exploratory Efficacy Endpoints

Exploratory efficacy analyses will include estimation of the proportion of patients achieving each of the following endpoints:

- For patients who have positive PET scans at EOI:
  - CR at 12 months, as determined by the IRC and by the investigator on the basis of PET-CT scans*, in FL patients*
  - *CR at EOC, as determined by the IRC and by the investigator on the basis of PET-CT scans, in DLBCL patients*

Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non-responders.

Exploratory efficacy analyses will also be performed on the following endpoints:

- PFS
- EFS
- DFS
- OS

PFS, EFS, DFS, and OS will be summarized descriptively using the Kaplan-Meier method (Kaplan and Meier 1958). For the PFS, EFS, and DFS analyses, data for patients without an event of interest will be censored at the date of the last tumor assessment. For patients without post-baseline tumor assessments, data will be censored at the date of initiation of study treatment plus 1. For the OS analysis, data for patients who have not died will be censored at the date the patient was last known to be alive. Where medians are reached, the corresponding estimated median will be provided, along with the 95% CI estimated using the method of Brookmeyer and Crowley (1982). In addition, landmark estimates of the proportion of patients who are

event free at 6 months, 9 months, 1 year, and 2 years will be provided, along with 95% asymptotic CIs using Greenwood's formula for standard errors.

6.7 PHARMACOKINETIC ANALYSES

Plasma/serum concentrations of obinutuzumab, *rituximab,* polatuzumab vedotin, and lenalidomide will be tabulated, summarized, and plotted after appropriate grouping. As appropriate, PK parameters (e.g., area under the curve [AUC], time to maximum concentration [t_{max}], maximum concentration [C_{max}], half-life [$t_{1/2}$]) may also be calculated, tabulated, and summarized after appropriate grouping. Additional PK and PK/PD analyses (e.g., population modelling including pooled analyses across studies) may also be performed as appropriate. If done, these additional analyses may be reported separately from the CSR. At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of polatuzumab vedotin or lenalidomide.

6.8 IMMUNOGENICITY ANALYSES

The numbers and proportions of post-treatment HAHA- *or HACA-,* and ATA-positive patients and HAHA- *or HACA-,* and ATA-negative patients at baseline and during both the treatment and follow-up periods will be summarized by histologic subtype. Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study treatment administration (treatment-induced ATA response) or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all post-baseline samples are negative or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between HAHA *or HACA,* and ATA status and safety, efficacy, PK, and biomarker endpoints will be explored as appropriate.

6.9 BIOMARKER ANALYSES

Exploratory analyses of biomarkers related to tumor biology and study treatment MOA will be conducted. Analyses will assess the prognostic and/or predictive value of candidate biomarkers separately for each histologic subtype with respect to both IRC- and investigator-assessed outcomes. Specifically, the association between candidate biomarkers and PET-CT–defined CR rate and objective response (CR+PR) rate, and potentially other measures of efficacy and safety, will be explored to assess potential prognostic or predictive value. These analyses may not be included in the final study report because of their exploratory nature. In addition to analysis in the context of this study, data will also be explored in aggregate with data from other studies.

6.10 INTERIM ANALYSES

It is anticipated that at least two interim analyses, one per histology, will be conducted during the expansion phase of the study, when at least 15 patients *in each histology* have been evaluated for PET-CT–defined CR at EOI. Additional analyses may be conducted to guide early stopping of enrollment for safety on the basis of observed toxicities and the ability to maintain chemotherapy dose intensity.

During the expansion phase, a *modified version of the* predictive probability design (Lee and Lui 2008) may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a PET-CT–defined CR at EOI in each indication-specific expansion cohort with that in historical controls. Updated estimates for the assumed historical control PET-CT–defined CR rate will be available from currently ongoing studies by the time of the first interim analysis. *The design is based on Lee and Lui 2008, with the modification that the uncertainty in the historical control data is fully taken into account by utilizing a beta posterior on the control response rate. Interim analysis decision rules will be based on the predicative probability that the trial will have a positive outcome if carried out to completion and will use the historical control data available at the time of analysis.*

If, at any time, an interim analysis suggests that the proportion of patients achieving a PET-CT–defined CR for one of the indication-specific expansion cohorts is lower than expected, the IMC will review the data and decide whether to recommend an early decision to stop enrollment in that subgroup.

Additional review of safety and/or efficacy data by the IMC may be requested by and carried out at the discretion of the Medical Monitor. Further details regarding the rules and guidelines of data review will be provided to the IMC in an IMC charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and any other externally-generated electronic study data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., 1 year after the last patient has completed the study).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol

amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Roche or an authorized representative.

Electronic data capture will be used for this study. An IxRS will be used to assign patient numbers. A central laboratory will be used for a subset of laboratory assessments as specified in Section 4.5.6; otherwise, local laboratories will be used. A central independent review facility will be used to collect PET-CT and CT scans, and the IRC will perform independent assessments of response for all patients enrolled in the study (separate IRC Charter will contain all details). Data from this study will be shared with an Expert Scientific Committee that will provide scientific input for the benefit-risk assessment.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any

country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma

	Screening [a]		Induction (6 months; 28-day cycles)								EOI	Maintenance (24 months)		EOM [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
			Cycle 1 (±1 day)				Cycles 2–6 (±2 days)									
	D –28 to D –1	D –14 to D –1	D1	D8	D15	D22	D1	D8	D15	D22	After Last Induction Dose [c]	Monthly (±3 days)	Every 2 months (±1 wk)	35 Days after Last Dose		
												D1	D1			
Informed consent [e]	x															
Demographic data	x															
Medical history	x															
ECOG Performance Status	x															
Vital signs [f]	x		x	x	x		x					x		x		
Height	x															
Weight	x		x				x									
12-lead ECG	x										x [g]			x		
Complete physical examination [h,i]	x															
Targeted physical examination [i,j]							D1, Cycles 2 and 4				x		x	x	x	
Ann Arbor, FLIPI, and FLIPI2	x															
B symptoms	x															
β_2 microglobulin			x [m]													
Hematology [k]		x	x [l,m]	x [m]	x [m]	x [m]	x [m]	x [m,n]	x [m,n]	x [m, n]	x [g]	x [m]		x		
Chemistry panel (serum or plasma) [o]		x	x [l,m]	x [m]	x [m]		x [m]		x [m,n]		x [g]	x [m]		x		
TSH, T3, T4	*x*		*Every 3 months*													

Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

	Screening [a]		Induction (6-months; 28-day cycles)								EOI	Maintenance (24 months)		EOM [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
			Cycle 1 (± 1 d)				Cycles 2–6 (± 2 d)									
	D –28 to D –1	D –14 to D –1	D1	D8	D15	D22	D1	D8	D15	D22	After Last Induction Dose [c]	Monthly (± 3 days)	Every 2 months (± 1 wk)	35 Days after Last Dose		
												D1	D1			
Coagulation (INR, aPTT [or PTT], and PT)		x														
Pregnancy test [p]		x [p]	x [p]	x [p]	x [p]	x [p]	x [p]									
Hepatitis B and C testing [q]	x															
HIV testing [q]	x															
Quantitative IgA, IgG, IgM			x [m]								x	x [r]		x	x [s]	
HAHA sample for obinutuzumab			x [t] (see Appendix 3)													
ATA sample for polatuzumab vedotin			x [t] (see Appendix 3)													
PK sample for obinutuzumab			x [t] (see Appendix 3)													
PK sample for polatuzumab vedotin			x [t] (see Appendix 3)													
PK sample for lenalidomide			x [t] (see Appendix 3)													
Whole blood for MRD [u]			x [m,u]								x [u]	x [r, u]				
Whole blood for lymphocyte immunophenotyping [v]			x [m]		x [m]		x [m]				x	x [r]		x	x [s]	
Plasma for cytokine analysis			x [m]				x [m, n]									
Optional peripheral blood sample for RCR [w]			x [m]													

Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

		Screening [a]		Induction (6-months; 28-day cycles)								EOI	Maintenance (24 months)		EOM [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
				Cycle 1 (± 1 d)				Cycles 2–6 (± 2 d)									
		D –28 to D –1	D –14 to D –1	D1	D8	D15	D22	D1	D8	D15	D22	After Last Induction Dose [c]	Monthly (± 3 days)	Every 2 months (± 1 wk)	35 Days after Last Dose		
													D1	D1			
Tumor tissue specimen		x [x]										(x[y])					
Concomitant medications		x [z]		To be recorded continually until end of treatment [z]													
Adverse events [aa]		x		To be assessed continually [aa]													
PET-CT scan		x [bb]										x [cc]	x [dd]				
CT scan [ee]		x [ee]						x [ff]				x [cc]	x [ff]		x [gg]	x [hh]	
Bone marrow biopsy and aspirate		x [ii]										x [cc,jj]	x [jj]		x [gg,jj]		
Study treatment administration	Obinutuzumab [kk]			x	x	x		x						x			
	Polatuzumab vedotin [kk]			x				x									
	Lenalidomide [kk]			D1–21					D1–21				D1–21				
New anti-lymphoma treatment																x	x
Survival follow-up																	x

ATA = anti-therapeutic antibody; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOI = end of induction; EOM = end of maintenance; FLIPI = Follicular Lymphoma International Prognostic Index; FU = follow-up; HAHA = human anti-human antibody; MRD = minimal residual disease; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; Q3M = every 3 months; RCR = Roche Clinical Repository; *T4 = thyroxine; TSH = thyroid-stimulating hormone;* wk = week.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] The screening period starts with the signing of the Informed Consent Form. Results of standard-of-care tests or examinations performed prior to obtaining

informed consent and within the defined window may be used as screening and baseline assessments; such tests do not need to be repeated for screening purposes.

[b] Patients who complete maintenance treatment or discontinue maintenance treatment prematurely will undergo assessments at EOM.

[c] EOI assessments should be performed 6–8 weeks after Day 1 of the last induction cycle. As an exception, patients who discontinue induction treatment prematurely because of an adverse event may undergo EOI assessments 4–8 weeks after their last dose of study treatment.

[d] Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments every 3 months during the post-treatment FU period, which will continue until disease progression, the start of new anti-lymphoma treatment, or the end of the study, whichever occurs first. The first post-treatment FU visit is 3 months after the EOI visit for patients who do not receive maintenance treatment and 3 months after the last dose for patients who receive maintenance treatment. Patients who experience disease progression will undergo limited assessments every 3 months during the survival FU period, which will continue until the end of the study. The end of the study is defined as the time when all enrolled patients have completed or discontinued study treatment or when the Sponsor ends the study.

[e] Informed consent must be documented before any study-specific screening procedure is performed.

[f] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For obinutuzumab infusions: For the first cycle and for patients who experience an infusion-related reaction, vital signs will be measured prior to the infusion, every 15 (±5) minutes for the first 90 minutes of the infusion, and then every 30 (±10) minutes until 1 hour after completion of the infusion. For the second and subsequent cycles, vital signs will be measured every 30 minutes during the infusion, except in patients who had experienced an infusion-related reaction during a prior infusion. For polatuzumab vedotin infusions: During the administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 15 (±5) minutes during the infusion, at the end of the infusion, and every 30 (±10) minutes for 90 minutes following completion of dosing at Cycle 1 and 30 (±10) minutes following completion of dosing in subsequent cycles.

[g] Perform only in patients who will not be receiving maintenance treatment.

[h] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[i] As part of tumor assessment, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate Tumor Assessment eCRF.

[j] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

[l] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 72 hours prior to Day 1 of Cycle 1.

[m] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle during induction or each month during maintenance, and within 24 hours prior to other timepoints during induction treatment. *CBC to be monitored every week for first 8 weeks of lenalidomide treatment.* Samples for exploratory biomarker research should be collected at the same time as hematology and chemistry samples. *For β2 microglobulin and Quantitative IgA, IgG, IgM: C1D1 requires predose collection.* For plasma cytokine analysis: C1D1 requires predose collection and 2-hour postdose collection. All other timepoints thereafter will be predose.

[n] Cycles 2 and 3 only.

[o] Includes sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, amylase, lipase, LDH, and uric acid (amylase and lipase only during induction).

