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

NCT Number: NCT02611323

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PROTOCOL

TITLE: **A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR** ***LYMPHOMA AND RITUXIMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA***

PROTOCOL NUMBER: GO29833

VERSION NUMBER: 4

EUDRACT NUMBER: 2015-001998-40

IND NUMBER: 115045

TEST PRODUCTS: Obinutuzumab (RO5072759)
Rituximab (RO0452294)
Polatuzumab vedotin (DCDS4501A; RO5541077)
Venetoclax (GDC-0199; ABT-199; RO5537382)

MEDICAL MONITOR: [redacted], Pharm.D.

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 15 July 2015

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Version 3: 1 August 2016
Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	[redacted]	17-Jan-2017 20:07:21

PROTOCOL AMENDMENT, VERSION 4
RATIONALE

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 venetoclax in combination with rituximab instead of obinutuzumab (see Section 3.3.1). 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 prednisone (CHOP) chemotherapy in patients with previously untreated DLBCL did not improve the primary endpoint of progression-free survival (PFS) compared with the standard regimen of rituximab + CHOP chemotherapy.

  The background (Section 1.2), rationale (Sections 1.5 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 venetoclax when combined with rituximab and polatuzumab at the 1.8 mg/kg dose level. Only venetoclax dosing will be escalated (Sections 3.1.2 and 3.1.3).

- Rituximab will be provided by the Sponsor as an investigational medicinal product. This addition of rituximab 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 (Section 5.1.5) have been updated accordingly.
- 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 Polatuzumab Vedotin Investigator's Brochure, Version 7 (July 2016).
- 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).
- The classification of second malignancies has been changed from a selected adverse event to an adverse event of special interest in order to monitor this adverse event more closely (Section 5.2.3).
- 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 7 and Table 13 have been updated accordingly.
- The defined primary populations to be analyzed have been changed to include patients who received at least one dose of <u>any</u> component of the combination (Section 6.3)

- The interim analysis was clarified to state 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 exploratory efficacy objective was clarified: If a patient with DLBCL has a positive PET-CT at end of induction, then they should have PET-CT repeated at end of consolidation (Section 2.2.3, Section 6.6.3, and footnote "cc" in Appendix 2)
- Duplicate sentence in Section 3.1.2.1.2 was removed as this sentence occurs later in the section on hospitalization for TLS (Section 5.1.6.2): "Patients determined by the investigator to be at particularly high risk for TLS may, in addition to hospitalization, delay the start of venetoclax to Day 8 in Cycle 1 following discussion with the Medical Monitor."
- The exclusion criteria for monoclonal antibodies and antibody–drug conjugate therapy have been clarified to consider half-lives in washout period (Section 4.1.2).
- The safety of immunization was clarified to include both live and attenuated viral vaccines following obinutuzumab therapy (Section 5.1.1.6).
- The number of patients in the study has been updated (Sections 3.1.1, 3.1.2, and 6.1).
- The immunogenicity analysis was updated to clarify that human anti-human antibodies will be collected for patients receiving obinutuzumab (Section 6.8).
- The time window for drawing β_2 microglobulin and quantitative IgA, IgG, and IgM as predose collections on C1D1 was included (footnote "o" in Appendix 1; footnote "o" in Appendix 2).
- The pharmacokinetic and immunogenicity sampling schedule time windows were clarified (Appendix 3 and Appendix 4).

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

PROTOCOL AMENDMENT, VERSION 4:
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 currently under investigation in a large clinical program, including multiple Phase III studies versus rituximab in indolent NHL and DLBCL~~*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.*

SECTION 1.2.2: Clinical Studies with Obinutuzumab

As of ~~31 October 2014~~ *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/IIIb studies (BO21004, GAO4753g, BO21005, BO21223, and MO28543) in patients with NHL or CLL. Available safety results from all patients and efficacy results from the NHL cohorts in these studies are summarized in Sections 1.2.2.1 and 1.2.2.2, respectively. Efficacy data from a Phase III study of obinutuzumab (GAO4753g) are also presented.

SECTION 1.2.2.1: Clinical Safety of Obinutuzumab

As of the safety data cutoff date of ~~31 October 2014~~ *4 July 2016*, an estimated *3636* ~~3484~~ patients with NHL (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 mg to 2000 mg. The overall safety and toxicity profile of obinutuzumab as monotherapy and as combination therapy was manageable.

[…]

Other important risks associated or potentially associated with obinutuzumab are tumor lysis syndrome (TLS), thrombocytopenia (including acute thrombocytopenia), neutropenia *(including prolonged and late onset neutropenia)*, prolonged B-cell depletion, infections (including progressive multifocal leukoencephalopathy [PML] and hepatitis B virus [HBV] reactivation), worsening of preexisting cardiac conditions, impaired immunization response, immunogenicity, gastrointestinal perforation, 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.

SECTION 1.2.2.2: Clinical Efficacy of Obinutuzumab in Patients with Non-Hodgkin's Lymphoma

In *early* studies of obinutuzumab in combination with chemotherapy (i.e., CHOP or bendamustine) in patients with previously untreated or R/R NHL (Studies BO21000, GAO4915g, and GAO4753g), the proportion of patients with a CR or PR at the end of induction 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.

A Phase III study, GAO4753g, investigated obinutuzumab plus bendamustine (GB) compared with bendamustine alone in patients with rituximab-refractory indolent NHL (n=396). Patients in the GB group who had not experienced disease progression at the end of induction 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 (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).*

A Phase III 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 indolent non-Hodgkin's lymphoma (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).*

A Phase III study, BO21005, investigated obinutuzumab plus CHOP (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 venetoclax (Vitolo et al. 2016).

SECTION 1.3.2: Clinical Studies with Polatuzumab Vedotin

Clinical data on polatuzumab vedotin in patients with NHL or CLL are available ~~as of February 2014~~ from one completed Phase I/Ib study (DCS4968g) and ~~one~~*the* ongoing Phase Ib/II ~~study~~*studies* (GO27834, ~~) and as of June 2014 from one ongoing Phase Ib/II study (~~, GO29044~~)~~*, GO29834, 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 R-CHP or 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.

GO29834 is evaluating polatuzumab vedotin in combination with lenalidomide and either obinutuzumab or rituximab in patients with R/R FL or DLBCL.

BO29561 is evaluating polatuzumab vedotin in combination with atezolizumab and either obinutuzumab or rituximab in patients with R/R FL or DLBCL.

Available safety results and efficacy results from these studies are summarized in Section 1.3.2.1 and Section 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 focused 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 Safety of Polatuzumab Vedotin

Clinical safety data are available from ~~180~~*327* patients with NHL 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 obinutuzumab or rituximab plus CHP (GO29044), and 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 mg/kg and 1.4 mg/kg) in combination with R-CHP in Study GO29044. 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 obinutuzumab or rituximab plus 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 rituxumab 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 in patients treated with polatuzumab vedotin combined with rituximab or obinutuzumab. The majority of deaths were judged as related to disease progression.

SECTION 1.3.2.2: Clinical Efficacy of Polatuzumab Vedotin in Patients with Non-Hodgkin's 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) for the 2.4 mg/kg dose and 6.6 months (95% CI: 2.3, 11.4) 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) for patients with indolent B-cell lymphoma and 5.0 months (95% CI: 2.3, 6.8) for patients with DLBCL. Median PFS was 4.6 months (95% CI: 1.4, 13.9) 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 R/R indolent NHL (FL, MZL, or SLL) and 4.9 months (95% CI: 2.5, 6.7 months) for patients with R/R 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 the 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).

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

~~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).~~

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) 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, 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 patients with CR) when combined with obinutuzumab.

SECTION 1.5: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Progress has been made in the treatment of FL and DLBCL; however, a significant number of patients will not be cured of their disease. Instead, they will experience relapse or die of progression or treatment-related toxicity. Patients who relapsed after receiving several prior treatments may not be able to tolerate more bone marrow toxicity, which limits their treatment options. There is a need for the continued development of safe and effective therapies for patients with disease that relapses or for those 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 venetoclax.

[…]

Obinutuzumab has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). *Obinutuzumab was also shown to be superior compared to rituximab when combined with chemotherapy in a Phase III trial (BO21223) in previously untreated FL patients (Marcus et al. 2016).* ~~Obinutuzumab is being compared with rituximab in two large Phase III studies, one study (BO21005) in patients with previously untreated DLBCL and one study (BO21223) in patients with previously untreated iNHL, including FL. Assuming that these studies demonstrate greater clinical benefit with obinutuzumab versus rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of incorporating obinutuzumab into treatment regimens. A fourth~~*The* Phase III study~~,~~ GAO4753g investigated obinutuzumab combined with bendamustine followed by obinutuzumab maintenance compared with bendamustine alone in patients with rituximab-refractory iNHL, including FL, *and showed improvement in PFS in the GB arm* (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 comparing R-CHOP to G-CHOP in patients with previously untreated DLBLC (BO21005; 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 venetoclax.

[…]

Obinutuzumab, *rituximab,* polatuzumab vedotin, and venetoclax are known to deplete circulating B cells and tumor burden, which may potentially impact the target-mediated clearance of obinutuzumab, *rituximab,* and polatuzumab vedotin. In R/R FL and DLBCL, the baseline B-cell count is very low; therefore, the likelihood of

pharmacodynamics (B-cell) mediated drug-drug interaction (DDI) is relatively low. This was confirmed by the observation that no interaction was observed between polatuzumab and rituximab in R/R FL and DLBCL.

[…]

Available nonclinical and clinical data suggest that there is a strong rationale to expect an improved benefit-risk profile with the triplet combination of obinutuzumab *or rituximab*, polatuzumab vedotin, and venetoclax. This novel triplet regimen may have the potential to extend treatment-free remissions and decrease toxicity by improving upon individual agents used as part of current standard of care. Patients with overlapping toxicities will be closely monitored; such events are expected to be manageable in the clinical setting (see Section 5.1.5).

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 venetoclax (G+Pola+V) in patients with R/R FL ~~or DLBCL~~ *and rituximab in combination with polatuzumab vedotin and venetoclax (R +Pola + V) in patients with R/R DLBCL~~,~~. Induction will be* followed by post-induction treatment with G+V *(referred to as maintenance)* in patients with FL who achieve a CR, PR, or stable disease at end of induction (EOI) and *post-induction treatment with R + V (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 in Sections 2.1–2.5.

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

SECTION 2.1: SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To determine the RP2D for polatuzumab vedotin and venetoclax when given in combination with a fixed dose of obinutuzumab *and the RP2D of venetoclax when given in combination with a fixed dose of polatuzumab vedotin* 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+V *and R +Pola + V* on the basis of the following outcome measures *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 G+Pola+V *in patients with R/R FL and R +Pola +V in patients with 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 G+Pola+V *and maintenance treatment with G +V in patients with R/R FL and R +Pola +V and consolidation treatment with R +V in patients with 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

SECTION 2.2.3: Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of G+Pola+V *and R +Pola +V* 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 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 (DFS), defined, among patients who achieve 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
- OS, defined as the time from initiation of study treatment to death from any cause

SECTION 2.3: PHARMACOKINETIC OBJECTIVE

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

- Observed serum concentration of obinutuzumab at specified timepoints
- *Observed serum concentration of rituximab at specified timepoints*
- Observed serum and plasma concentrations of polatuzumab vedotin and relevant analytes (total antibody, antibody-conjugated MMAE [acMMAE] and unconjugated MMAE) at specified timepoints
- Observed plasma concentration of venetoclax at specified timepoints

SECTION 3.1.1: Overview of Study

This is a Phase Ib/II, open-label, multicenter, non-randomized study that will evaluate the safety, efficacy, and pharmacokinetics of G+Pola+V in patients with R/R FL *and R+Pola+V in patients with R/R DLBCL.* ~~or DLBCL. The study will include an initial dose-escalation phase designed to determine the RP2D for polatuzumab vedotin and the RP2D for venetoclax in this treatment combination, followed by an expansion phase during which polatuzumab vedotin and venetoclax will be given at their RP2Ds (see Section 3.1.2.2). Patients will receive induction treatment with obinutuzumab, polatuzumab vedotin, and venetoclax as outlined in Section 3.1.2. Patients with FL who achieve a CR, PR, or SD at EOI and patients with DLBCL who achieve a CR or PR at EOI will receive post induction treatment with obinutuzumab and venetoclax (see Section 3.1.2 for details).~~

The study will include an initial dose-escalation phase followed by an expansion phase during which polatuzumab vedotin and venetoclax will be given at their RP2Ds (see Sections 3.1.2 and 3.1.2.2). Patients will receive induction treatment with obinutuzumab or rituximab, polatuzumab vedotin, and venetoclax as outlined in Sections 3.1.2 and 3.1.3. Patients with FL who achieve a CR, PR, or SD at EOI will receive post-induction treatment with obinutuzumab and venetoclax, and patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment with rituximab and venetoclax (see Sections 3.1.2 and 3.1.3 for details). A study schema is provided in Figure 2.

Approximately ~~104–119~~*113–134* patients are expected to be enrolled in this study at approximately 20–25 investigative sites worldwide.

[…]

To characterize the PK properties of obinutuzumab, *rituximab,* polatuzumab vedotin, and venetoclax, blood samples will be obtained at various timepoints before and during study treatment administration (see Appendix 3 and Appendix 4).

FIGURE 2: Study Schema

Figure 2 has been revised to include rituximab.

SECTION 3.1.2: ***Obinutuzumab Plus Polatuzumab Vedotin Plus Venetoclax Treatment Group (Patients with Follicular Lymphoma)***

This is a new section heading to highlight the distinct patient groups.

SECTION 3.1.2.1: ***Follicular Lymphoma*** **Dose-Escalation Phase**

The purpose of the *FL* dose-escalation phase is to identify the RP2D for polatuzumab vedotin and the RP2D for venetoclax when combined with a fixed dose of obinutuzumab as induction treatment. ~~The~~*This* dose-escalation phase will include FL patients only; these patients may receive post-induction treatment if eligible. The RP2D will be based on the maximum tolerated doses (MTDs) and the totality of data for polatuzumab vedotin and venetoclax.

Approximately ~~24~~*21*–39 patients will be enrolled in the *FL* dose-escalation phase. Initially, the study enrolled 3 patients starting in Cohort 1 at a dose level of 400 mg venetoclax and 1.4mg/kg polatuzumab vedotin. With Amendment 3, Cohort 1a ~~has been~~*was* added to the dose-escalation phase with a starting dose level of 200 mg venetoclax and 1.4mg/kg polatuzumab vedotin. The original Cohort 1 dose level combination will be repeated to gather additional safety data in this dose level. Dosing cohorts of 3–6 patients each will be treated in accordance with the treatment regimen and dose-escalation rules described in Sections 3.1.2.1.2 and 3.1.2.1.3, respectively.

Patients will be closely monitored for adverse events during a DLT assessment window, which will be defined as the first treatment cycle (from Day 1 of Cycle 1 to Day 1 of Cycle 2). Adverse events that meet the criteria for DLT, as defined in 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 completion of the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD 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 venetoclax 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.

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

~~Patients determined by the investigator to be at particularly high risk for TLS may, in addition to hospitalization, delay the start of venetoclax to Day 8 in Cycle 1 following discussion with the Medical Monitor.~~

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

The Table 1 title has been revised to specify the FL group.

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

The Table 2 title has been revised to specify the FL group.

SECTION 3.1.2.1.3: Dose-Escalation Rules

Intrapatient dose escalation will be allowed only for the Cohort 1a patients receiving 200 mg of venetoclax. In this cohort, the venetoclax dose may be escalated from 200 mg to 400 mg once Cohorts 2 and 3 open after approval by the Medical Monitor. Intrapatient dose escalation is not allowed in other cohorts. The ~~overall~~*FL* dose-escalation plan is depicted in Figure 3, and the doses for each cohort are summarized in Table 3.