[p] All women of childbearing potential will have two negative serum pregnancy test results prior to initiating treatment: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1. Urine pregnancy tests are required after treatment initiation (including times of treatment interruption) as follows: every week during the first cycle and then every 4 weeks during treatment for women with regular menstrual cycles or every 2 weeks during treatment for women with irregular menstrual cycles, any time the patient misses her period or has unusual menstrual bleeding, at the time of treatment discontinuation, and at *Days 14 and 28 following* the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody. HIV test should also be performed if required by local requirements.

[r] Perform at the same time as tumor assessments at 12, 18, and 24 months after initiation of induction treatment.

[s] Perform every 3 months until recovery to either normal range or baseline level, disease progression, or the start of new anti-lymphoma treatment, whichever occurs first.

[t] See Appendix 3 for detailed PK collection schedule.

[u] Perform only for patients enrolled in the expansion phase. Includes circulating lymphoma cells and/or cell-free circulating tumor DNA.

[v] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK-cell counts (CD16 and CD56).

[w] Requires separate patient consent for RCR participation. Not applicable for a site that has not been granted approval for RCR sampling.

[x] Availability of adequate archival (obtained within 12 months prior to the initiation of study treatment) or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6 for details).

[y] A tumor biopsy sample will be collected at the time of progression unless no adequate tumor site is accessible.

[z] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from *7* days prior to the screening period to the visit at EOI or at the end of post-induction treatment, whichever occurs later.

Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

[aa] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment (see Section 5.6). An exception is made for Grade 3 and 4 infections (related and unrelated), which should be reported until up to 2 years after the last dose of *obinutuzumab*. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to any of the study treatment components or trial-related procedures until a final outcome can be reported.

[bb] The screening PET-CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[cc] Perform only for patients who have received at least two cycles of induction treatment.

[dd] If PET-CT scan is positive at EOI, perform at 12 months after initiation of induction treatment, within 14 days prior to treatment administration.

[ee] Includes CT scan of the neck (if clinically indicated), chest, abdomen, and pelvis. If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. Combined PET/CT scanners may be used to collect diagnostic CT scans, but only according to the technical guidelines in the imaging manual. The screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[ff] Perform *within 7 days prior to Day 1 of Cycle 3* and at 12, 18, and 24 months after initiation of induction treatment.

[gg] Perform only if not done within the previous 3 months.

[hh] Perform every 6 months.

[ii] Bone marrow biopsy and aspirate must be performed within approximately 3 months prior to Day 1 of Cycle 1.

[jj] For patients with bone marrow involvement at screening, a repeat assessment will be performed at EOI if there is radiologic evidence of a complete response, and during maintenance or at EOM if there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression).

[kk] Refer to Section 4.3.2 for details on dosing and schedule. At each cycle, each patient will be supplied with only enough lenalidomide for that cycle. During maintenance treatment, lenalidomide will be administered for a maximum of 12 months.

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma

	Screening [a]		Induction (6 months; 28-day cycles)								EOI	Consolidation (6 months)		EOC [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
			Cycle 1 (±1 day)				Cycles 2–6 (±2 days)									
	D –28 to D –1	D –14 to D –1	D1	D8	D15	D22	D1	D8	D15	D22	After Last Induction Dose [c]	Monthly (±3 days)	Every 2 months (±1 wk)	35 Days after Last Dose		
												D1	D1			
Informed consent [e]	x															
Demographic data	x															
Medical history	x															
ECOG Performance Status	x															
Vital signs [f]	x		x				x					x		x		
Height	x															
Weight	x		x				x									
12-lead ECG	x										x [g]			x		
Complete physical examination [h,i]	x															
Targeted physical examination [i,j]							D1, Cycles 2 and 4				x		x	x	x	
Ann Arbor and IPI	x															
B symptoms	x															
β_2 microglobulin			x													
Hematology [k]		x	x [l, m]	x [m]	x [m]	*x* [m]	x [m]	*x* [m,n]	x [m,n]	*x* [m,n]	x [g]	x [m]		x	x	
Chemistry panel (serum or plasma) [o]		x	x [l, m]		x [m]		x [m]		x [m,n]		x [g]	x [m]		x	x	
TSH, T3, T4	*x*		*Every 3 months*													

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma (cont.)

	Screening [a]		Induction (6-months; 28-day cycles)								EOI	Consolidation (6 months)		EOC [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
			Cycle 1 (± 1 d)				Cycles 2–6 (± 2 d)									
	D –28 to D –1	D –14 to D –1	D1	D8	D15	D22	D1	D8	D15	D22	After Last Induction Dose [c]	Monthly (± 3 days)	Every 2 months (± 1 wk)	35 Days after Last Dose		
												D1	D1			
Coagulation (INR, aPTT [or PTT], and PT)		x														
Pregnancy test [p]		x [p]	x [p]	x [p]	x [p]	x [p]	x [p]									
Hepatitis B and C testing [q]	x															
HIV testing [q]	x															
Quantitative IgA, IgG, IgM			x								x			x	x	
HACA sample for *rituximab*			x [r] (see Appendix 4)													
ATA sample for polatuzumab vedotin			x [r] (see Appendix 4)													
PK sample for *rituximab*			x [r] (see Appendix 4)													
PK sample for polatuzumab vedotin			x [r] (see Appendix 4)													
PK sample for lenalidomide			x [r] (see Appendix 4)													
Whole blood for MRD [s]			x [m,s]								x [s]	At Month 3 [s]				
Whole blood for lymphocyte immunophenotyping [t]			x [m]		x [m]		x [m]				x			x	x [u]	

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma (cont.)