[…]

Relevant demographic, adverse event, laboratory, dosing 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 (from Day 1 of Cycle 1 to Day 1 of Cycle 2), cumulative or late toxicities that occur beyond the first cycle may be considered in determination of 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 3: ~~Overall~~ *Follicular Lymphoma* Dose-Escalation Plan

The Figure 3 title has been revised to specify the FL group.

TABLE 3: *Follicular Lymphoma* Dose-Escalation Cohorts

The Table 3 title has been revised to specify the FL group.

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 venetoclax 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.

All patients enrolled in the expansion phase will receive induction treatment, administered in 21-day cycles as outlined in Table 4. When study treatments are given

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

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment. ~~Patients with DLBCL who achieve a CR or PR at EOI will receive post induction treatment (referred to as consolidation) with obinutuzumab and venetoclax, and patients~~*Patients* with FL who achieve a CR, PR, or SD at EOI will receive post-induction treatment (referred to as maintenance) with obinutuzumab and venetoclax, as outlined in Table 5. Polatuzumab vedotin will not be given as post-induction treatment. Post-induction treatment will continue until disease progression or unacceptable toxicity for up to ~~8 months for consolidation treatment or~~ 24 months for maintenance treatment. When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab.

The schedules of assessments are provided in Appendix 1 (FL). ~~and Appendix 2 (DLBCL).~~

TABLE 4: Induction Treatment for *the Follicular Lymphoma* Expansion Phase

The Table 4 title has been revised to specify that the treatment is relevant to the FL group.

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

The Table 5 title has been revised to specify that the treatment is relevant to the FL group. In addition, the treatment information about the consolidation treatment for patients with DLBCL has been removed.

SECTION 3.1.3: *Rituximab Plus Polatuzumab Vedotin Plus Venetoclax Treatment Group (Patients with DLBCL)* (NEW SECTION)

Based on the safety and efficacy results from the Phase III study (BO21005) in patients with DLBCL, the protocol has been amended to explore dose-finding of venetoclax 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 in Relapsed or Refractory DLBCL Patients* (NEW SECTION)

The DLBCL dose-escalation phase will open with the purpose of identifying the RP2D for venetoclax 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 venetoclax 400-mg dose level and increase through Cohorts A, B, and C (see Figure 4).

Approximately 12–18 patients will be enrolled in the DLBCL 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 3.1.3.1.2.

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 above (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 dose of polatuzumab vedotin or rituximab or five consecutive daily doses of venetoclax 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 + V for a total of six cycles. Patients achieving a CR or PR at EOI will be eligible to receive consolidation treatment with R + V. A study schema is provided in Figure 2.

SECTION 3.1.3.1.1: *Treatment Regimens for DLBCL Dose-Escalation Phase* (NEW SECTION)

Patients enrolled in the DLBCL dose-escalation phase will receive induction treatment, administered in 21-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: venetoclax, rituximab, and polatuzumab vedotin.

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment (referred to as consolidation). Patients who achieve a CR or PR at EOI will receive consolidation treatment with rituximab and venetoclax, as outlined in Table 7. Polatuzumab vedotin will not be given as consolidation treatment. Consolidation treatment will continue until disease progression or unacceptable toxicity for up to 8 months. When study treatments are given on the same day, venetoclax will be administered prior to rituximab.

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 DLBCL Dose-Escalation Phase***

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

SECTION 3.1.3.1.2: ***Dose-Escalation Phase Rules*** **(NEW SECTION)**

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 venetoclax 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 4 and Table 8.

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 venetoclax in the R +Pola +V 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 MTD venetoclax in the R +Pola +V 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 venetoclax in the R +Pola +V treatment combination.*

If the MTD is exceeded in any cohort, de-escalation of the venetoclax dose and/or polatuzumab vedotin dose, and/or adjustment of treatment schedules (e.g., venetoclax 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, dosing administration/intensity, and PK (if available) data will be reviewed 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 (from Day 1 of Cycle 1 to Day 1 of Cycle 2), cumulative or late toxicities that occur beyond the first cycle may be considered in determination of 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 information with the IMC for approval.

FIGURE 4: ***DLBCL Dose-Escalation Plans***

Figure 4 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 venetoclax 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: venetoclax, rituximab, and polatuzumab vedotin.

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment. Patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with rituximab and venetoclax, as outlined in Table 10. Polatuzumab vedotin will not be given as post-induction treatment. Post-induction treatment will continue until disease progression or unacceptable toxicity for up to 8 months for consolidation treatment. When study treatments are given on the same day, venetoclax will be administered prior to rituximab.

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

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

TABLE 10: *Consolidation 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 FL patients 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 DLBCL patients 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 4.5 years.

SECTION 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 active and well-tolerated agents are needed following relapse. 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, which highlights the urgent need for novel therapeutic approaches for these patients.

On the basis of a compelling biologic and clinical rationale, as presented in Section 1.5 the addition of polatuzumab vedotin to obinutuzumab *or rituximab* and venetoclax is a promising approach to expand the number of patients with *R/R* FL and DLBCL who achieve remission and to prolong the duration of response 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 venetoclax and the RP2D for polatuzumab vedotin when given with obinutuzumab *in patients with R/R FL and the RP2D for venetoclax 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.~~

SECTION 3.3.2: Rationale for the Triplet Combination

This study combines treatments with different mechanisms of action that have demonstrated clinical activity against B-cell lymphoma. Refer to Appendix 12 for descriptions of clinical studies that use the study drugs as single or doublet treatment.

As mentioned in Section 1.5, there is a strong rationale to expect an improved benefit-risk profile with the triplet combination of obinutuzumab~~,~~ *or rituximab combined with* polatuzumab vedotin~~,~~ and venetoclax. 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 5.1.6).

Rituximab is established as a standard of care to treat B-cell lymphomas. 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 (Study BO21005) and FL (Study BO21223).

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 obinutuzumab plus CHOP (G-CHOP) compared with rituximab plus CHOP (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, current protocol amendment patients with R/R FL will continue to receive obinutuzumab in combination with polatuzumab vedotin and venetoclax, while patients with R/R DLBCL will instead receive rituximab in combination with polatuzumab vedotin and venetoclax.

SECTION 3.3.3.1: Rationale for Obinutuzumab Dosing Regimen *in Follicular Lymphoma Patients*

The dose and schedule of obinutuzumab in the induction regimen *for FL patients* will be 1000 mg intravenously (IV) on Days 1, 8, and 15 of Cycle 1 and Day 1 of each subsequent 21-day cycle (Cycles 2–6). This is based on the recommended dose and schedule (6–8 cycles depending on the trial) of obinutuzumab in the ongoing Phase III program in patients with NHL. 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 GAO4753g study (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 up~~

~~to 6 months. The consolidation regimen was modeled after the FL maintenance therapy.~~
The GAO4753g study 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 plus bendamustine followed by obinutuzumab maintenance arm vs. 14.9 months in the bendamustine arm; stratified HR = 0.55; 95% CI: 0.40, 0.74; p = 0.0001, by log-rank test).

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

For this study, dose escalation of polatuzumab vedotin for R/R FL patients 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 polatuzumab vedotin dosing for ~~this study~~*the FL dose escalation phase* is 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 R/R NHL, the majority of whom had R/R FL or DLBCL. Most evidence of anti-tumor activity was observed at doses ≥ 1.8 mg/kg alone or in combination with rituximab (Advani et al. 2015; Palanca-Wessels et al. 2015).

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 R/R DLBCL and in R/R NHL 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 G-bendamustine. Since polatuzumab vedotin is being combined with obinutuzumab and chemotherapy (CHP or bendamustine) at 1.4 mg/kg or 1.8 mg/kg, dose escalation of polatuzumab vedotin *for the patients with R/R FL in this study* will begin at a dose level of 1.4 mg/kg (1 dose level below the highest allowed polatuzumab vedotin dose) and will escalate to a final dose of 1.8 mg/kg, if tolerated. This novel triplet, G + Pola + V, substitutes out the standard chemotherapy components with venetoclax, 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 plus Obinutuzumab-Containing Regimens for the Treatment of *Follicular* Lymphoma

Table 11 has been revised to include follicular lymphoma and delete the R/R DLBCL population treatment information.

SECTION 3.3.3.2.2: *Rationale for Polatuzumab Vedotin Dose in DLBCL Patients*

On the basis of the preliminary data from the DLBCL patients treated in Studies GO29044 and GO29365 at the dose level of polatuzumab vedotin at 1.8 mg/kg, this dose 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 preferredto 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 and venetoclax. In this amdendment, the R/R DLBCL dose-escalation phase will start at the dose level of 1.8 mg/kg and only the venetoclax dose will be escalated to determine an RP2D in this population.

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

The number of induction cycles (six 21-day cycles) ~~of this regimen (G+Pola+V) that will be evaluated in this study is similar to~~ *is in line with* other anti-CD20 plus polatuzumab vedotin regimens studied in R/R NHL.

SECTION 3.3.3.3: Rationale for Venetoclax Dosing Regimen

In patients with R/R FL, the starting dose of venetoclax in this study will be 200 mg. *Because a case of laboratory TLS in a FL patient treated in this trial at a dose level of 400 mg venetoclax and 1.4 mg/kg polatuzumab has been observed, the* lower venetoclax dose level cohort of 200 mg was added in order to collect additional safety information for this novel triplet combination. Given that venetoclax will be given in conjunction with obinutuzumab and polatuzumab vedotin, potentially resulting in synergistic toxicities, doses of venetoclax up to the MTD achieved when given as monotherapy may not be tolerable in this combination. Following the 200 mg Cohort 1a clearing, subsequent dose cohorts will explore progressively higher starting and target doses up to a final daily dose of 800 mg if tolerated. The number of cycles of dosing (six 21-day cycles) is designed to provide a treatment duration consistent with other therapies for NHL that have been shown to be sufficient to provide durable responses.

In patients with R/R DLBCL, the starting dose of venetoclax in the dose-escalation phase will be 400 mg (Figure 4). Ongoing studies in the DLBCL population have confirmed that the TLS risk with doses up to 800 mg is low. No cases of TLS occurred in DLBCL patients in a trial with 800 mg venetoclax given intermittently at Days 4–10 of Cycle 1 and Days 1–10 of Cycles 2–8 in combination with R-CHOP (Zelenetz et al. 2016). The duration of venetoclax dosing is designed to provide

overlapping exposure with obinutuzumab *or rituximab*. Extended dosing of venetoclax up to 1 year with obinutuzumab *or rituximab* will allow exploration of whether additional activity is observed during the extended (post-induction) dosing period.

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, *8*~~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 3 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 + V treatment group*: R/R FL after treatment with at least 1 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: B-cell lymphoma classified as either of the following:~~
    - ~~R/R FL after treatment with at least 1 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~~
- *ForR + Pola + V treatment group:* R/R DLBCL after treatment with at least 1 prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody, with no curative option as determined by the investigator
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 12 months after the last dose of polatuzumab vedotin, 30 days after the last dose of venetoclax, and *12 months after last dose of rituximab, or* 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 (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal

contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

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, 30 days after the last dose of venetoclax, and 3 months after the last dose of obinutuzumab *or rituximab*. Men must refrain from donating sperm for the 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, 30 days after the last dose of venetoclax, and 3 months after the last dose of obinutuzumab *or rituximab*.

  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

- Prior standard or investigational anti-cancer therapy as specified below:
  - 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 the obinutuzumab, *rituximab,* polatuzumab vedotin, or venetoclax 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.

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT

This is a Phase Ib/II, open-label, multicenter, non-randomized study of G+Pola+V in patients with R/R FL ~~or~~ *and R+Pola+V in patiens 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 venetoclax dose combinations, through use of

an interactive voice or Web-based response system (IxRS). During the *FL* expansion phase, all patients will be treated at RP2Ds for polatuzumab vedotin and venetoclax. If more than one combination of RP2Ds is identified, patients will be enrolled into multiple cohorts to allow for those combinations to be evaluated during the expansion phase. Post-induction treatment (for eligible patients only) will depend on lymphoma histology. Patients with FL will receive maintenance treatment with obinutuzumab and venetoclax for 24 months, and patients with DLBCL will receive consolidation treatment with ~~obinutuzumab~~*rituximab* and venetoclax for 8 months (see Section 3.1 for details). Patients enrolled in the dose-escalation phase and expansion phase will receive fixed doses of obinutuzumab *or rituximab*.

SECTION 4.3: STUDY TREATMENTS

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

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 21-day cycles of induction treatment with obinutuzumab *or rituximab*, polatuzumab vedotin, and venetoclax. When study treatments are given on the same day, they will be administered sequentially in the following order: venetoclax, obinutuzumab *or rituximab*, and polatuzumab vedotin.

After completion of induction treatment, patients in both phases will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. However, venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment.

During both phases, patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with venetoclax and ~~obinutuzumab~~*rituximab* for 8 months, and patients with FL who achieve a CR, PR, or SD at EOI will receive post-induction treatment (referred to as maintenance) with venetoclax for 8 months and obinutuzumab for 24 months. When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab *or rituximab*.

FIGURE 5: Induction and Post-Induction Treatment Regimens

Figure 5 has been revised to more fully distinguish between the FL and DLBCL treatment groups.

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 (eligible patients with DLBCL only) or~~ maintenance treatment (eligible patients with FL only). A month is defined as 28 days.

FIGURE 7: Guidelines for Obinutuzumab Infusions: Second and Subsequent Infusions

Figure 7 has been revised to differentiate between the levels of IRR.

SECTION 4.3.2.2: *Rituxumab* (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. If a patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as a rapid infusion (over 60–90 minutes) in accordance with local institutional guidelines.

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 5.1.7.

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 9.

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

~~During~~*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.

SECTION 4.3.2.4: Venetoclax

All patients who receive venetoclax must receive prophylaxis for TLS (see Section 5.1.6) before the initiation of venetoclax in the G+Pola+V *and R +Pola + V* combination treatment. Patients who receive venetoclax who are at high risk for TLS or with compromised renal function must be hospitalized on the first day of Cycle 1 (see Section 5.1.6.2).

TABLE 13: Premedication

Table 13 has been revised to detail premedication and administration on Cycle 1 (Days 8 and 15) and Cycle 2 and beyond (Day 1).

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

All IMPs required for completion of this study (obinutuzumab, *rituximab,* polatuzumab vedotin, and venetoclax) 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.

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

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

SECTION 4.4.2: Prohibited and Cautionary Therapy for Concomitant Medications

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

- Any anti-cancer therapy, approved or investigational, other than intrathecal CNS 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 4.5.6: Laboratory, Biomarker, and Other Biological Samples

[…]

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 rituximab PK analysis using a validated assay*

[…]

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

~~Biological samples will be destroyed when the final clinical study report (CSR) has been completed,~~ Unless the patient gives specific consent for ~~the~~*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).

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, venetoclax, 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, PBMCs, plasma, and serum)

SECTION 4.6.2: Study Treatment Discontinuation

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 completion of 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, patients who discontinue study treatment prior to receiving at least one dose of each component of the combination will be replaced.~~
- Patients who discontinue before having received at least one dose of each component of the combination will be replaced.

SECTION 5.1: SAFETY PLAN

~~Venetoclax and p~~*P*olatuzumab vedotin ~~are~~ *is* not *a* marketed product~~s~~, and *venetoclax*~~obinutuzumab~~ is not approved for R/R FL or DLBCL. *Obinutuzumab is only approved in combination with bendamustine for the treatment of R/R FL and rituximab is not approved for the treatment of 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 venetoclax in completed and ongoing studies. The anticipated important safety risks of obinutuzumab, *rituximab,* polatuzumab vedotin, and venetoclax are outlined below. Please refer to the Obinutuzumab*, Rituximab*, Polatuzumab Vedotin, and Venetoclax Investigator's Brochures for a complete summary of safety information.

SECTION 5.1.1: Risks Associated with Obinutuzumab

~~As of the safety cutoff date of October 2014~~*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: *Impaired* Immunizations ~~s~~ *Response*

The safety of immunization with live ~~virus~~ *or attenuated viral* 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), progressive multifocal leukoencephalopathy (PML), Hepatitis B reactivation, neutropenia (including prolonged neutropenia), TLS, impaired immunization response, severe skin reactions (Stevens-Johnson syndrome/toxic epidermal necrolysis), 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 (Grade 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, which 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 (Grade 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 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, since 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 1 to 13 weeks following rituximab exposure. The majority of the Stevens-Johnson syndrome and toxic epidermal necrolysis 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 Stevens-Johnson syndrome and toxic epidermal necrolysis.

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: *Risks Associated with* Polatuzumab Vedotin

The title of this section was revised.

SECTION 5.1.3.1: *Identified Risks* ~~Known Risks: Neutropenia and Peripheral Neuropathy~~

The title of this section was revised.

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

[…]

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 JCV by polymerase chain reaction 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 4.3.2.1)~~. Precautions for suspected anaphylactic reaction during study drug infusions are provided in Section 4.3.2.5. 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 4.3.2.5). Significant issues with polatuzumab vedotin IRRs have not been observed.

Similar considerations regarding infusion reactions are applicable for obinutuzumab. Refer to Section 4.3.2.5 for additional information.

Tumor Lysis Syndrome

There is a potential risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. Patients will receive tumor lysis prophylaxis (e.g., allopurinol ≥300 mg/day orally or a suitable alternative treatment [according to institutional practice] starting prior to study treatment) and must be well hydrated before the initiation of study treatment at Cycle 1 Day 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 Grade 3 laboratory TLS was reported in this ongoing study. 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 patient was asymptomatic. The TLS event was considered related to all 3 study treatments and resolved in 4 days with supportive care. One case of TLS attributed to polatuzumab vedotin has been reported (GO27834); however, the laboratory elevations did not meet the Howard criteria for TLS (see Appendix 13). The suspected TLS event resolved after 3 days of supportive care (see polatuzumab vedotin IB for case details).

SECTION 5.1.5: Risks of Overlapping Toxicities

The overlapping toxicities from the combined administration of obinutuzumab *or rituximab*, polatuzumab vedotin, and venetoclax are anticipated in this clinical trial and will be closely monitored and managed 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 NHL, obinutuzumab was associated with a 5% incidence of Grade 3–4 neutropenia. Because obinutuzumab is expected to have an incidence of neutropenia that is higher than 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. Any applicable findings from this study that affect patient safety will be applied to this study.

Venetoclax has also been associated with hematologic adverse events, including neutropenia. Therefore, the combination of obinutuzumab *or rituximab*, polatuzumab

vedotin, and venetoclax is anticipated to have overlapping hematologic toxicity and will be closely monitored. Guidelines for management of patients who develop hematologic toxicities are provided in Section 5.1.6. In addition to the standard hematologic monitoring, patients enrolled in this study will be closely monitored for evidence of infections.

There is the identified risk of TLS if treatment with obinutuzumab *or rituximab* or venetoclax and a theoretical risk for polatuzumab vedotin since 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 Section 5.1.6.

SECTION 5.1.7: Management of Specific Adverse Events

Patients should be assessed clinically before each study treatment administration. Guidelines for management of toxicities are based on laboratory values obtained within 72 hours prior to Day 1 of each cycle during induction or each month during maintenance (FL) or consolidation (DLBCL) or within 24 hours prior to Days 8 and 15 of Cycle 1 *for patients receiving obinutuzumab*. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.

There will be no dose reductions of obinutuzumab *or rituximab*. There will be no dose reductions of polatuzumab vedotin for any toxicity except neurotoxicity (see Section 5.1.7.2). *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.* Study treatment may be delayed for toxicity for a maximum amount of time (e.g., 21 days), as specified in the tables below. If study treatment is delayed for longer than the specified maximum, study treatment will be permanently discontinued. When a treatment cycle is delayed because of toxicity resulting from any component of the regimen, all study treatments 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.

TABLE 18: Guidelines for Management of Hematologic Toxicities That Occur during Induction Treatment (Except Days 8 and 15 of Cycle 1 *for Patients Receiving Obinutuzumab*)

Table 18 has been revised to not apply to patients receiving obinutuzumab on Days 8 and 15 of Cycle 1.

TABLE 19: Guidelines for Management of Hematologic Toxicities That Occur on Days 8 and 15 of Cycle 1 *for Patients Receiving Obinutuzumab*

Table 19 has been revised to specify only patients receiving obinutuzumab on Days 8 and 15 and to clarify when venetoclax should be held.

TABLE 20: Guidelines for Management of Non-Hematologic Toxicities That Occur During Induction

Table 20 has been revised to include rituximab.

TABLE 21: Guidelines for Management of Toxicities That Occur during Consolidation or Maintenance Treatment

Table 21 has been revised to include rituximab.

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 FL patients receiving obinutuzumab, 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

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"). 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)
- 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).* An exception is *for FL patients receiving obinutuzumab, 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*. 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 5.4.3.2: 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 3 months after the last dose for obinutuzumab ~~and~~ *or rituximab, 30 days after the last dose of* venetoclax and 5 months after last dose of polatuzumab vedotin. 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.

SECTION 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 FL 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~~ *obinutuzumab.*

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

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

- Obinutuzumab Investigator's Brochure
- *Rituximab Investigator's Brochure*
- Polatuzumab Vedotin Investigator's Brochure
- Venetoclax in combination with Obinutuzumab Investigator's Brochure

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase Ib/II, open-label, multicenter, non-randomized study of obinutuzumab in combination with polatuzumab vedotin and venetoclax (G+Pola+V) in patients with R/R FL ~~or~~*and rituximab in combination with polatuzumab vedotin and venetoclax (R+Pola+V) in patients with R/R* DLBCL.

The dose-escalation phase *in patients with FL* is designed to determine the RP2D for *both* polatuzumab vedotin and ~~RP2D for~~ venetoclax when combined with fixed doses of obinutuzumab *(1000 mg).* The dose-escalation phase ~~will include patients with FL only~~ *in patients with DLBCL is designed to determine the RP2D of venetoclax when combined with fixed doses of polatuzumab vedotin (1.8 mg/kg) and rituximab (375 mg/m²).* The expansion phase is designed to assess the safety and efficacy of polatuzumab vedotin and venetoclax at their respective RP2Ds in combination with obinutuzumab *or rituximab.*

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 6 cohorts of 3–6 patients each, for a total of *21–36*~~24–39~~ patients, will be required to establish the RP2D during the dose-escalation phase *for patients with R/R FL. There are 3 possible cohorts of 3–6 patients each, for a total of 12–18 patients with replapsed or refractory DLBCL.*

Approximately 80 patients (40 patients with FL and 40 patients with DLBCL) will be enrolled during the expansion phase. Overall, approximately *113–134*~~104–119~~ patients will be enrolled in this study.

[…]

Table 23 provides 90% Clopper-Pearson exact CIs for the probability of achieving an EOI PET-CT–defined CR for a range of observed proportions based on a sample of 40 patients. 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 6.3: DEFINITION OF ANALYSIS POPULATIONS

~~The primary safety and efficacy~~ *The following* population*s are defined:*

- *The primary safety and efficacy populations* will include patients who receive at least one dose of ~~each~~ *any* component of the combination.

- The ~~safety and efficacy analyses will also be performed on the ITT~~ *intent-to-treat* population~~, which~~ 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). Patients in the dose-escalation phase will be summarized by cohort *and histology type*, and patients in the ~~dose~~ expansion phase will be summarized by histology type (FL or DLBCL).

[…]

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 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 venetoclax 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 6.6.3: Exploratory Efficacy 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

Serum or plasma concentrations of obinutuzumab*, rituximab*, polatuzumab vedotin and relevant analytes, and venetoclax will be tabulated and plotted over time after appropriate grouping. Summary statistics of concentration data will be computed for each scheduled sampling time for each analyte after appropriate grouping. Interpatient

variability and drug accumulation after multiple doses will be evaluated as appropriate. Compartmental, non-compartmental, and/or population approaches will be considered as appropriate. Potential correlations between PK variability and pharmacodynamic, efficacy, and safety endpoints may be explored by exploratory graphical analysis and PK-pharmacodynamic modeling. The exploratory analyses may be reported separately from the CSR.

SECTION 6.8: IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one predose and one postdose *HAHA or* ATA assessment, with patients grouped according to histology.

The numbers and proportions of *HAHA- or* ATA-positive patients and *HAHA- or* ATA-negative patients during both the treatment and follow-up periods will be summarized by histology group. Patients are considered to be *HAHA- or* ATA-positive if they are *HAHA- or* ATA-negative at baseline but develop an *HAHA or* ATA response following study drug administration (treatment-induced *HAHA or* ATA response), or if they are *HAHA- or* ATA-positive at baseline and the titer of 1 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 *HAHA or* ATA response). Patients are considered to be *HAHA- or* ATA-negative if they are *HAHA- or* ATA-negative at baseline and all post-baseline samples are negative, or if they are *HAHA- or* 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* ATA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses. *Considering the historically low immunogenicity rate of rituximab in NHL patients, human anti-chimeric antibodies against rituximab will not be monitored in this study.*

SECTION 6.10: INTERIM ANALYSES

It is anticipated that at least one interim analysis will be conducted during the expansion phase of the study, when at least 15 patients *in each treatment group* have been evaluated for PET-CT–defined CR at the 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 ~~Liu~~*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 expansion cohort with that in historical controls. ~~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 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 cohort because of futility. ~~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.

SECTION 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. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

SECTION 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.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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 DLBCL

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 Venetoclax 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 Venetoclax in Relapsed or Refractory DLBCL Patients*

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

APPENDIX 10: Sample List of Excluded and Cautionary Medications

The list of excluded and cautionary medications has been updated in Appendix 10.

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 VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR *LYMPHOMA AND RITUXIMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA***
PROTOCOL NUMBER:	GO29833
VERSION NUMBER:	4
EUDRACT NUMBER:	2015-001998-40
IND NUMBER:	115045
TEST PRODUCT:	Obinutuzumab (RO5072759) *Rituximab (RO0452294)* Polatuzumab vedotin (DCDS4501A; RO5541077) Venetoclax (GDC-0199; ABT-199; RO5537382)
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 VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR** *LYMPHOMA AND RITUXIMAB IN COMBINATION WITH POLATUZUMAB VEDOTIN AND VENETOCLAX IN PATIENST WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA*
PROTOCOL NUMBER:	GO29833
VERSION NUMBER:	4
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TEST PRODUCTS:	Obinutuzumab (RO5072759) *Rituximab (RO0452294)* Polatuzumab vedotin (DCDS4501A; RO5541077) Venetoclax (GDC-0199; ABT-199; RO5537382)
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 venetoclax (G+Pola+V) in patients with relapse or refractory (R/R) follicular lymphoma (FL) *and rituximab in combination with polatuzumab vedotin and venetoclax (R +Pola + V) in patients with R/R* diffuse large B-cell lymphoma (DLBCL). *Induction will be* followed by post-induction treatment with obinutuzumab incombination with venetoclax (G+V*; 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 nd *post-induction treatment with R + V (referred to as consolidation)* in patients with DLBCL who achieve a CR or PR at EOI. Specific objectives and corresponding outcome measures for the study are outlined below.

Safety Objectives

The safety objectives for this study are as follows:

- To determine the recommended Phase II dose (RP2D) for polatuzumab vedotin and venetoclax when given in combination with a fixed dose of obinutuzumab *and the RP2D of venetoclax when given in combination with a fixed dose of polatuzumab vedotin* 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 + V *and R + Pola + V* on the basis of the following outcome measures *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 Objectives

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

The primary efficacy objective for this study is to evaluate the efficacy of G + Pola + V *in patients with R/R FL and R + Pola + V in patients with 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

The secondary efficacy objective for this study is to evaluate the efficacy of G + Pola + V *and maintenance treatment with G + V in patients with R/R FL and R + Pola + V and consolidation treatment with R + V in patients with 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

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of G + Pola + V *and R + Pola + V* 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 EOC as determined by the IRC and by the investigator on the basis of PET-CT scans in DLBCL patients*
- Progression-free survival, 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
- Event-free survival, 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, defined, among patients who achieve 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, 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 venetoclax when given in combination, on the basis of the following endpoints:

- Observed serum concentration of obinutuzumab at specified timepoints
- *Observed serum concentration of rituximab 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 at specified timepoints
- Observed plasma concentration of venetoclax at specified timepoints

Immunogenicity Objective

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab 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 anti-therapeutic antibody (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 ATAs and other endpoints on the basis of the following endpoint:

- Correlation between HAHA or ATA status and 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, PK, or immunogenicity endpoints

Study Design

Description of Study

This is a Phase Ib/II, open-label, multicenter, non-randomized study that will evaluate the safety, efficacy, and pharmacokinetics of G + Pola + V in patients with R/R FL *and R + Pola + V 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 venetoclax will be given at their RP2Ds. Patients will receive induction treatment with obinutuzumab or rituximab, polatuzumab vedotin, and venetoclax. Patients with FL who achieve a CR, PR, or stable disease at EOI will receive post-induction treatment with obinutuzumab and venetoclax, and patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment with rituximab and venetoclax.

Approximately *113–134* 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. 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 venetoclax, 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 the IRC assessment of response.

In this study, a DLT is defined as any one of the following events that occurs during the first cycle of treatment and is 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 more than 14 days in the start of the next treatment cycle
- Any Grade 3 or 4 non-hematologic adverse event, **with the following exceptions:**
  - Grade 3 or 4 infusion-related reactions (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 fatigue that resolves to Grade $\leq$ 2 within 7 days
  - Grade 3 laboratory tumor lysis syndrome without manifestations of clinical tumor lysis syndrome (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 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 ($<5\times$ 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 $>3\times$ baseline AND an increase in direct bilirubin $>2\times$ 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 $\geq 3\times$ baseline lasting >7 days will be considered a DLT.
- Hematologic adverse event that meets any 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 clinically relevant and related to study treatment, as determined by the investigator and the Medical Monitor, may also be considered DLTs.

Obinutuzumab Plus Polatuzumab Vedotin Plus Venetoclax Treatment Group Treatment Group (Patients with Follicular Lymphoma)

All patients enrolled in the FL dose-escalation phase will receive induction treatment, administered in 21-day cycles. When study treatments are given on the same day, they will be administered sequentially in the following order: venetoclax, obinutuzumab, and polatuzumab vedotin.

Cycle 1:

- Venetoclax 200, 400, 600, or 800 mg by mouth (PO) once daily on Days 1–21
- Obinutuzumab 1000 mg intravenously (IV) on Days 1, 8, and 15
- Polatuzumab vedotin 1.4 or 1.8 mg/kg IV on Day 1

Cycles 2–6:

- Venetoclax 200, 400, 600, or 800 mg PO once daily on Days 1–21
- Obinutuzumab 1000 mg IV on Day 1
- Polatuzumab vedotin 1.4 or 1.8 mg/kg IV on Day 1

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment (referred to as maintenance). Patients who achieve a CR, PR, or stable disease at EOI will receive maintenance treatment with obinutuzumab and venetoclax. Polatuzumab vedotin will not be given as maintenance treatment. Maintenance treatment will continue until disease progression or unacceptable toxicity for up to 24 months. When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab.

Maintenance treatment consisting of the following, administered for 24 months (Months 1–24):

- Venetoclax 200, 400, 600, or 800 mg PO once daily for 8 months (Months 1–8)
- Obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months) for 24 months, starting with Month 2 (e.g., Months 2, 4, 6, 8, etc.)

A $3+3$ 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 1a are 1.4 mg/kg for polatuzumab vedotin and 200 mg for venetoclax. In Cohorts 1–6, dose escalation of polatuzumab vedotin and venetoclax will proceed in increments that parallel the magnitude of dose increases tested in ongoing Phase Ib trials. For polatuzumab vedotin, there are 2 possible dose levels: 1.4 or 1.8 mg/kg. For venetoclax, there are 4 dose levels: 200, 400, 600, or 800 mg.