		Screening [a]		Induction (6-months; 28-day cycles)								EOI	Consolidation (6 months)		EOC [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
				Cycle 1 (± 1 d)				Cycles 2–6 (± 2 d)									
		D –28 to D –1	D –14 to D –1	D1	D8	D15	D22	D1	D8	D15	D22	After Last Induction Dose [c]	Monthly (± 3 days)	Every 2 months (± 1 wk)	35 Days after Last Dose		
				D1									D1	D1			
Plasma for cytokine analysis				x [m]				x [m, n]									
Optional peripheral blood sample for RCR [v]				x [m]													
Tumor tissue specimen		x [w]										(x [x])					
Concomitant medications		x [y]		To be recorded continually until end of treatment [y]													
Adverse events [z]		x		To be assessed continually [z]													
PET-CT scan		x [aa]										x [bb]			x [jj]		
CT scan [cc]		x [cc]						x [dd]				x [bb]	At end of Month 3		x [ee]	x [ff]	
Bone marrow biopsy and aspirate		x [gg]										x [bb, hh]	x [hh]		x [ee, hh]		
Study treatment administration	*Rituximab* [ii]			x				x						x			
	Polatuzumab vedotin [ii]			x				x									
	Lenalidomide [ii]			D1–21					D1–21				D1–21				
New anti-lymphoma treatment																x	x
Survival follow-up																	x

ATA = anti-therapeutic antibody; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOC = end of consolidation; EOI = end of induction; FU = follow-up; HAHA = human anti-human antibody; IPI = International Prognostic Index; MRD = minimal residual disease; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; Q3M = every 3 months; RCR = Roche Clinical Repository; wk = week.

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma (cont.)

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] The screening period starts with the signing of the Informed Consent Form. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the defined window may be used as screening and baseline assessments; such tests do not need to be repeated for screening purposes.

[b] Patients who complete consolidation treatment or discontinue consolidation treatment prematurely will undergo assessments at EOC.

[c] EOI assessments should be performed 6–8 weeks after Day 1 of the last induction cycle. As an exception, patients who discontinue induction treatment prematurely because of an adverse event may undergo EOI assessments 4–8 weeks after their last dose of study treatment.

[d] Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments every 3 months during the post-treatment FU period, which will continue until disease progression, the start of new anti-lymphoma treatment, or the end of the study, whichever occurs first. The first post-treatment FU visit is 3 months after the EOI visit for patients who do not receive consolidation treatment and 3 months after the last dose for patients who receive consolidation treatment. Patients who experience disease progression will undergo limited assessments every 3 months during the survival FU period, which will continue until the end of the study. The end of the study is defined as the time when all enrolled patients have completed or discontinued study treatment.

[e] Informed consent must be documented before any study-specific screening procedure is performed.

[f] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For *rituximab* infusions: *Vital signs monitoring during infusion should be determined as per local label.* For polatuzumab vedotin infusions: During the administration of polatuzumab vedotin, vital signs should be assessed before the start of the infusion, every 15 (±5) minutes during the infusion, at the end of the infusion, and every 30 (±10) minutes for 90 minutes following completion of dosing at Cycle 1 and 30 (±10) minutes following completion of dosing in subsequent cycles.

[g] Perform only in patients who will not be receiving consolidation treatment.

[h] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[i] As part of tumor assessment, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate Tumor Assessment eCRF.

[j] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[l] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 72 hours prior to Day 1 of Cycle 1.

[m] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle during induction or each month during consolidation, and within 24 hours prior to other timepoints during induction treatment. *CBC to be monitored every week during first 8 weeks of lenalidomide therapy.* Samples for exploratory biomarker research should be collected at the same time as hematology and chemistry samples. *For β2 microglobulin and Quantitative IgA, IgG, IgM: C1D1 requires predose collection.* For plasma cytokine analysis: C1D1 requires predose collection and 2-hour post-dose collection. All other timepoints thereafter will be predose.

[n] Cycles 2 and 3 only.

[o] Includes sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, amylase, lipase, LDH, and uric acid (amylase and lipase only during induction).

[p] All women of childbearing potential will have two negative serum pregnancy test results prior to initiating treatment: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1. Urine pregnancy tests are required after treatment initiation (including times of treatment interruption) as follows: every week during the first cycle and then every 4 weeks during treatment for women with regular menstrual cycles or every 2 weeks during treatment for women with irregular menstrual cycles, any time the patient misses her period or has unusual menstrual bleeding, at the time of treatment discontinuation, and at *Days 14 and 28 following* the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody. HIV test should also be performed if required by local regulatory requirements.

[r] See Appendix 4 for detailed PK collection schedule.

[s] Perform only for patients enrolled in the expansion phase. Includes circulating lymphoma cells and/or cell-free circulating tumor DNA.

[t] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK-cell counts (CD16 and CD56).

[u] Perform every 3 months until recovery to either normal range or baseline level, disease progression, or the start of new anti-lymphoma treatment, whichever occurs first.

[v] Requires separate patient consent for RCR participation. Not applicable for a site that has not been granted approval for RCR sampling.

[w] Availability of adequate archival (obtained within 6 months prior to the initiation of study treatment) or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6 for details).

[x] A tumor biopsy sample will be collected at the time of progression unless no adequate tumor site is accessible.

[y] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from *7* days prior to the screening period to the visit at EOI or at the end of post-induction treatment, whichever occurs later.

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma (cont.)

[z] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to any of the study treatment components or trial-related procedures until a final outcome can be reported.

[aa] The screening PET-CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[bb] Perform only for patients who have received at least two cycles of induction treatment.

[cc] Includes CT scan of the neck (if clinically indicated), chest, abdomen, and pelvis. If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. Combined PET/CT scanners may be used to collect diagnostic CT scans, but only according to the technical guidelines in the imaging manual. The screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[dd] Perform within 7 days prior to Day 1 of Cycle *3*.

[ee] Perform only if not done within the previous 3 months.

[ff] Perform every 6 months.

[gg] Bone marrow biopsy and aspirate must be performed within approximately 3 months prior to Day 1 of Cycle 1.

[hh] For patients with bone marrow involvement at screening, a repeat assessment will be performed at EOI if there is radiologic evidence of a complete response, and during consolidation or at EOC if there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression).

[ii] Refer to Section 4.3.2 for details on dosing and schedule. At each cycle, each patient will be supplied with only enough lenalidomide for that cycle. During consolidation treatment, lenalidomide will be administered for a maximum of 6 months.

jj If PET-CT scan is positive at EOI, perform repeat PET-CT at EOC.

Appendix 3
Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory FL Patients*

Study Visit		Serum Obinutuzumab PK Sample [a,b]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a,b]	Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE [a]	Plasma Lenalidomide PK Sample [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Dose-Escalation Phase (FL Patients; 28-Day Cycles)							
Cycle 1	Day 1	Pre-infusion *(anytime prior to dose);* 30 ± 10 min after end of infusion[d]	Pre-infusion *(anytime prior to dose)*	Pre-infusion *(anytime prior to dose);* 30 ± 10 min after end of infusion	Predose *(anytime prior to dose);* 2 hr post-dose *(± 10 min)* [c]	Pre-infusion *(anytime prior to dose)*	Pre-infusion *(anytime prior to dose)*
	Day 8	–	–	Anytime during visit	–	–	–
	Day 15	–	–	Anytime during visit	Predose *(within15 min prior to dose);* 0.5 *hr (± 5 min),* 1 *hr (± 5 min*, 2 *hr (± 10 min),* 4 *hr (± 10 min),* 8 hr post-dose *(± 30 min)* [c]	–	–
Cycle 2	Day 1	Pre-infusion *(within 5 hr prior to dose);* 30 ± 10 min after end of infusion	Pre-infusion *(within 5 hr prior to dose)*	Pre-infusion *(within 5 hr prior to dose);* 30 ± 10 min after end of infusion	–	–	Pre-infusion *(within 5 hr prior to dose)*

Appendix 3
Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory FL Patients* (cont.)

Study Visit		Serum Obinutuzumab PK Sample [a,b]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a,b]	Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE [a]	Plasma Lenalidomide PK Sample [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Cycle 4	Day 1	Pre-infusion *(within 5 hr prior to dose);* 30 ± 10 min after end of infusion	Pre-infusion *(within 5 hr prior to dose)*	Pre-infusion *(within 5 hr prior to dose);* 30 ± 10 min after end of infusion	–	–	Pre-infusion *(within 5 hr prior to dose)*
Cycle 6	Day 1	Pre-infusion *(within 5 hr prior to dose);* 30 ± 10 min after end of infusion	–	Pre-infusion *(within 5 hr prior to dose)*	2 hr post-dose *(± 10 min)* [c]	Pre-infusion *(within 5 hr prior to dose)*	–
Expansion Phase *FL patients* (Induction Treatment; 28-Day Cycles)							
Cycle 1	Day 1	Pre-infusion *(anytime prior to dose);* 30 ± 10 min after end of infusion [d]	Pre-infusion *(anytime prior to dose)*	Pre-infusion *(anytime prior to dose);* 30 ± 10 min after end of infusion	Predose *(anytime prior to dose);* 2 hr post-dose [c]	Pre-infusion *(anytime prior to dose)*	Pre-infusion *(anytime prior to dose)*
	Day 8	–	–	Anytime during visit	–	–	–
	Day 15	–	–	Anytime during visit	Predose *(within 15 min prior*	–	–

Appendix 3
Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory FL Patients* (cont.)

Study Visit		Serum Obinutuzumab PK Sample [a,b]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a,b]	Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE [a]	Plasma Lenalidomide PK Sample [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
					to dose); 0.5hr (±5 min), 1hr (±5 min, 2 hr (±10 min), 4hr (±10 min), 8 hr post-dose (±30 min) [c]		
Cycle 2	Day 1	Pre-infusion *(within 5 hr prior to dose);* 30±10 min after end of infusion	Pre-infusion *(within 5 hr prior to dose)*	Pre-infusion *(within 5 hr prior to dose);* 30±10 min after end of infusion	–	–	Pre-infusion *(within 5 hr prior to dose)*
Cycle 4	Day 1	Pre-infusion *(within 5 hr prior to dose);* 30±10 min after end of infusion	Pre-infusion *(within 5 hr prior to dose)*	Pre-infusion *(within 5 hr prior to dose);* 30±10 min after end of infusion	–	–	Pre-infusion *(within 5 hr prior to dose)*

Appendix 3
Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory FL Patients* (cont.)

Study Visit		Serum Obinutuzumab PK Sample [a,b]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a,b]	Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE [a]	Plasma Lenalidomide PK Sample [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Cycle 6 (End of Induction)	Day 1	Pre-infusion *(within 5 hr prior to dose)*; 30 ± 10 min after end of infusion	–	Pre-infusion *(within 5 hr prior to dose)*	2 hr post-dose *(± 10 min)* [c]	Pre-infusion *(within 5 hr prior to dose)*	–
Maintenance Phase (Post-Induction—FL Patients; 28-Day cycles)							
Month 1	Day 1	Pre-infusion *(within 5 hr prior to dose)*	–	–	–	–	–
Month 7	Day 1	Pre-infusion *(within 5 hr prior to dose)*	–	–	–	–	=
Month 13	Day 1	Pre-infusion *(within 5 hr prior to dose)*	–	–	–	–	=
Month 19	Day 1	Pre-infusion *(within 5 hr prior to dose)*	–	–	–	–	=

Appendix 3
Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory FL Patients* (cont.)

Study Visit	Serum Obinutuzumab PK Sample [a,b]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a,b]	Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE [a]	Plasma Lenalidomide PK Sample [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Treatment discontinuation	Anytime during visit	Anytime during visit		–	Anytime during visit	Anytime during visit
20 *±30* days after last dose *of obinutuzumab and polatuzumab (as appropriate for sample)*	Anytime during visit	Anytime during visit	–	–	Anytime during visit	Anytime during visit
1-2 years after last dose *of obinutuzumab*	Anytime during visit (if patient in clinic)	Anytime during visit	–	–	Anytime during visit (if patient in clinic)	Anytime during visit (if patient in clinic)

Appendix 3
Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory FL Patients* (cont.)

ATA = anti-therapeutic antibody; HAHA = human anti-human antibody; " – " = not applicable; PK = pharmacokinetic.

[a] Sample collection timing is relative to specified drug.

[b] *Samples collected for PK, HAHA, and ATA analysis may be used for additional PK, HAHA and/or ATA assay development and validation and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.*

[c] On lenalidomide PK sampling visits, lenalidomide dose will be taken at the clinic appointment.