Intrapatient dose escalation will be allowed only for the Cohort 1a patients receiving 200 mg of venetoclax. In this cohort, the venetoclax dose may be escalated from 200 mg to 400 mg once Cohorts 2 and 3 open after approval by the Medical Monitor. Intrapatient dose escalation is not allowed in other cohorts.

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 according to the dose-escalation plan described above.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to at least 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 according to 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 patients), the dose combination at which this occurs will be considered intolerable and the maximum-tolerated dose (MTD) will have been exceeded for polatuzumab vedotin and/or venetoclax in the G + Pola + V treatment combination. However, enrollment may continue in alternative cohorts.
- If the MTD is exceeded in any cohort, the highest dose combination at which fewer than 33% (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 venetoclax in the G + Pola + V treatment combination).
- If the MTD is not exceeded in any cohort, the highest dose combination administered in this study will be declared the maximum administered doses for polatuzumab vedotin and venetoclax in the G + Pola + V treatment combination.

If the MTD is exceeded in any cohort, de-escalation of the polatuzumab vedotin dose and/or venetoclax dose and adjustment of treatment schedules (e.g., venetoclax 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 venetoclax 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 pharmacodynamic 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, dosing 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 (from Day 1 of Cycle 1 to Day 1 of Cycle 2), cumulative or late toxicities that occur beyond the first cycle may be considered in determination of 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.*

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

All patients enrolled in the *FL* expansion phase will receive induction treatment, administered in 21-day cycles. When study treatments are given on the same day, they will be administered sequentially in the following order: venetoclax, obinutuzumab, and polatuzumab vedotin.

Cycle 1:

- Venetoclax 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:

- Venetoclax 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

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment. Patients with FL who achieve a CR, PR, or stable disease at EOI will receive post-induction treatment (referred to as maintenance) with obinutuzumab and venetoclax. Polatuzumab vedotin will not be given as post-induction treatment. Post-induction treatment will continue until disease progression or unacceptable toxicity for up to 24 months for maintenance treatment. When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab.

Follicular Lymphoma

Maintenance treatment consisting of the following, administered for 24 months (Months 1–24):

- Venetoclax at the RP2D (mg) PO once daily for 8 months (Months 1–8)
- Obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months) for 24 months, starting with Month 2 (e.g., Months 2, 4, 6, 8, etc.)

Rituximab Plus Polatuzumab Vedotin Plus Venetoclax Treatment Group (Patients with DLBCL)

Patients enrolled in the DLBCL dose-escalation phase will receive induction treatment, administered in 21-day cycles. When study treatments are given on the same day, they will be administered sequentially in the following order: venetoclax, rituximab, and polatuzumab vedotin.

Cycles 1–6:

- *Venetoclax 400, 600, or 800 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*

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment (referred to as consolidation). Patients who achieve a CR or PR at EOI will receive consolidation treatment with rituximab and venetoclax. Polatuzumab vedotin will not be given as consolidation treatment. Consolidation treatment will continue until disease progression or unacceptable toxicity for up to 8 months. When study treatments are given on the same day, venetoclax will be administered prior to rituximab.

Consolidation treatment consisting of the following, administered for 8 months (Months 1–8):

- *Venetoclax 400, 600, or 800 mg PO once daily for 8 months (Months 1–8)*
- *Rituximab 375 mg/m² IV on Day 1 of every other month (i.e., every 2 months), starting with Month 2 (e.g., Months 2, 4, 6, 8) for 8 months*

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 venetoclax will be dose escalated. The polatuzumab dose of 1.8 mg/kg is based on ongoing Phase II trials. Intrapatient dose escalation is not allowed.

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 venetoclax in the R + Pola + V 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 MTD venetoclax in the R + Pola + V 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 venetoclax in the R + Pola + V treatment combination.*

If the MTD is exceeded in any cohort, de-escalation of the venetoclax dose and/or polatuzumab vedotin dose, and/or adjustment of treatment schedules (e.g., venetoclax 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, dosing administration/intensity, and PK (if available) data will be reviewed 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 (from Day 1 of Cycle 1 to Day 1 of Cycle 2), cumulative or late toxicities that occur beyond the first cycle may be considered in determination of 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.

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

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

Cycles 1–6:

- *Venetoclax at the RP2D (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*

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment. Patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with rituximab and venetoclax. Polatuzumab vedotin will not be given as post-induction treatment. Post-induction treatment will continue until disease progression or unacceptable toxicity for up to 8 months for consolidation treatment. When study treatments are given on the same day, venetoclax will be administered prior to rituximab.

Diffuse Large B-Cell Lymphoma

Consolidation treatment consisting of the following, administered for 8 months (Months 1–8):

- *Venetoclax at the RP2D (mg) PO once daily for 8 months (Months 1–8)*
- *Rituximab 375 mg/m² IV on Day 1 of every other month (i.e., every 2 months) starting with Month 2 (i.e., Months 2, 4, 6, 8) for 8 months*

Number of Patients

Approximately *113–134* patients are expected be enrolled in this study at approximately 20–25 investigative sites worldwide. This includes approximately 80 patients (40 patients with FL and 40 patients with DLBCL) who will be enrolled during the expansion phase.

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 + V treatment group*: R/R FL after treatment with at least 1 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 + V treatment group:* R/R DLBCL after treatment with at least 1 prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody, with no curative option as determined by the investigator
- Histologically documented CD20-positive non-Hodgkin's 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, 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 core-needle biopsy is strongly recommended.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 12 months after the last dose of polatuzumab vedotin, 30 days after the last dose of venetoclax, *12 months after last dose of rituximab, or* 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 (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  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, 30 days after the last dose of venetoclax, and 3 months after the last dose of obinutuzumab *or rituximab*. Men must refrain from donating sperm for the 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, 30 days after the last dose of venetoclax, and 3 months after the last dose of obinutuzumab *or rituximab*.

  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:

- Known CD20-negative status at relapse or progression
- Prior allogeneic stem cell transplant (SCT)
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1
- Prior standard or investigational anti-cancer therapy as specified below:
  - 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 $\leq$2 (per NCI CTCAE v4.0) prior to Day 1 of Cycle 1
- Grade 3b FL
- History of transformation of indolent disease to DLBCL
- Current Grade $>$1 peripheral neuropathy
- CNS lymphoma or leptomeningeal infiltration
- Treatment with systemic corticosteroids $>$20 mg/day prednisone or equivalent

  Patients who are receiving corticosteroids $\leq$20 mg/day, prednisone or equivalent, for non-lymphoma treatment reasons must be documented to be on a stable dose for at least 4 weeks prior to Day 1 of Cycle 1.

  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 start 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 the obinutuzumab, *rituximab,* polatuzumab vedotin, or venetoclax 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.
- Requirement for warfarin treatment (because of potential drug-drug interactions that may increase the exposure of warfarin)
- Treatment with the following agents within 7 days prior to the first dose of venetoclax:
  - Strong and moderate CYP3A inhibitors such as fluconazole, ketoconazole, and clarithromycin
  - Strong and moderate CYP3A inducers such as rifampin and carbamazepine
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade that contains Seville oranges), or star fruit within 3 days prior to the first dose of venetoclax
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- 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 $\geq$ 2 years prior to enrollment

- 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 $< 1.5 \times 10^9$/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 with the use of 24-hour creatinine clearance or modified Cockcroft-Gault equation (eCCr; with use of the ideal body mass [IBM] instead of mass):

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{IBM (kg)} \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

    Or, if serum creatinine is in μmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{IBM (kg)} \bullet [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine (μmol/L)}}$$

  - AST or ALT $> 2.5 \times$ by 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 a negative serum pregnancy test result within 7 days 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 FL patients 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 DLBCL patients 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 4.5 years.

Length of Study

The length of study will be the time from screening of the first enrolled patient through 2 years after the treatment completion visit for the last enrolled patient. The length of study is expected to be approximately 4.5 years.

Investigational Medicinal Products

The investigational medicinal products used in this study are obinutuzumab, *rituximab,* polatuzumab vedotin, and venetoclax.

Obinutuzumab Plus Polatuzumab Vedotin Plus Venetoclax Treatment Group (Patients with Follicular Lymphoma)

Obinutuzumab

- Induction: Patients will receive obinutuzumab 1000 mg IV on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent 21-day cycle for up to 6 total cycles.
- Post-Induction:

  Patients will receive obinutuzumab 1000 mg IV every other treatment cycle (i.e., every 2 months) starting on Cycle 8 through Cycle 30 (i.e., Months 2–24) for approximately 24 months of additional treatment.

Polatuzumab Vedotin

- Induction: Patients will receive polatuzumab vedotin 1.4 mg/kg or 1.8 mg/kg IV on Day 1 of each 21-day cycle for a total of 6 cycles.
- In the Phase Ib portion (dose-escalation phase) of the study, the total dose of polatuzumab vedotin for each patient will depend on dose level assignment and the patient's weight on Day 1 of Cycle 1 (or within 96 hours before Cycle 1 Day 1).
- In the Phase II portion (dose-expansion phase) of the study, the total dose of polatuzumab vedotin for each patient will depend on the RP2D established in the Phase Ib portion and the patient's weight on Day 1 of Cycle 1 (or within 96 hours before Cycle 1 Day 1).
- Post-Induction: No polatuzumab vedotin will be administered.

Venetoclax

- Induction: Patients will receive venetoclax 200 mg, 400 mg, 600 mg, or 800 mg PO daily

  In the Phase Ib portion (dose-escalation phase) of the study, the dose of venetoclax for each patient will depend on dose level assignment on Day 1 of Cycle 1.

  In the Phase II portion (dose-expansion phase) of the study, the dose of venetoclax for each patient will depend on the RP2D established in the Phase Ib.
- Post-Induction, dose-escalation phase: Patients will receive venetoclax 200 mg, 400 mg, 600 mg, or 800 mg PO daily (starting on Cycle 7 through Cycle 13) for for approximately 8 months of additional treatment.
- Post-Induction, expansion phase: Patients will receive venetoclax at RP2D PO daily (starting on Cycle 7 through Cycle 13) for approximately 8 months of additional treatment

Rituximab Plus Polatuzumab Vedotin Plus Venetoclax Treatment Group (Patients with DLBCL)

Rituximab

- *Induction: Patients will receive rituximab 375 mg/m² IV on Day 1 of Cycles 1−6.*
- *Post-Induction:*

  Patients will receive rituximab 375 mg/m² IV every other treatment cycle (i.e., every 2 months) starting with Month 2 (e.g., Months 2, 4, 6, 8) for 8 months

Polatuzumab Vedotin

- Induction: Patients will receive polatuzumab vedotin 1.8 mg/kg IV on Day 1 of each 21-day cycle for a total of 6 cycles.
- In the Phase Ib portion (dose-escalation phase) of the study, the total dose of polatuzumab vedotin for each patient will depend on dose level assignment and the patient's weight on Day 1 of Cycle 1 (or within 96 hours before Cycle 1 Day 1).
- In the Phase II portion (dose-expansion phase) of the study, the total dose of polatuzumab vedotin for each patient will depend on the RP2D established in the Phase Ib portion and the patient's weight on Day 1 of Cycle 1 (or within 96 hours before Cycle 1 Day 1).

- Post-Induction: No polatuzumab vedotin will be administered.

Venetoclax

- Induction: Patients will receive venetoclax 400 mg, 600 mg, or 800 mg PO daily

  In the Phase Ib portion of the study, the dose of venetoclax for each patient will depend on dose level assignment on Day 1 of Cycle 1.

  In the Phase II portion of the study, the dose of venetoclax for each patient will depend on the RP2D established in the Phase Ib.
- Post-Induction, dose-escalation phase: Patients will receive venetoclax 400 mg, 600 mg, or 800 mg PO once daily (starting on Cycle 7 through Cycle 13) for approximately 8 months
- Post-Induction, dose-expansion phase: Patients will receive venetoclax at RP2D PO once daily (starting on Cycle 7 through Cycle 13) for approximately 8 months of additional treatment

Statistical Methods

Primary Analysis

Response will be determined on the basis of PET-CT scans or CT scans alone, using the Lugano 2014 criteria.

The primary efficacy endpoint is the proportion of patients achieving a CR at EOI, as determined by the IRC on the basis of PET-CT scans according to Lugano 2014. Point estimates will be presented, along with the corresponding 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 6 cohorts of 3–6 patients each, for a total of *21–36* patients, will be required to establish the RP2D during the dose-escalation phase *for patients with R/R FL. There are three possible cohorts of 3–6 patients each, for a total of 12–18 patients with replapsed or refractory DLBCL.*

Approximately 80 patients (40 patients with FL and 40 patients with DLBCL) will be enrolled during the expansion phase. Overall, approximately *113–134* patients will be enrolled in this study.

The primary analysis will be 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 around 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 one interim analysis will be conducted during the expansion phase of the study, when at least 15 patients *in each treatment group* have been evaluated for PET-CT–defined CR at the 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 expansion cohort with that in historical controls. *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 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 cohort because of futility.

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
^{18}F-FDG	^{18}F-fluorodeoxyglucose
ABC	activated B cell–like (subgroup)
acMMAE	antibody-conjugated mono-methyl auristatin E
ADC	antibody–drug conjugate
AE	adverse event
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC	area under the concentration–time curve
AUC_{inf}	area under the concentration–time curve extrapolated to infinity
BCRP	breast cancer receptor proteins
BR	bendumustine plus rituximab
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CR	complete response
Cri	complete response with incomplete bone marrow recovery
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
DDI	drug–drug interaction
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOP	delta-opioid receptor
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCCr	estimation of creatinine clearance
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EOI	end of induction
EOC	*end of consolidation*
EORTC	European Organization for Research and Treatment of Cancer

Abbreviation	Definition
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 + Pola + V	obinutuzumab plus polatuzumab vedotin plus venetoclax
G + V	obinutuzumab plus venetoclax
GB	obinutuzumab plus bendamustine
GCB	germinal-center B cell–like (subgroup)
G-CHP	obinutuzumab in combination with cyclophosphamide, doxorubicin, and prednisone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HAHA	human anti-human antibody
HbA_{1c}	glycosylated hemoglobin
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
IBM	ideal body mass
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
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
IUD	intrauterine device
IV	intravenous
IxRS	interactive voice or web-based response system

Abbreviation	Definition
JCV	John Cunningham virus
MCL	mantle cell lymphoma
MMAE	mono-methyl auristatin E
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 estimable*
NHL	non-Hodgkin's lymphoma
NK	natural killer
NOAEL	no observed adverse effect level
ORR	objective response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PR	partial response
QTc	corrected QT interval
R	rituximab
R + Pola + V	*rituximab in combination with polatuzumab vedotin and venetoclax*
R + V	*rituximab in combination with venetoclax*
R/R	relapsed or refractory
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone
R-CHP	rituximab in combination with cyclophosphamide, doxorubicin, and prednisone
RCR	Roche Clinical Repository
RP2D	recommended Phase II dose
SC	subcutaneous
SCT	stem-cell transplantation
SLL	small lymphocytic lymphoma
$t_{1/2}$	half-life

Abbreviation	Definition
TAb	total antibody
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
ULN	upper limit of normal
vcMMAE	valine-citrulline monomethyl auristatin E
V_{SS}	volume at steady state
WM	Waldenström's macroglobulinemia

1. BACKGROUND

1.1 BACKGROUND ON NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma (NHL) is the most common hematologic malignancy in adults. In 2015, there will be an estimated 71,850 new cases and 19,790 deaths due to the disease in the United States (SEER 2015). In Europe, there were an estimated 93,400 new cases and 37,900 deaths in 2012 (Ferlay et al. 2013). NHL is most often of B-cell origin. This includes a range of different subtypes of B-cell lymphoma, which are 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 NHLs. Follicular lymphoma (FL) is the most common subtype of indolent B-cell lymphoma; it accounts for about 22% of all newly diagnosed cases of NHL (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 (seen as R in drug combination regimens), an anti-CD20 monoclonal antibody, to commonly used induction chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); fludarabine; or bendamustine (Marcus et al. 2008; Hochster et al. 2009; Dreyling et al. 2014; Zelenetz 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 therapy in patients who responded 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. Currently, approved therapies for relapsed FL include rituximab, bendamustine, idelalisib (refractory FL), and radioimmunotherapy. New treatments are needed to improve the outcomes for patients with relapsed NHL.