[d] *If the Cycle 1 Day 1 dose of obinutuzumab is split over two days, take the 30 minutes post-end of infusion obinutuzumab PK sample relative to the end of the infusion on Day 2 and ensure that the date and time of the PK collection are accurately recorded.*

Appendix 4

Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory DLBCL Patients

Study Visit		*Serum Rituximab PK Sample* [a,b]	*Serum Polatuzumab Vedotin PK Sample for Total Antibody* [a,b]	*Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE* [a]	*Plasma Lenalidomide PK Sample* [a]	*Serum Rituximab HACA Sample* [a]	*Serum Polatuzumab Vedotin ATA Sample* [a]
Dose-Escalation Phase (DLBCL Patients; 28-Day Cycles)							
Cycle 1	*Day 1*	*Pre-infusion (any time prior to dose); 30 ±10 min after end of infusion* [d]	*Pre-infusion (any time prior to dose)*	*Pre-infusion (any time prior to dose); 30 ±10 min after end of infusion*	*Predose (anytime prior to dose); 2 hr post-dose (±10 min)* [c]	*Pre-infusion (any time prior to dose)*	*Pre-infusion (any time prior to dose)*
	Day 8	–	–	*Anytime during visit*	–	–	–
	Day 15	–	–	*Anytime during visit*	*Predose (within 15 min prior to dose); 0.5 (± 5 min), 1 (± 5 min), 2 (± 10 min), 4 (± 10 min), 8 hr post-dose (± 30 min)*	–	–
Cycle 2	*Day 1*	*Pre-infusion (within 5 hr prior to dose)*	*Pre-infusion (within 5 hr prior to dose)*	*Pre-infusion (within 5 hr prior to dose); 30 ±10 min after end of infusion*	–	*Pre-infusion (within 5hr prior to dose)*	*Pre-infusion (within 5 hr prior to dose)*

Appendix 4

***Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory DLBCL Patients* (cont.)**

Study Visit		Serum Rituximab PK Sample [a,b]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a,b]	Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE [a]	Plasma Lenalidomide PK Sample [a]	Serum Rituximab HACA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Cycle 4	Day 1	Pre-infusion (within 5 hr prior to dose); 30 ±10 min after end of infusion	Pre-infusion (within 5 hr prior to dose)	Pre-infusion; 30 ±10 min after end of infusion	–	Pre-infusion (within 5hr prior to dose)	Pre-infusion (within 5 hr prior to dose)
Cycle 6	Day 1	Pre-infusion within 5 hr prior to dose); 30 ±10 min after end of infusion	–	Pre-infusion (within 5 hr prior to dose)	2 hr post-dose (±10 min) [c]	Pre-infusion (within 5hr prior to dose)	–
Expansion Phase DLBCL Patients (Induction Treatment; 28-Day Cycles)							
Cycle 1	Day 1	Pre-infusion any time prior to dose); 30 ±10 min after end of infusion [d]	Pre-infusion (any time prior to dose)	Pre-infusion (any time prior to dose); 30 ±10 min after end of infusion	Predose (anytime prior to dose); 2 hr post-dose (±10 min) [c]	Pre-infusion (any time prior to dose)	Pre-infusion (any time prior to dose)
	Day 8	–	–	Anytime during visit	–	–	–
	Day 15	–	–	Anytime during visit	Predose (within 15 min prior to dose); 0.5 (± 5 min), 1 (± 5 min), 2 (± 10 min, 4 (± 10 min), 8 hr post-dose (±30 min)	–	–

Appendix 4

Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory DLBCL Patients (cont.)

Study Visit		Serum Rituximab PK Sample [a,b]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a,b]	Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE [a]	Plasma Lenalidomide PK Sample [a]	Serum Rituximab HACA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Cycle 2	Day 1	Pre-infusion (within 5 hr prior to dose); 30 ±10 min after end of infusion	Pre-infusion (within 5 hr prior to dose)	Pre-infusion (within 5 hr prior to dose); 30 ±10 min after end of infusion	–	Pre-infusion (within 5 hr prior to dose)	Pre-infusion (within 5 hr prior to dose)
Cycle 4	Day 1	Pre-infusion (within 5 hr prior to dose); 30 ±10 min after end of infusion	Pre-infusion (within 5 hr prior to dose)	Pre-infusion (within 5 hr prior to dose); 30 ±10 min after end of infusion	–	Pre-infusion (within 5 hr prior to dose)	Pre-infusion (within 5 hr prior to dose)
Cycle 6 (End of Induction)	Day 1	Pre-infusion (within 5 hr prior to dose); 30 ±10 min after end of infusion	–	Pre-infusion (within 5 hr prior to dose)	2 hr post-dose (±10 min) [c]	Pre-infusion (within 5 hr prior to dose)	–
Consolidation Phase (Post-Induction – DLBCL Patients; 28-Day Cycles)							
Treatment discontinuation		–	Anytime during visit	–	–	Anytime during visit	Anytime during visit
120 days after last dose		–	Anytime during visit	–	–	Anytime during visit	Anytime during visit
1–2 years after last dose		–	Anytime during visit	–	–	Anytime during visit	Anytime during visit

Appendix 4

Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory DLBCL Patients (cont.)

Study Visit	*Serum Rituximab PK Sample* [a,b]	*Serum Polatuzumab Vedotin PK Sample for Total Antibody* [a,b]	*Plasma Polatuzumab Vedotin PK Sample for Antibody Conjugated MMAE and Unconjugated MMAE* [a]	*Plasma Lenalidomide PK Sample* [a]	*Serum Rituximab HACA Sample* [a]	*Serum Polatuzumab Vedotin ATA Sample* [a]

ATA =anti-therapeutic antibody; HACA =human anti-chimeric antibody; " – " =not applicable; PK =pharmacokinetic.

[a] *Sample collection timing is relative to specified drug.*

[b] *Samples collected for PK, HACA, and ATA analysis may be used for additional PK, HACA, and ATA assay development and validation and additionalimmunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.*

[c] *On lenalidomide PK sampling visits, lenalidomide dose will be taken at the clinic appointment.*

[d] *If the Cycle 1 Day 1 dose of rituximab is split over two days, take the 30 minutes post-end of infusion rituximab PK sample relative to the end of the infusion on Day 2 and ensure that the date and time of the PK collection are accurately recorded.*

Appendix 5 *Modified* Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

In this study, the designation of a complete response (CR) using positron emission tomography and computed tomography (PET-CT)–based response, requires normal bone marrow by morphology for patients with bone marrow involvement at baseline. If indeterminate by morphology, immunohistochemistry should be negative. *Additionally, designation of PET-CT based PR requires that CT-based response criteria for a CR or PR be met in addition to the PET-CT based response criteria for a PR.*

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] 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.	Target nodes/nodal masses must regress to $\leq$ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Appendix 5
Modified Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease.	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease.	When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable

Appendix 5
Modified Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	$<$50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Appendix 5
Modified Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following:
Individual target nodes/nodal masses	Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisting non-measured lesions

Appendix 5
Modified Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

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

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

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured 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 (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

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

Appendix 6
ECOG Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about $>$50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair $>$50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 7
Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine clearance (men)} = \frac{(140 - \text{Age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine clearance (women)} = \frac{0.85 \times (140 - \text{Age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Taken from: Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine [editorial]. Nephron 1992;62:249.

Appendix 8
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous (IV), and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

- Stop the study treatment infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer glucocorticoids, antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 9
Ann Arbor Staging

Grade	Description
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) [a]
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES)
Stage IV [b]	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

Note: All cases are subclassified to indicate the absence (A) or presence (B) of the systemic B symptoms of significant unexplained fever (>38°C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

[a] The designation "E" generally refers to extranodal contiguous extension (i.e., proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the only site of disease should be classified as IE, rather than Stage IV.

[b] Involvement of bone marrow at screening will always qualify for Ann Arbor Stage IV and should be recorded as extranodal involvement.

Adapted from:

Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971;31:1860–1.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. J Clin Oncol 1989;7:1630–6.

Appendix 10
Follicular Lymphoma International Prognostic Index and International Prognostic Index

Table 1 Follicular Lymphoma International Prognostic Index

FLIPI Risk Factor
Ann Arbor Stage III or IV
Age >60 years
Serum LDH $>1\times$ULN
Anemia (hemoglobin <120 g/L)
Involved nodal areas >4

FLIPI Risk Group	Number of FLIPI Risk Factors
Low	0–1
Intermediate	2
High	3–5

FDG = fluorodeoxyglucose; FLIPI = Follicular Lymphoma International Prognostic Index; PET = positron emission tomography; ULN = upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of FLIPI since this prognostic score was established without FDG-PET.

Adapted from: Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258–64.

Appendix 10
Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

Table 2 Follicular Lymphoma International Prognostic Index 2

FLIPI2 Risk Factor
Bone marrow involvement
Age >60 years
$\beta 2$ microglobulin $>1\times$ ULN
Anemia (hemoglobin <120 g/L)
Longest diameter of largest involved node >6 cm

FLIPI2 Risk Group	Number of FLIPI2 Risk Factors
Low	0
Intermediate	1–2
High	3–5

FDG = fluorodeoxyglucose; FLIPI2 = Follicular Lymphoma International Prognostic Index 2; PET = positron emission tomography; ULN = upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of FLIPI2 since this prognostic score was established without FDG-PET.

Adapted from: Federico M, Bellei M, Marcheselli L, et al. Follicular Lymphoma International Prognostic Index 2: a new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009;27:4555–62.

Appendix 10
Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

Table 3 International Prognostic Index

IPI Risk Factor
Ann Arbor Stage III or IV
Age > 60 years
Serum LDH > 1 × ULN
ECOG Performance Status ≥ 2
Extranodal involvement ≥ 2

IPI Risk Group	Number of IPI Risk Factors
Low	0 or 1
Low – Intermediate	2
High – Intermediate	3
High	4 or 5

ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; IPI = International Prognostic Index; PET = positron emission tomography; ULN = upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of IPI since this prognostic score was established without FDG-PET.

Adapted from: Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987–94.

Appendix 11
Treatment of Relapsed or Refractory Follicular and Diffuse Large B-Cell Lymphomas

Table 1 Treatment Regimens for Relapsed or Refractory Follicular Lymphoma

	Single Agents			Doublet Anti-CD20 + Polatuzumab Vedotin		Doublet Anti-CD20 + Lenalidomide		
	Obinutuzumab [a]	Polatuzumab Vedotin [b]	Lenalidomide [c]	R + Pola [d]	G + Pola (GO27834)	R-Len [e]	R + Len [f]	G + Len [g]
Number of patients	22 (20 FL, 1 MZL, 1 SLL)	47	43 (22 FL, 18 SLL, 3 MZL)	20	46 (will enroll)	27 (iNHL)	44	19
Anti-CD20 dose	G: 1600/800 mg	–	–	R: 375 mg/m^2 Q3W × 8 cycles	G: 1000 mg D1, 8, 15 in C1, then D1 in C2-8	R: 375 mg/m^2 on D15 in C1, then QW × 4 doses	R: 375 mg/m^2 QW × 4	G: 1000 mg D8, 15, 22 in C1, then D1 in C2-6
Pola dose	–	2.4 mg/kg (n = 43) 1.8 mg/kg (n = 4)	–	1.8 mg/kg	1.8 mg/kg	–	–	–
Len dose	–	–	25 mg D1-22/28 × 52 weeks	–	–	25 mg D1-22/28 × 52 weeks	15 mg in C1, then 20 mg in C2-12 on D1-22/28 × 12	10, 15, 20, 25 mg on D1-21 in C1, then D2-22 C2-6
ORR CR/CRu DoR PFS	54.5% 9.1% 17.2 m 11.9 m	52% (DLBCL)/53% iNHL 10% (DLBCL)/20% iNHL – 151 d (DLBCL)/264 d (iNHL)	27% 9% > 16.5 m (all pt) 4.4 m (all pt)	75% 10% – NR	Results not available	74% 44% 15.4 m 12.4 m	75% 32% – 2 year	68% 10 pt – –
Heme toxicity & infection (Grade 3/4)	Neutropenia (n = 3) FN (n = 1) TCP (n = 1) Infection (n = 1)	Neutropenia (n = 5)	Neutropenia 46% FN 2% TCP 20%	Neutropenia 35% FN 10%	Results not available	Neutropenia 55%	Neutropenia 19%	Neutropenia 53% Infection 37%

Appendix 11
Treatment Regimens for Relapsed or Refractory Follicular and Diffuse Large B-Cell Lymphomas (cont.)