1.1.2 Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive NHL; it accounts for approximately 30% of all NHLs diagnosed annually (Armitage and Weisenburger 1998). The use of immunochemotherapy, most commonly rituximab plus 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 old) 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 40% following treatment with R-CHOP (Zhou et al. 2014).

Second-line therapies include high-dose chemotherapy regimens such as rituximab plus ifosfamide, carboplatin, and etoposide or 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 have 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 that are predictive of poor outcomes 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 (known as "double-hit" DLBCL), which is observed in 2%–11% of DLBCL patients, represents a subset of DLBCL patients who have inferior outcomes (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 18%–30% of patients with DLBCL (Lossos and Morgensztern 2006) and are strong predictors of poor overall survival (OS; Young et al. 2008).

DLBCL remains a disease with a high unmet medical need. Novel targeted therapies are needed to move treatment options beyond R-CHOP.

1.2 BACKGROUND ON OBINUTUZUMAB

Obinutuzumab (also known as GA101 and seen as G in drug combination regimens) 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. This results in enhanced antibody–dependent cellular cytotoxicity and antibody–dependent cellular phagocytosis (Beers et al. 2010;

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

For more detailed information on nonclinical studies of 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/IIIb studies (BO21004, GAO4753g, BO21005, BO21223, and MO28543) in patients with NHL or CLL. Available safety results from all patients and efficacy results from the NHL cohorts in these studies are summarized in Sections 1.2.2.1 and 1.2.2.2, respectively. Efficacy data from a Phase III study of obinutuzumab (GAO4753g) are also presented.

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

1.2.2.1 Clinical Safety of Obinutuzumab

As of the safety data cutoff date of *4 July 2016*, an estimated *3636* patients with NHL (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 mg to 2000 mg. The overall safety and toxicity profile of obinutuzumab as monotherapy and as 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, which compared obinutuzumab 1000 mg versus 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 who received obinutuzumab plus chlorambucil (Study BO21004) to 100% in patients with relapsed or refractory (R/R) disease who received obinutuzumab monotherapy (pooled data from Studies BO21003 and BO20999).

In the NHL population, the incidence of IRRs in studies of obinutuzumab monotherapy was 73%–75% (pooled data from Study BO21003 and high-dose NHL cohorts from Study BO20999). In studies of obinutuzumab in combination with either CHOP (Study GAO4915g) or bendamustine (Study BO21000), the incidence of IRRs considered to be related to obinutuzumab was 56%–59%.

Other important risks associated or potentially associated with obinutuzumab are tumor lysis syndrome (TLS), thrombocytopenia (including acute thrombocytopenia), neutropenia *(including prolonged and late onset neutropenia)*, prolonged B-cell depletion, infections (including progressive multifocal leukoencephalopathy [PML] and hepatitis B virus [HBV] reactivation), worsening of preexisting cardiac conditions, impaired immunization response, immunogenicity, gastrointestinal perforation, 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.

1.2.2.2 Clinical Efficacy of Obinutuzumab in Patients with Non-Hodgkin's Lymphoma

In studies of obinutuzumab monotherapy in patients with R/R NHL (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 (i.e., CHOP or bendamustine) in patients with previously untreated or R/R NHL (Studies BO21000, GAO4915g, and GAO4753g), the proportion of patients with a CR or PR at the end of induction 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.

A Phase III study, GAO4753g, investigated obinutuzumab plus bendamustine (GB) compared with bendamustine alone in patients with rituximab-refractory indolent NHL (n=396). Patients in the GB group who had not experienced disease progression at the end of induction 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 (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).*

A Phase III 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 indolent non-Hodgkin's lymphoma (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).*

A Phase III study, BO21005, investigated obinutuzumab plus CHOP (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 venetoclax (Vitolo et al. 2016).

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 NHL 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 NHL.

1.3.1 Nonclinical Studies with Polatuzumab Vedotin

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamic, 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 mouse xenograft models of human CD79b-positive NHL. Additionally, polatuzumab vedotin when combined with rituximab plus chemotherapy (R-CHP or bendamustine) 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 [BR]) in xenograft models of NHL. 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 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 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

Clinical data on polatuzumab vedotin in patients with NHL or CLL are available from one completed Phase I/Ib study (DCS4968g) and *the* ongoing Phase Ib/II *studies* (GO27834, GO29044*, GO29834, 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 R-CHP or 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.

GO29834 is evaluating polatuzumab vedotin in combination with lenalidomide and either obinutuzumab or rituximab in patients with R/R FL or DLBCL.

BO29561 is evaluating polatuzumab vedotin in combination with atezolizumab and either obinutuzumab or rituximab in patients with R/R FL or DLBCL.

Available safety results and efficacy results from these studies are summarized in Section 1.3.2.1 and Section 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 Safety of Polatuzumab Vedotin

Clinical safety data are available from *327* patients with NHL 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 obinutuzumab or rituximab plus CHP (GO29044), and 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 (reported 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 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 mg/kg 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%–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 obinutuzumab or rituximab plus 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 rituxumab 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 in patients treated with polatuzumab vedotin combined with rituximab or obinutuzumab. The majority of deaths were judged as related to disease progression.

1.3.2.2 Clinical Efficacy of Polatuzumab Vedotin in Patients with Non-Hodgkin's 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 the 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 for patients in Study GO27834 who received polatuzumab vedotin (2.4 mg/kg) in combination with rituximab, objective 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 (1.8 mg/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) 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, 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 patients with CR) when combined with obinutuzumab.

1.4 BACKGROUND ON VENETOCLAX

Venetoclax (synonymous with ABT-199 and GDC-0199) is a highly selective, orally available small–molecule Bcl-2 family protein inhibitor that binds with high affinity (dissociation constant [K_i] <0.10 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-XL and Bcl-w (>480- and >2000-fold lower affinity than to Bcl-2, respectively). Overexpression of anti–apoptotic Bcl-2 family proteins is associated with resistance to chemotherapy, and antagonism of the action of these proteins might overcome resistance and enhance response to therapy. Anti–apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for anti-tumor therapy.

1.4.1 Nonclinical Studies with Venetoclax

In vitro, venetoclax demonstrated broad cell-killing activity against a panel of lymphoma and leukemia cells, including B-cell FL, mantle cell lymphoma (MCL), DLBCL, and acute myeloid leukemia. Venetoclax was especially potent against cell lines that expressed high levels of Bcl-2. Leukemia and lymphoma cell lines that bear the t(14;18) translocation were significantly more sensitive to venetoclax than wild–type cell lines.

Venetoclax inhibited subcutaneous (SC) murine xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia and NHL.

The PK profile of venetoclax was evaluated in multiple animal species. In mice, rats, monkeys, and dogs, low plasma clearance and low volumes of distribution characterized the venetoclax PK profile. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs. Food had a marked effect on the oral bioavailability in dogs.

Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins ($>99.9\%$). In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Liver metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes.

In vitro, venetoclax is metabolized by cytochrome (CYP) 3A4 and is a moderate inhibitor of CYP2C8 and a potent inhibitor of CYP2C9. It is not a potent inhibitor of CYP3A4, CYP1A2, CYP2B6, CYP2C19, or CYP2D6 ($IC_{50}>30$ μM) and does not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM. Venetoclax has the potential to inhibit P-glycoprotein (P-gp).

A more detailed discussion of the nonclinical activity of venetoclax, including pharmacokinetic, toxicology, and metabolism, is provided in the current Venetoclax Investigator's Brochure.

1.4.2 Clinical Studies with Venetoclax

As of 28 November 2014, a total of 639 patients had been dosed with venetoclax in AbbVie and Genentech/Roche oncology studies. Doses administered in venetoclax clinical studies ranged from 20 to 1200 mg. A total of 345 patients with CLL/SLL and 155 patients with NHL have been treated with venetoclax as single agent or in combination (see Appendix 12).

Two studies, GP28331 and GO27878, include the combination of obinutuzumab and venetoclax in CLL and NHL, respectively. In addition, Study BO25323, a randomized Phase III study evaluating the efficacy of obinutuzumab plus venetoclax compared with obinutuzumab plus chlorambucil in patients with previously untreated CLL, has recently been initiated.

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

1.4.2.1 Clinical Results in Non-Hodgkin's Lymphoma

Study M12-175, the first in-human venetoclax monotherapy dose-escalation study, is ongoing in patients with R/R CLL/SLL and NHL. Two DLTs have been reported in patients with NHL who were treated with venetoclax in Study M12-175. Both DLTs occurred at the 600-mg dose in Cohort 5 (which enrolled a total of 10 patients and had a 300-mg lead-in dose and 600-mg designated cohort dose). One patient experienced a DLT of serious Grade 3 febrile neutropenia, and the other patient experienced a DLT of non-serious Grade 4 neutropenia. Dosing was interrupted and patients were treated with medication; the events resolved and the patients restarted therapy at a reduced venetoclax dose of 300 mg. No DLTs were reported in Cohorts 6–8, with the maximum dose studied of 1200 mg.

The most common adverse events in the NHL cohort of Study M12-175 were nausea, anemia, diarrhea, and fatigue, all occurring in ≥20% of patients. Grade ≥3 hematologic toxicity was less common in patients with NHL than in patients with CLL. In Study M12-175, 13% of patients with NHL experienced Grade ≥3 neutropenia and 10% experienced Grade ≥3 thrombocytopenia.

As of 4 December 2014, a total of 105 patients with R/R NHL had been enrolled (70 in the dose-escalation cohorts and 35 in the safety expansion cohort) and evaluated for objective response following the International Working Group criteria (patients with Waldenstrom's macroglobulinemia [WM] were evaluated using the International Workshop-WM criteria). In the dose-escalation cohorts, the objective response rate (ORR) was 57%, the CR rate was 11%, and median time in the study was approximately 6 months. In the safety expansion cohort, the ORR was 17%, the CR rate was 3%, and median time in the study was approximately 3 months. This group had limited follow-up at the time of the clinical cutoff.

Study M12-630 is a study of venetoclax in combination with BR in patients with R/R NHL. Patients receive this regimen for 6 cycles. In Study M12-630, preliminary efficacy data are available for 27 patients (17 male patients [63%]) with R/R NHL as of 7 October 2014. Hematologic toxicity in Study M12-630 (venetoclax in combination with BR in patients with NHL) was not significantly greater than that expected with BR alone. The ORR was 64% (18 of 27 evaluable patients): 4 patients (14%) with CR and 14 patients (50%) with PR. An additional 3 patients (11%) had stable disease.

Efficacy data are not yet available for the other NHL studies listed.

Data on venetoclax and human pregnancy or venetoclax and drug abuse and drug dependency are not available.

Additional details on the clinical activity and safety of venetoclax are provided in the Venetoclax Investigator's Brochure.

1.4.2.2 Clinical Pharmacokinetics and Pharmacodynamics

Preliminary PK data with venetoclax are available from ongoing Studies M12-175, M12-630, and M13-365 in patients with hematologic malignancies.

The venetoclax formulation currently used in clinical studies is a tablet formulation with strengths of 10, 50, and 100 mg. The tablet formulation was orally administered after a low-fat meal. Food increased the bioavailability of venetoclax by 3- to 4-fold. Preliminary PK results indicated that the absorption of venetoclax after the oral dosing was relatively slow. Venetoclax plasma concentrations peaked at approximately 6 hours after dosing. The mean terminal-phase elimination half-life of venetoclax was approximately 17 hours, and the mean oral clearance was approximately 13 L/hr after a single dose. There was no apparent difference in the pharmacokinetics of venetoclax in patients with CLL/SLL or NHL. The combined data from patients with CLL/SLL and NHL suggested that venetoclax exposure was approximately dose proportional across the 150- to 900-mg dose levels. In the limited number of patients to date, co-administration of BR did not show apparent effect on venetoclax pharmacokinetics.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Progress has been made in the treatment of FL and DLBCL; however, a significant number of patients will not be cured of their disease. Instead, they will experience relapse or die of progression or treatment-related toxicity. Patients who relapsed after receiving several prior treatments may not be able to tolerate more bone marrow toxicity, which limits their treatment options. There is a need for the continued development of safe and effective therapies for patients with disease that relapses or for those 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 venetoclax.

B-cell lymphoma, including FL and DLBCL, express the CD20 antigen, and anti-CD20 therapy (rituximab) has been demonstrated to provide enhanced anti-tumor activity in combination with other agents, leading to increased response rates, PFS, and OS (Coiffier et al. 2002, 2007, 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). Rituximab has been accepted as a standard component in initial therapy.

Obinutuzumab has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). *Obinutuzumab was also shown to be superior compared to rituximab when combined with chemotherapy in a Phase III trial (BO21223) in previously untreated FL patients (Marcus et al. 2016). The* Phase III study GAO4753g investigated obinutuzumab combined with bendamustine followed by obinutuzumab maintenance compared with bendamustine alone in patients with rituximab-refractory iNHL, including FL, *and showed improvement in PFS in the GB arm* (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 comparing R-CHOP to G-CHOP in patients with previously untreated DLBLC (BO21005; 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 venetoclax.

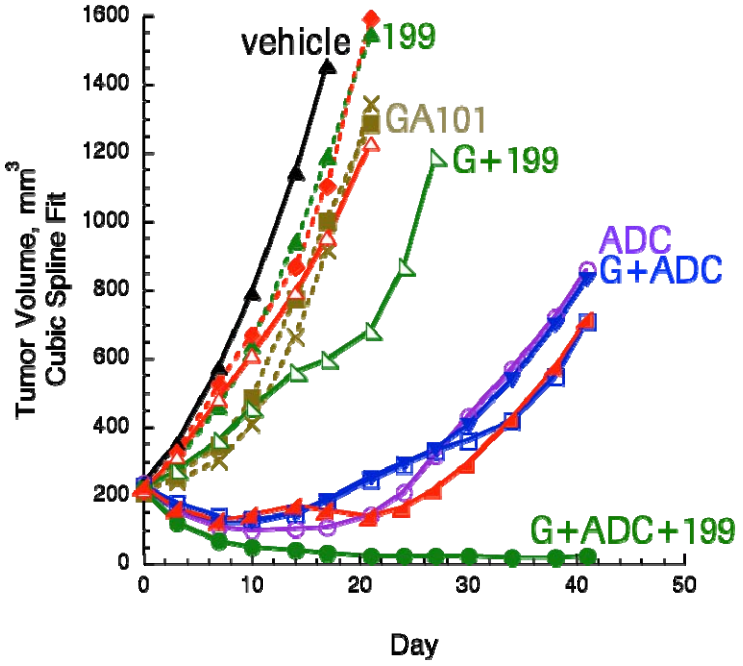
In addition to the potential of next-generation anti-CD20 therapy to enhance the efficacy of current standard immunochemotherapy regimens the development of ADC may have the potential to add benefit when combined with standard systemic chemotherapy, or to replace these agents, in certain lymphoma combination regimens. Polatuzumab vedotin is an ADC designed for the targeted delivery of MMAE, a potent microtubule inhibitor to lymphoma cells that express CD79b. MMAE has a mechanism of action that is similar to that of vincristine.

Venetoclax is a specific inhibitor of the Bcl-2 anti–apoptotic protein expressed in many NHL cells. Bcl-2 is overexpressed in most FL and many DLBCLs as a consequence of the t(14;18) chromosomal translocation or gene amplification and is associated with a poor prognosis in multiple tumor types (Cory and Adams 2002; Cory et al. 2003; Reed 2008; Iqbal et al. 2011). Bcl-2 has been shown to contribute to resistance of malignant cells to chemotherapies with varied mechanisms of action, consistent with its role as an inhibitor of the final common steps of apoptosis and is likely to play a role in resistance to the pro-apoptotic activities of immunotherapy and chemotherapy. In solid and hematologic tumor models, anti-mitotic drugs (taxanes and auristatin) were shown to modulate Bcl-2 pro-survival proteins to induce cell death in vitro (Haldar et al 1996; Poruchynsky et al. 1998; Wertz et al. 2011). MMAE in polatuzumab vedotin may be able to down regulate Mcl-1, a known resistant factor for venetoclax. Therefore, the addition

of venetoclax, a Bcl-2 inhibitor, to a polatuzumab vedotin-containing regimen may have the potential to significantly enhance the anti-lymphoma activity and to result in improved clinical outcomes.

Nonclinical data that support the triplet combination of obinutuzumab, polatuzumab vedotin, and venetoclax include WSU-DLCL2 model in CB17 severely compromised immunodeficient (SCID) mice that demonstrated significantly improved anti-tumor activity of the triplet combination over the activity of any treatment regimen alone or doublet combination (obinutuzumab plus venetoclax or obinutuzumab plus polatuzumab vedotin; see Figure 1).

Figure 1 Anti-Tumor Activity with Obinutuzumab, Polatuzumab Vedotin, and Venetoclax in WSU-DLCL2 Model in CB17 SCID Mice



ADC = antibody drug conjugate (polatuzumab vedotin); 199 = venetoclax; G or GA101 = obinutuzumab; SCID = severely compromised immunodeficient mice.

Early clinical data that evaluated obinutuzumab, polatuzumab vedotin, and venetoclax, each given as single agents, have demonstrated efficacy but have been associated with neutropenia (refer to Section 1.2.2, Section 1.3.2, and Section 1.4.2, respectively).

Obinutuzumab, *rituximab,* polatuzumab vedotin, and venetoclax are known to deplete circulating B cells and tumor burden, which may potentially impact the target-mediated clearance of obinutuzumab, *rituximab,* and polatuzumab vedotin. In R/R FL and DLBCL, the baseline B-cell count is very low; therefore, the likelihood of pharmacodynamics (B-cell) mediated drug-drug interaction (DDI) is relatively low. This

was confirmed by the observation that no interaction was observed between polatuzumab and rituximab in R/R FL and DLBCL.

The likelihood of cytochrome P450 (CYP) and P-gp mediated DDI among obinutuzumab, polatuzumab vedotin, and venetoclax is assessed below.

First, the risk of cytokine modulation related CYP expression change and the resulted DDI is low for polatuzumab vedotin and obinutuzumab because studies in cynomolgous monkey and in vitro suggested the risk of systemic cytokine release following anti-CD79 antibody treatment is low (Schmidt and Wittrup 2009) and obinutuzumab only results in highly transient increases in cytokine concentrations in patients after the first infusion.

Second, in vitro, the MMAE component of polatuzumab vedotin is mainly metabolized by CYP3A4. MMAE did not induce any major CYP450 enzymes. MMAE inhibits CYP3A4/5 as a weak competitive and a time-dependent inhibitor. Simulations based on a physiologically-based PK model (Chen et al. 2015) showed that unconjugated MMAE exposure following polatuzumab vedotin administration with strong CYP3A4 inhibitors or inducers is unlikely to be altered by $>50\%$, and MMAE is unlikely to be a perpetrator of drug interactions with CYP substrates. In vitro, MMAE was a substrate but not a potent inhibitor of P-gp.

Third, in vitro, venetoclax is metabolized by CYP3A4. Venetoclax is a reversible inhibitor of UGT1A1, CYP2C9 and CYP2C8. M27, a primary human metabolite of venetoclax, is a reversible inhibitor of UGT1A1, CYP2C9, UGT2B7, CYP2C8, CYP3A4, UGT1A4 and UGT1A6 in vitro. Model prediction suggested that venetoclax and M27 are unlikely to cause clinically significant interaction with CYP and UGTs substrates. Venetoclax is a substrate for P-gp and BCRP and has the potential to inhibit P-gp and BCRP.

Therefore, when polatuzumab vedotin is combined with venetoclax, the risk of CYP-mediated DDI risk is low between MMAE and venetoclax (and its major human metabolite M27). It is possible that MMAE exposure may be affected in the presence of venetoclax mediated by P-gp. It is unknown whether the risk of breast cancer resistance protein (BCRP)-mediated DDIs exists. The patients who receive other concomitant medications, which are strong P-gp or BCRP inhibitors, should be closely monitored for adverse reactions.

Available nonclinical and clinical data suggest that there is a strong rationale to expect an improved benefit-risk profile with the triplet combination of obinutuzumab or $rituximab$, polatuzumab vedotin, and venetoclax. This novel triplet regimen may have the potential to extend treatment-free remissions and decrease toxicity by improving upon individual agents used as part of current standard of care. Patients with overlapping toxicities will be closely monitored; such events are expected to be manageable in the clinical setting (see Section 5.1.5).

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 venetoclax (G+Pola+V) in patients with R/R FL *and rituximab in combination with polatuzumab vedotin and venetoclax (R+Pola+V) in patients with R/R DLBCL. Induction will be* followed by post-induction treatment with obinutuzumab in combination with venetoclax (G+V; *referred to as maintenance)* in patients with FL who achieve a CR, PR, or stable disease at end of induction (EOI) and *post-induction treatment with rituximab in combination with venetoclax (R+V; 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 in Sections 2.1–2.5.

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

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To determine the RP2D for polatuzumab vedotin and venetoclax when given in combination with a fixed dose of obinutuzumab *and the RP2D of venetoclax when given in combination with a fixed dose of polatuzumab vedotin* 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+V *and R+Pola+V* on the basis of the following outcome measures *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 and computed tomography (PET-CT) scans or CT scans alone, using Revised Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix 4), hereinafter referred to as 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 G+Pola+V *in patients with R/R FL and R+Pola+V in patients with 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 G+Pola+V *and maintenance treatment with G + V in patients with R/R FL and R + Pola + V and consolidation treatment with R + V in patients with 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+V *and R + Pola + V* 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 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 who achieve 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
- 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 venetoclax when given in combination, on the basis of the following endpoints:

- Observed serum concentration of obinutuzumab at specified timepoints
- *Observed serum concentration of rituximab at specified timepoints*

- Observed serum and plasma concentrations of polatuzumab vedotin and relevant analytes (total antibody, antibody-conjugated MMAE [acMMAE] and unconjugated MMAE) at specified timepoints
- Observed plasma concentration of venetoclax at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab 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 anti-therapeutic antibody (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 ATAs and other endpoints on the basis of the following endpoint:

- Correlation between HAHA or ATA status and 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, PK, or immunogenicity endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study

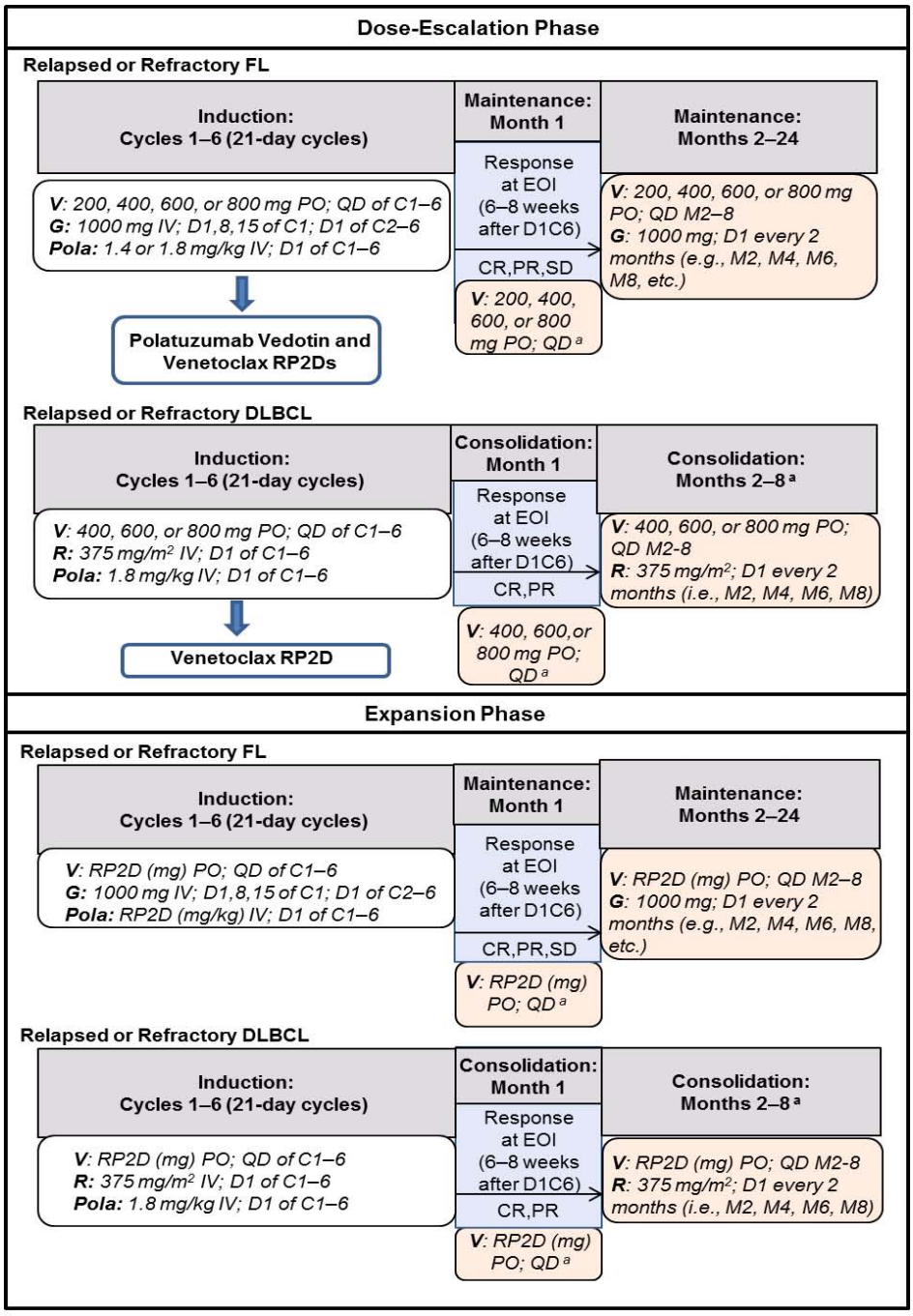
This is a Phase Ib/II, open-label, multicenter, non-randomized study that will evaluate the safety, efficacy, and pharmacokinetics of G+Pola+V in patients with R/R FL *and R+Pola+V in patients with R/R DLBCL.*

The study will include an initial dose-escalation phase followed by an expansion phase during which polatuzumab vedotin and venetoclax will be given at their RP2Ds (see Sections 3.1.2 and 3.1.2.2). Patients will receive induction treatment with obinutuzumab or rituximab, polatuzumab vedotin, and venetoclax as outlined in Sections 3.1.2 and 3.1.3. Patients with FL who achieve a CR, PR, or stable disease at

EOI will receive post-induction treatment with obinutuzumab and venetoclax, and patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment with rituximab and venetoclax (see Sections 3.1.2 and 3.1.3 for details). A study schema is provided in Figure 2.

Approximately *113–134* patients are expected to be enrolled in this study at approximately 20–25 investigative sites worldwide.

Figure 2 Study Schema



C = cycle; CR = complete response; D = day; D1C6 = Day 1 of Cycle 6; DLBCL = diffuse large B-cell lymphoma; EOI = end of induction; FL = follicular lymphoma; G = obinutuzumab; IV = intravenous; M = month; PO = by mouth; Pola = polatuzumab vedotin; PR = partial response; QD = once a day; *R = rituximab;* RP2D = recommended Phase II dose; SD = stable disease; V = venetoclax.

[a] After completion of induction treatment, all patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment.

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 venetoclax, blood samples will be obtained at various timepoints before and during study treatment administration (see Appendix 3 and Appendix 4).

Response will be determined by the IRC (see Section 3.1.5) and the investigator using the Lugano 2014 criteria (see Appendix 5). The primary efficacy endpoint will be based on the IRC assessment of response. Refer to Section 4.5.5 for details on tumor assessments.

3.1.2 *Obinutuzumab Plus Polatuzumab Vedotin Plus Venetoclax Treatment Group (Patients with Follicular Lymphoma)*

3.1.2.1 *Follicular Lymphoma* Dose-Escalation Phase

The purpose of the *FL* dose-escalation phase is to identify the RP2D for polatuzumab vedotin and the RP2D for venetoclax 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. The RP2D will be based on the maximum tolerated doses (MTDs) and the totality of data for polatuzumab vedotin and venetoclax.

Approximately *21*–39 patients will be enrolled in the *FL* dose-escalation phase. Initially, the study enrolled 3 patients starting in Cohort 1 at a dose level of 400 mg venetoclax and 1.4 mg/kg polatuzumab vedotin. With Amendment 3, Cohort 1a *was* added to the dose-escalation phase with a starting dose level of 200 mg venetoclax and 1.4 mg/kg polatuzumab vedotin. The original Cohort 1 dose level combination will be repeated to gather additional safety data in this dose level. Dosing cohorts of 3–6 patients each will be treated in accordance with the treatment regimen and dose-escalation rules described in Sections 3.1.2.1.2 and 3.1.2.1.3, respectively.

Patients will be closely monitored for adverse events during a DLT assessment window, which will be defined as the first treatment cycle (from Day 1 of Cycle 1 to Day 1 of Cycle 2). Adverse events that meet the criteria for DLT, as defined in 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 completion of the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD 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 venetoclax 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 one of the following events that occurs during the first cycle of treatment and is 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 more than 14 days in the start of the next treatment cycle
- Any Grade 3 or 4 non-hematologic adverse event, **with the following exceptions**:
  - 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 fatigue that resolves to Grade ≤ 2 within 7 days
  - 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 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 ($< 5 \times$ 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 $> 3 \times$ baseline AND an increase in direct bilirubin $> 2 \times$ 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 (DILI; 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 $\geq 3 \times$ 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 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 21-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: venetoclax, obinutuzumab, and polatuzumab vedotin.

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

	G + Pola + V (21-Day Cycles)
Cycle 1	• Venetoclax 200, 400, 600, or 800 mg PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Days 1, 8, and 15 • Polatuzumab vedotin 1.4 or 1.8 mg/kg IV on Day 1
Cycle 2–6	• Venetoclax 200, 400, 600, or 800 mg PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Day 1 • Polatuzumab vedotin 1.4 or 1.8 mg/kg IV on Day 1

G = obinutuzumab; IV = intravenous; PO = by mouth; Pola = polatuzumab vedotin; V = venetoclax.
Note: When study treatments are given on the same day, they will be administered sequentially in the following order: venetoclax, obinutuzumab, and polatuzumab vedotin.

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment (referred to as maintenance). Patients who achieve a CR, PR, or stable disease at EOI will receive maintenance treatment with obinutuzumab and venetoclax, as outlined in Table 2. Polatuzumab vedotin will not be given as maintenance treatment. Maintenance treatment will continue until disease progression

or unacceptable toxicity for up to 24 months. When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab.

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

Maintenance treatment consisting of the following, administered for 24 months (Months 1–24): • Venetoclax 200, 400, 600, or 800 mg PO once daily for 8 months (Months 1–8) • Obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months) for 24 months, starting with Month 2 (e.g., Months 2, 4, 6, 8, etc.)

IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

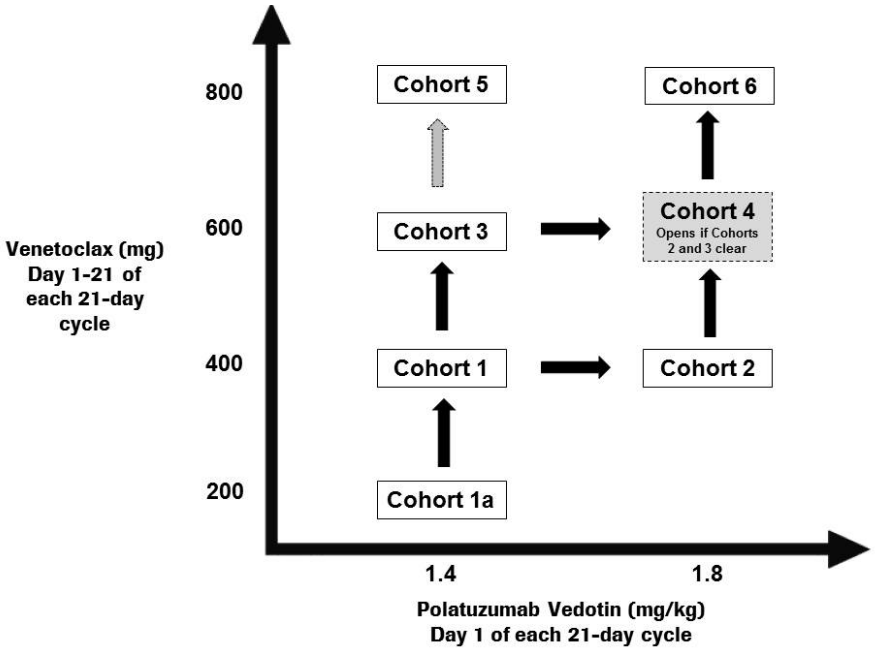
Note: When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab. A month is defined as 28 days.

3.1.2.1.3 Dose-Escalation Rules

A 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 1a are 1.4 mg/kg for polatuzumab vedotin and 200 mg for venetoclax. In Cohorts 1–6, dose escalation of polatuzumab vedotin and venetoclax will proceed in increments that parallel the magnitude of dose increases tested in ongoing Phase Ib trials (see Sections 3.3.3.2 and 3.3.3.2.2). For polatuzumab vedotin, there are 2 possible dose levels: 1.4 or 1.8 mg/kg. For venetoclax, there are 4 dose levels: 200, 400, 600, or 800 mg.

Intrapatient dose escalation will be allowed only for the Cohort 1a patients receiving 200 mg of venetoclax. In this cohort, the venetoclax dose may be escalated from 200 mg to 400 mg once Cohorts 2 and 3 open after approval by the Medical Monitor. Intrapatient dose escalation is not allowed in other cohorts. The *FL* dose-escalation plan is depicted in Figure 3, and the doses for each cohort are summarized in Table 3.

Figure 3 *Follicular Lymphoma* **Dose-Escalation Plan**



If Cohort 1a doses are deemed safe and tolerable, escalation will continue with Cohort 1.

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 venetoclax 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 venetoclax dose will increase).

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

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

Cohort	Obinutuzumab [a]	Polatuzumab Vedotin [b]	Venetoclax [c]
1a	1000 mg	1.4 mg/kg	200 mg
1	1000 mg	1.4 mg/kg	400 mg
2	1000 mg	1.8 mg/kg	400 mg
3	1000 mg	1.4 mg/kg	600 mg
4	1000 mg	1.8 mg/kg	600 mg
5	1000 mg	1.4 mg/kg	800 mg
6	1000 mg	1.8 mg/kg	800 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 cycle.

[c] Venetoclax will be administered orally every day of each cycle. Venetoclax should always be given before other agents administered on the same day, if applicable.

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 according to the dose-escalation plan described above.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to at least 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 according to 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 patients), the dose combination at which this occurs will be considered intolerable and the MTD will have been exceeded for polatuzumab vedotin and/or venetoclax in the G + Pola + V 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 fewer than 33% (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 venetoclax in the G + Pola + V treatment combination).
- If the MTD is not exceeded in any cohort, the highest dose combination administered in this study will be declared the maximum administered doses for polatuzumab vedotin and venetoclax in the G + Pola + V treatment combination.

If the MTD is exceeded in any cohort, de-escalation of the polatuzumab vedotin dose and/or venetoclax dose and adjustment of treatment schedules (e.g., venetoclax 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 venetoclax 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 pharmacodynamic 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, dosing 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 (from Day 1 of Cycle 1 to Day 1 of Cycle 2), cumulative or late toxicities that occur beyond the first cycle may be considered in determination of 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 venetoclax at their respective RP2Ds when combined with a fixed dose of obinutuzumab *in FL patients*.

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

All patients enrolled in the expansion phase will receive induction treatment, administered in 21-day cycles as outlined in Table 4. When study treatments are given on the same day, they will be administered sequentially in the following order: venetoclax, obinutuzumab, and polatuzumab vedotin.

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

	G + Pola + V (21-Day Cycles)
Cycle 1	• Venetoclax 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	• Venetoclax 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

IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

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

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment. Patients with FL who achieve a CR, PR, or stable disease at EOI will receive post-induction treatment (referred to as maintenance) with obinutuzumab and venetoclax, as outlined in Table 5. Polatuzumab vedotin will not be given as post-induction treatment. Post-induction treatment will continue until disease progression or unacceptable toxicity for up to 24 months for maintenance treatment. When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab.

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

Patients with FL	Maintenance treatment consisting of the following, administered for 24 months (Months 1–24): • Venetoclax at the RP2D (mg) PO once daily for 8 months (Months 1–8) • Obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months) for 24 months, starting with Month 2 (e.g., Months 2, 4, 6, 8, etc.)

FL = follicular lymphoma; IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

Note: When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab. A month is defined as 28 days.

The schedules of assessments are provided in Appendix 1 (FL).

3.1.3 *Rituximab Plus Polatuzumab Vedotin Plus Venetoclax Treatment Group (Patients with DLBCL)*

Based on the safety and efficacy results from the Phase III study (BO21005) in patients with DLBCL, the protocol has been amended to explore dose-finding of venetoclax 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 in Relapsed or Refractory DLBCL Patients*

The DLBCL dose-escalation phase will open with the purpose of identifying the RP2D for venetoclax 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 venetoclax 400-mg dose level and increase through Cohorts A, B, and C (see Figure 4).

Approximately 12–18 patients will be enrolled in the DLBCL 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 3.1.3.1.2.

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 above (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 dose of polatuzumab vedotin or rituximab or five consecutive daily doses of venetoclax 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 + V for a total of six cycles. Patients achieving a CR or PR at EOI will be eligible to receive consolidation treatment with R + V. A study schema is provided in Figure 2.

3.1.3.1.1 *Treatment Regimens for DLBCL Dose-Escalation Phase*

Patients enrolled in the DLBCL dose-escalation phase will receive induction treatment, administered in 21-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: venetoclax, rituximab, and polatuzumab vedotin.

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

Cycle	*R + Pola + V (21-Day Cycles)*
Cycles 1-6	• *Venetoclax 400, 600, or 800 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 + V = rituximab in combination with polatuzumab vedotin and venetoclax.

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

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment (referred to as consolidation). Patients who achieve a CR or PR at EOI will receive consolidation treatment with rituximab and venetoclax, as outlined in Table 7. Polatuzumab vedotin will not be given as consolidation treatment. Consolidation treatment will continue until disease progression or unacceptable toxicity for up to 8 months. When study treatments are given on the same day, venetoclax will be administered prior to rituximab.

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

Patient Population	*Regimen*
Patients with DLBCL	*Consolidation treatment consisting of the following, administered for approximately 8 months (from Months 1–8):* • *Venetoclax 400, 600, or 800 mg PO once daily for 8 months (Months 1–8)* • *Rituximab 375 mg/m² IV on Day 1 of every other month (i.e., every 2 months) starting with Month 2 (i.e., Months 2, 4, 6, and 8) for 8 months*

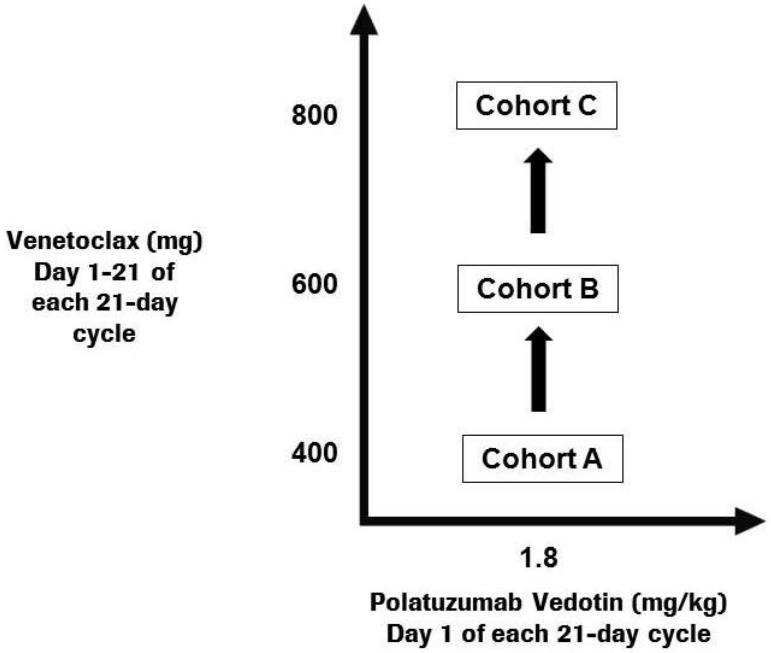
DLBCL = diffuse large B-cell lymphoma; IV = intravenous; PO = by mouth; QD = every day.

Note: A month is defined as 28 days. Treatments will be administered sequentially in the following order: venetoclax followed by rituximab.

3.1.3.1.2 *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 venetoclax 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 4 and Table 8.

Figure 4 *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]	*Venetoclax*
A	*375 mg/m²*	*1.8 mg/kg*	*400 mg*
B	*375 mg/m²*	*1.8 mg/kg*	*600 mg*
C	*375 mg/m²*	*1.8 mg/kg*	*800 mg*

[a] *Rituximab will be administered intravenously at a dose of 375 mg/m² on Day 1 of each 21-day cycle of induction*

[b] *Polatuzumab vedotin will be administered intravenously at a dose of 1.8 mg/kg on Day 1 of each 21-day cycle of induction*

[c] *Venetoclax will be administered orally on Days 1–21 of each 21-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 venetoclax in the R +Pola +V 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 MTD venetoclax in the R +Pola +V 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 venetoclax in the R +Pola +V treatment combination.*

If the MTD is exceeded in any cohort, de-escalation of the venetoclax dose and/or polatuzumab vedotin dose, and/or adjustment of treatment schedules (e.g., venetoclax 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, dosing administration/intensity, and PK (if available) data will be reviewed 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 (from Day 1 of Cycle 1 to Day 1 of Cycle 2), cumulative or late toxicities that occur beyond the first cycle may be considered in determination of 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 information 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 venetoclax 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: venetoclax, rituximab, and polatuzumab vedotin.

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

Cycle	*R + Pola + V (21-Day Cycles)*
Cycles 1-6	*Venetoclax at the RP2D (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 + V = rituximab in combination with polatuzumab vedotin and venetoclax.

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

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment. Patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with rituximab and venetoclax, as outlined in Table 10. Polatuzumab vedotin will not be given as post-induction treatment. Post-induction treatment will continue until disease progression or unacceptable toxicity for up to 8 months for consolidation treatment. When study treatments are given on the same day, venetoclax will be administered prior to rituximab.

Table 10 ***Consolidation Treatment for the DLBCL Expansion Phase***

Patients with DLBCL	*Consolidation treatment consisting of the following, administered for 8 months (Months 1–8):* • *Venetoclax at the RP2D (mg) PO once daily for 8 months (Months 1–8)* • *Rituximab 375 mg/m² IV on Day 1 of every other month (i.e., every 2 months) starting with Month 2 (i.e., Months 2, 4, 6, and 8) for 8 months*

DLBCL = diffuse large B-cell lymphoma; IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

Note: When study treatments are given on the same day, venetoclax will be administered prior to rituximab. A month is defined as 28 days.

3.1.4 Internal Monitoring Committee

An IMC will monitor patient safety throughout the study. The IMC will include 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 assessed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative, including data required for determination of the RP2Ds, 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, 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 review will consist of 2 parts: a radiology review and an oncology review. 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 the 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 in Section 3.2), 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 [FL] and Appendix 2 [DLBCL]).

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 FL patients 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 DLBCL patients 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 4.5 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 active and well-tolerated agents are needed following relapse. 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, which highlights the urgent need for novel therapeutic approaches for these patients.

On the basis of a compelling biologic and clinical rationale, as presented in Section 1.5 the addition of polatuzumab vedotin to obinutuzumab *or rituximab* and venetoclax is a promising approach to expand the number of patients with *R/R* FL and DLBCL who achieve remission and to prolong the duration of response 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 venetoclax and the RP2D for polatuzumab vedotin when given with obinutuzumab *in patients with R/R FL and the RP2D for venetoclax 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 mechanisms of action that have demonstrated clinical activity against B-cell lymphoma. Refer to Appendix 12 for descriptions of clinical studies that use the study drugs as single or doublet treatment.

As mentioned in Section 1.5, there is a strong rationale to expect an improved benefit-risk profile with the triplet combination of obinutuzumab *or rituximab combined with* polatuzumab vedotin and venetoclax. 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 5.1.6).

Rituximab is established as a standard of care to treat B-cell lymphomas. 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 (Study BO21005) and FL (Study BO21223).

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 obinutuzumab plus CHOP (G-CHOP) compared with rituximab plus CHOP (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, current protocol amendment patients with R/R FL will continue to receive obinutuzumab in combination with polatuzumab vedotin and venetoclax, while patients with R/R DLBCL will instead receive rituximab in combination with polatuzumab vedotin and venetoclax.

3.3.3 Rationale for Dose and Schedule

3.3.3.1 Rationale for Obinutuzumab Dosing Regimen *in Follicular Lymphoma Patients*

The dose and schedule of obinutuzumab in the induction regimen *for FL patients* will be 1000 mg intravenously (IV) on Days 1, 8, and 15 of Cycle 1 and Day 1 of each subsequent 21-day cycle (Cycles 2–6). This is based on the recommended dose and schedule (6–8 cycles depending on the trial) of obinutuzumab in the ongoing Phase III program in patients with NHL. 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 GAO4753g study (Sehn et al. 2015). The GAO4753g study 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 plus bendamustine followed by obinutuzumab maintenance arm vs. 14.9 months in the bendamustine arm; stratified 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 Follicular Lymphoma Patients*

For this study, dose escalation of polatuzumab vedotin for R/R FL patients 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 polatuzumab vedotin dosing for *the FL dose escalation phase* is 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 R/R NHL, the majority of whom had R/R FL or DLBCL. Most evidence of anti-tumor activity was observed at doses ≥1.8 mg/kg alone or in combination with rituximab (Advani et al. 2015; Palanca-Wessels et al. 2015).

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=approximately 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

1L=first line; CHP=cyclophosphamide, doxorubicin, prednisone; FL=follicular lymphoma; NHL=non-Hodgkin's lymphoma; Ph=phase; R/R=relapsed/refractory.