	Single Agents			Doublet Anti-CD20 + Polatuzumab Vedotin		Doublet Anti-CD20 + Lenalidomide		
	Obinutuzumab [a]	Polatuzumab Vedotin [b]	Lenalidomide [c]	R + Pola [d]	G + Pola (GO27834)	R-Len [e]	R + Len [f]	G + Len [g]
Neuro-toxicity	NR	Grade 1/2: 42% Grade 3/4: 10%	NR	Grade 2-4: 25%	Results not available	NR	NR	NR

C = cycle; CR = complete response; CRu = CR unconfirmed; D = day; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; FL = follicular lymphoma; FN = febrile neutropenia; G = obinutuzumab; iNHL = indolent non-Hodgkin's lymphoma; Len = lenalidomide; m = months; MZL = marginal zone lymphoma; NR = not reported; ORR = overall response rate; PFS = progression-free survival; Pola = polatuzumab vedotin; pt = patients; Q3W = every 3 weeks; QW = once per week; R = rituximab; SLL = small lymphocytic lymphoma; TCP = thrombocytopenia; wk = week.

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Appendix 11
Treatment Regimens for Relapsed or Refractory Follicular and Diffuse Large B-Cell Lymphomas (cont.)

Table 2 Treatment Regimens for Relapsed or Refractory DLBCL

	Single Agents				Doublet Anti-CD20 + Polatuzumab Vedotin		Doublet Anti-CD20 + Lenalidomide	
	Obinutuzumab [a]	Polatuzumab Vedotin [b]	Lenalidomide [c]	Lenalidomide [d]	R + Pola [e]	G + Pola (GO27834)	R + Len [f] ()	R +Len [g,h]
Number of patients	19 (15 DLBCL, 4 MCL)	47	26	108	39	46 (will enroll)	45	23
Anti-CD20 dose	G: 1600/800 mg	–	–	–	R: 375 mg/m^2	G: 1000 mg D1, 8, 15 in C1, then D1 in C2-8	R: 375 mg/m^2	R: 375 mg/m^2
Pola dose	–	2.4 mg/kg (n = 43) 1.8 mg/kg (n = 4)	–	–	2.4 mg/kg	1.8 mg/kg	–	–
Len dose	–	–	25 mg D1-22/28 × 52 wk	25 mg D1-22/28 until PD		–	20 mg D1-22/28 × 52 wk	15 mg in C1, then 20 mg in C2-12 on D1-22/28 × 52 wk
ORR CR/CRu DoR PFS	32% 0% 9.8 m 2.7 m	52% (DLBCL)/53% iNHL 10% (DLBCL)/20% iNHL – 151 d (DLBCL)/264 d (iNHL)	19% 12% – –	28% 7% 4.6 m 2.7 m	56% 15% – 5.4 m	Results not available	33% 20% 10.2 m 3.7 m	35% 30% 32 m 1-year DFS: 35%

Appendix 11
Treatment Regimens for Relapsed or Refractory Follicular and Diffuse Large B-Cell Lymphomas (cont.)

	Single Agents				Doublet Anti-CD20 + Polatuzumab Vedotin		Doublet Anti-CD20 + Lenalidomide	
	Obinutuzumab [a]	Polatuzumab Vedotin [b]	Lenalidomide [c]	Lenalidomide [d]	R + Pola [e]	G + Pola (GO27834)	R + Len [f] ()	R + Len [g,h]
Heme toxicity & infection (Grade 3/4)	Neutropenia (n = 1)	Neutropenia (n = 5)	Neutropenia 33% FN 6%	Neutropenia 41% FN 2%	Neutropenia 24% FN 4%	Results not available	Neutropenia 53% FN 34%	Neutropenia 30% FN 14%
Neuro-toxicity	NR	Grade 1/2: 42% Grade 3/4: 10%	NR	NR	39% (any grade)	Results not available	NR	NR

Appendix 11
Treatment Regimens for Relapsed or Refractory Follicular and Diffuse Large B-Cell Lymphomas (cont.)

	Single Agents				Doublet Anti-CD20 + Polatuzumab Vedotin		Doublet Anti-CD20 + Lenalidomide	
	Obinutuzumab [a]	Polatuzumab Vedotin [b]	Lenalidomide [c]	Lenalidomide [d]	R + Pola [e]	G + Pola (GO27834)	R + Len [f] ()	R + Len [g,h]

C = cycle; CR = complete response; CRu = CR unconfirmed; D = day; DFS = disease-free survival; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; FL = follicular lymphoma; FN = febrile neutropenia; G = obinutuzumab; iNHL = indolent non-Hodgkin's lymphoma; Len = lenalidomide; m = months; MCL = mantel zone lymphoma; NR = not reported; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; Pola = polatuzumab vedotin; pt = patients; Q3W = every 3 weeks; QW = once per week; R = rituximab; SLL = small lymphocytic lymphoma; TCP = thrombocytopenia; wk = week.

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Appendix 12
Diagnostic Criteria for Tumor Lysis Syndrome

	Lab Value Threshold	
Lab Changes	*Uric acid*	*≥ 476 µmol/L (8 mg/dL)*
	Potassium	*≥ 6mmol/L (6 mEq/L)*
	Phosphorus	*≥ 1.45 mmol/L (4.5 mg/dL)*
	Calcium	*≤ 1.75 mmol/L (7 mg/dL)*
Cairo-Bishop Definition	*2 or more of above lab changes or if change is more than 25% from baseline*	*Laboratory TLS*
	Occurs within 3 days before or 7 days after therapy	
	Laboratory TLS accompanied by cardiac arrhythmia, sudden death, seizure, or acute renal failure (serum creatinine ≥ 1.5× ULN)	*Clinical TLS*
Howard Definition (in addition to Cairo-Bishop definition)	*2 or more above lab changes occur simultaneously*	*Laboratory TLS*
	25% change is not a criteria	
	Symptomatic hypocalcemia	*Clinical TLS*

TLS =Tumor Lysis Syndrome; ULN =upper limit of normal.