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

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

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

[d] In the Phase Ib portion of the study, *1 R/R FL patient was treated* with polatuzumab vedotin at 1.4 mg/kg*, and 1 R/F FL patient was treated with polatuzumab vedotin at* 1.8 mg/kg *(Forero-Torres 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 G-bendamustine. Since polatuzumab vedotin is being combined with obinutuzumab and chemotherapy (CHP or bendamustine) at 1.4 mg/kg or 1.8 mg/kg, dose escalation of polatuzumab vedotin *for the patients with R/R FL in this study* will begin at a dose level of 1.4 mg/kg (1 dose level below the highest allowed polatuzumab vedotin dose) and will escalate to a final dose of 1.8 mg/kg, if tolerated. This novel triplet, G+Pola+V, substitutes out the standard chemotherapy components with venetoclax, which in this combination may have the potential to extend treatment-free remissions and decrease toxicity, compared to combinations with standard chemotherapy components.

Because both obinutuzumab and venetoclax have their own degree of myelosuppression, the maximum dose of polatuzumab vedotin, 1.8 mg/kg, which can be

studied, may not be reached when combined with standard fixed doses of obinutuzumab and varied venetoclax doses and dose de-escalation may be warranted.

3.3.3.2.2 *Rationale for Polatuzumab Vedotin Dose in DLBCL Patients*

On the basis of the preliminary data from the DLBCL patients treated in Studies GO29044 and GO29365 at the dose level of polatuzumab vedotin at 1.8 mg/kg, this dose 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 preferredto 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 and venetoclax. In this amdendment, the R/R DLBCL dose-escalation phase will start at the dose level of 1.8 mg/kg and only the venetoclax dose will be escalated to determine an RP2D in this population.

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

The number of induction cycles (six 21-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 Venetoclax Dosing Regimen

Venetoclax dosing for this study is based on the experience from the Phase I study (M12-175) with single-agent venetoclax in patients with R/R NHL and from the Phase Ib study (M12-630) of venetoclax in combination with BR in patients with R/R NHL. In NHL, all responses in patients with FL have occurred at doses ≥600 mg daily. Although nonclinical data exist for synergistic activity at a dose equivalent of 400 mg daily (Souers et al. 2013), it is desirable to give venetoclax at the higher doses at which single-agent activity has been observed.

The M12-175 study explored a step-up dosing schedule in order to safely administer venetoclax by reducing the risk for TLS. This study showed safety of initial doses of up to 400 mg without clinically significant TLS in NHL. Final single-agent target doses of up to 800 mg have been shown to be tolerable in patients with CLL. Patients with NHL have received single-agent target doses of 1200 mg without DLTs.

Furthermore, Study M12-630 has shown tolerability of starting doses of venetoclax of up to 600 mg in combination with chemoimmunotherapy without observation of clinically significant TLS. To date, dose escalation is continuing with an 800-mg cohort.

In patients with R/R FL, the starting dose of venetoclax in this study will be 200 mg. *Because a case of laboratory TLS in a FL patient treated in this trial at a dose level of 400 mg venetoclax and 1.4 mg/kg polatuzumab has been observed, the* lower venetoclax dose level cohort of 200 mg was added in order to collect additional safety information for this novel triplet combination. Given that venetoclax will be given in conjunction with obinutuzumab and polatuzumab vedotin, potentially resulting in synergistic toxicities, doses of venetoclax up to the MTD achieved when given as monotherapy may not be tolerable in this combination. Following the 200 mg Cohort 1a clearing, subsequent dose cohorts will explore progressively higher starting and target doses up to a final daily dose of 800 mg if tolerated. The number of cycles of dosing (six 21-day cycles) is designed to provide a treatment duration consistent with other therapies for NHL that have been shown to be sufficient to provide durable responses.

In patients with R/R DLBCL, the starting dose of venetoclax in the dose-escalation phase will be 400 mg (Figure 4). Ongoing studies in the DLBCL population have confirmed that the TLS risk with doses up to 800 mg is low. No cases of TLS occurred in DLBCL patients in a trial with 800 mg venetoclax given intermittently at Days 4–10 of Cycle 1 and Days 1–10 of Cycles 2–8 in combination with R-CHOP (Zelenetz et al. 2016). The duration of venetoclax dosing is designed to provide overlapping exposure with obinutuzumab *or rituximab*. Extended dosing of venetoclax up to 1 year with obinutuzumab *or rituximab* will allow exploration of whether additional activity is observed during the extended (post-induction) dosing period.

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 to evaluate the triple combination as post-induction treatment.

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. 2013). A Phase III study, GAO4753g, investigated GB compared with bendamustine alone in patients with rituximab-refractory iNHL (n=396). Patients in the GB group who had not experienced disease progression at the end of induction 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.

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, *8* 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 3 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 Positron Emission Tomography-Computed Tomography-Defined Complete Response as the Primary Efficacy Endpoint

In DLBCL, the prognostic value of the post-treatment fluorodeoxyglucose (^{18}F-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 (see Appendix 5) and are commonly used to assess efficacy in medical practice and clinical trials in lymphoma. More recently, the value of post-induction PET-CT status has been investigated as a prognostic marker for long-term outcomes in patients with FL. In the first-line setting, results from a pooled analysis of 246 patients enrolled in 3 studies and who had 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 the Phase II study (BO21003) that compared obinutuzumab to 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 in 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 (Lugano 2014 criteria; Cheson et al. 2014).

3.3.5 Rationale for Biomarker Assessments

3.3.5.1 Rationale for Analysis of Diffuse Large B-Cell Lymphoma Subtype, *BCL2*, and *MYC*

There is increasing evidence for prognostic subgroups of DLBCL with differential response to standard treatments. DLBCL cell-of-origin subgroups (ABC and GCB), which are defined using gene expression profiling, have been associated with different clinical outcomes in patients who receive R-CHOP for DLBCL; GCB subgroups have demonstrated an improved prognosis compared with ABC groups (3-year survival rate of 84% vs. 56%, respectively; $p < 0.001$; Lenz et al. 2008).

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; the mutation is 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 (Savage et al. 2009; Dunleavy et al. 2014). 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; Johnson et al. 2012; Hu et al. 2013).

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). Activity of ADCs such as polatuzumab vedotin may depend 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 levels will be assessed.

Bcl-2 is an anti-apoptotic molecule overexpressed in many hematologic malignancies, including DLBCL, either through translocation of the *BCL2* gene in juxtaposition with the *IGH* gene t(14;18), through gene amplification, or by other mechanisms (Gascoyne et al. 1997). To evaluate the relationship between Bcl-2 protein expression and venetoclax activity in this study, Bcl-2 will be assessed.

3.3.5.3 Rationale for Assessment of Minimum Residual Disease

MRD measurement is an increasingly recognized tool for response assessment in B-cell malignancies. Circulating lymphoma cells and/or tumor DNA can be detected and quantified at low levels as MRD to assess treatment dynamics and monitor patients after treatment. 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 be predictive of 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 FDG-PET results caused by infiltration of metabolically active immune cells into the tumor (Kurtz et al. 2015). For these reasons, initially an MRD analysis will be performed in FL and subsequently analysis in DLBCL may be performed.

In this study, MRD will be quantified by circulating lymphoma cells and/or cell-free circulating tumor DNA as an exploratory endpoint.

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

Measurement of relevant protein, RNA and, DNA (including Bcl-2 and family members, genes associated with apoptosis, and those related to disease biology) will be performed at baseline to identify potential biomarkers that may be predictive of efficacy and also to understand mechanisms of resistance.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll patients with R/R FL or R/R 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 + V treatment group*: R/R FL after treatment with at least 1 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 + V treatment group:* R/R DLBCL after treatment with at least 1 prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody, with no curative option as determined by the investigator
- Histologically documented CD20-positive NHL 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, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

  Further details are provided in Section 4.5.6.

  If the patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, a core-needle biopsy is strongly recommended.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$1% per year during the treatment period and for at least 12 months after the last dose of polatuzumab vedotin, 30 days after the last dose of venetoclax, *12 months after last dose of rituximab, or* 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 ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  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, 30 days after the last dose of venetoclax, and 3 months after the last dose of obinutuzumab *or rituximab*. Men must refrain from donating sperm for the 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, 30 days after the last dose of venetoclax, and 3 months after the last dose of obinutuzumab *or rituximab*.

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:

- Known CD20-negative status at relapse or progression
- Prior allogeneic SCT
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1
- Prior standard or investigational anti-cancer therapy as specified below:
  - 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 $\leq$2 (per NCI CTCAE v4.0) prior to Day 1 of Cycle 1
- Grade 3b FL
- History of transformation of indolent disease to DLBCL
- Current Grade $>$1 peripheral neuropathy
- CNS lymphoma or leptomeningeal infiltration
- Treatment with systemic corticosteroids $>$20 mg/day prednisone or equivalent

  Patients who are receiving corticosteroids $\leq$20 mg/day, prednisone or equivalent, for non-lymphoma treatment reasons must be documented to be on a stable dose for at least 4 weeks prior to Day 1 of Cycle 1.

  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 start 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 the obinutuzumab, *rituximab,* polatuzumab vedotin, or venetoclax 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.
- Requirement for warfarin treatment (because of potential DDIs that may increase the exposure of warfarin)
- Treatment with the following agents within 7 days prior to the first dose of venetoclax:
  - Strong and moderate CYP3A inhibitors such as fluconazole, ketoconazole, and clarithromycin (see Appendix 10 for examples)
  - Strong and moderate CYP3A inducers such as rifampin and carbamazepine (see Appendix 10 for examples)
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade that contains Seville oranges), or star fruit within 3 days prior to the first dose of venetoclax
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- 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 PML
- 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
- 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 $< 1.5 \times 10^9$/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 with the use of 24-hour creatinine clearance or modified Cockcroft-Gault equation (eCCr; with use of the ideal body mass [IBM] instead of mass):

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{IBM (kg)} \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

    Or, if serum creatinine is in μmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{IBM (kg)} \bullet [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine (μmol/L)}}$$

  - AST or ALT $> 2.5 \times$ by 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 a negative serum pregnancy test result within 7 days 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 study of G + Pola + V in patients with R/R FL *and R + Pola + V in patiens 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 venetoclax dose combinations, through use of an interactive voice or Web-based response system (IxRS). During the *FL* expansion phase, all patients will be treated at RP2Ds for polatuzumab vedotin and venetoclax. If more than one combination of RP2Ds is identified, patients will be enrolled into multiple cohorts to allow for those combinations to be evaluated during the expansion phase. Post-induction treatment (for eligible patients only) will depend on lymphoma histology. Patients with FL will receive maintenance treatment with obinutuzumab and venetoclax for 24 months, and patients with DLBCL will receive consolidation treatment with *rituximab* and venetoclax for 8 months (see Section 3.1 for details). Patients enrolled in

the dose-escalation phase and expansion phase will receive fixed doses of obinutuzumab *or rituximab*.

Enrollment tracking will be performed through use of the IxRS. 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.

4.3 STUDY TREATMENTS

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

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Obinutuzumab

Obinutuzumab will be supplied by the Sponsor as a single-dose, sterile liquid formulation in a 50-mL glass vial that contains 1000 mg of obinutuzumab. For information on the formulation and handling of obinutuzumab, see the pharmacy manual and the Obinutuzumab Investigator's Brochure.

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 Venetoclax

Venetoclax will be supplied by the Sponsor as oral film-coated tablets of 100-mg strength in high-density polyethylene plastic bottles. For information on the formulation and handling of venetoclax, see the pharmacy manual and the Venetoclax Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

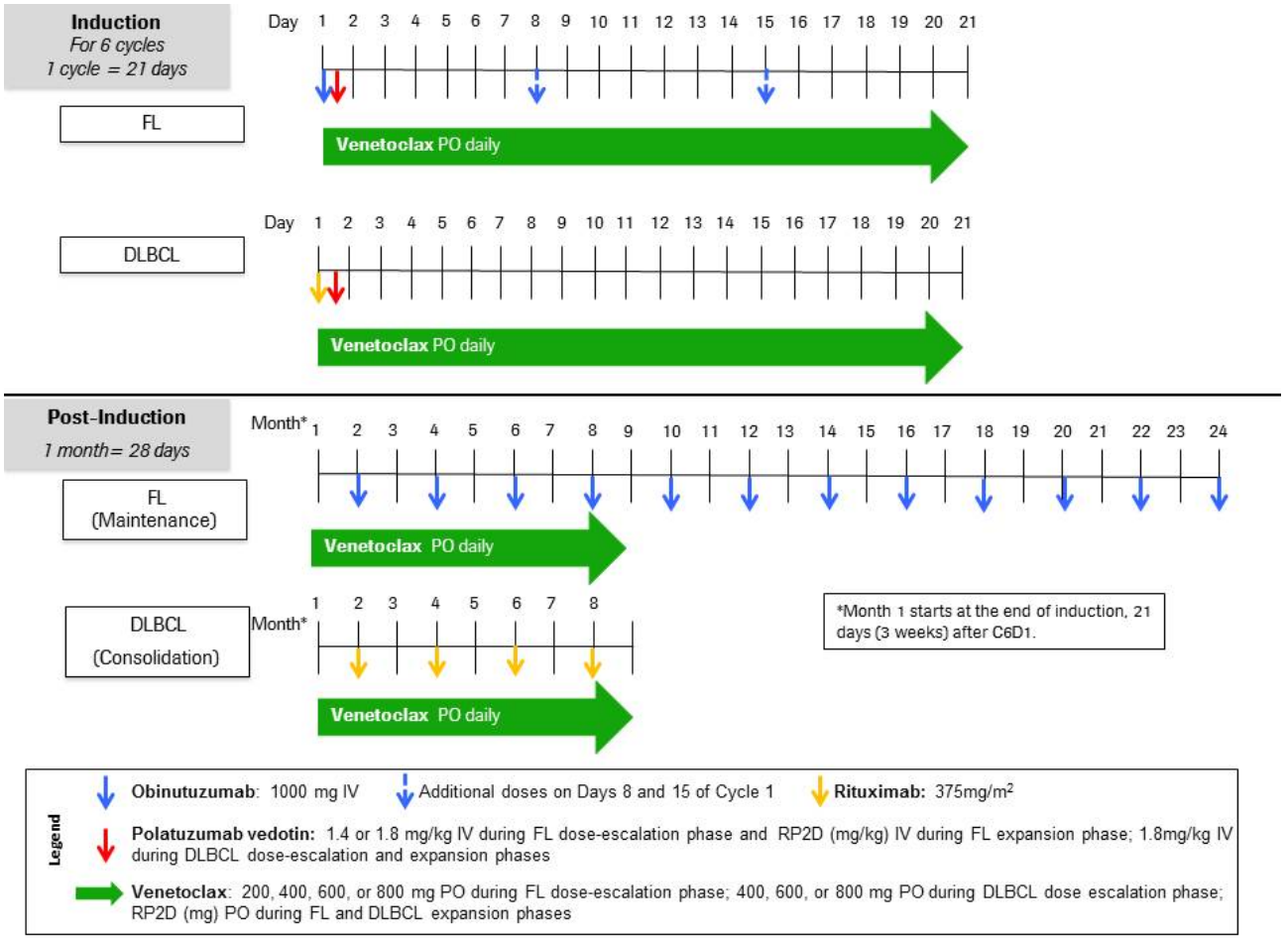
The treatment regimens are summarized in Section 3.1 and depicted in Figure 5.

Patients enrolled in the dose-escalation phase or the expansion phase will receive six 21-day cycles of induction treatment with obinutuzumab *or rituximab*, polatuzumab vedotin, and venetoclax. When study treatments are given on the same day, they will be administered sequentially in the following order: venetoclax, obinutuzumab *or rituximab*, and polatuzumab vedotin.

After completion of induction treatment, patients in both phases will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. However, venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment.

During both phases, patients with DLBCL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as consolidation) with venetoclax and *rituximab* for 8 months, and patients with FL who achieve a CR, PR, or stable disease at EOI will receive post-induction treatment (referred to as maintenance) with venetoclax for 8 months and obinutuzumab for 24 months. When study treatments are given on the same day, venetoclax will be administered prior to obinutuzumab *or rituximab*.

Figure 5 Induction and Post-Induction Treatment Regimens



DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

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

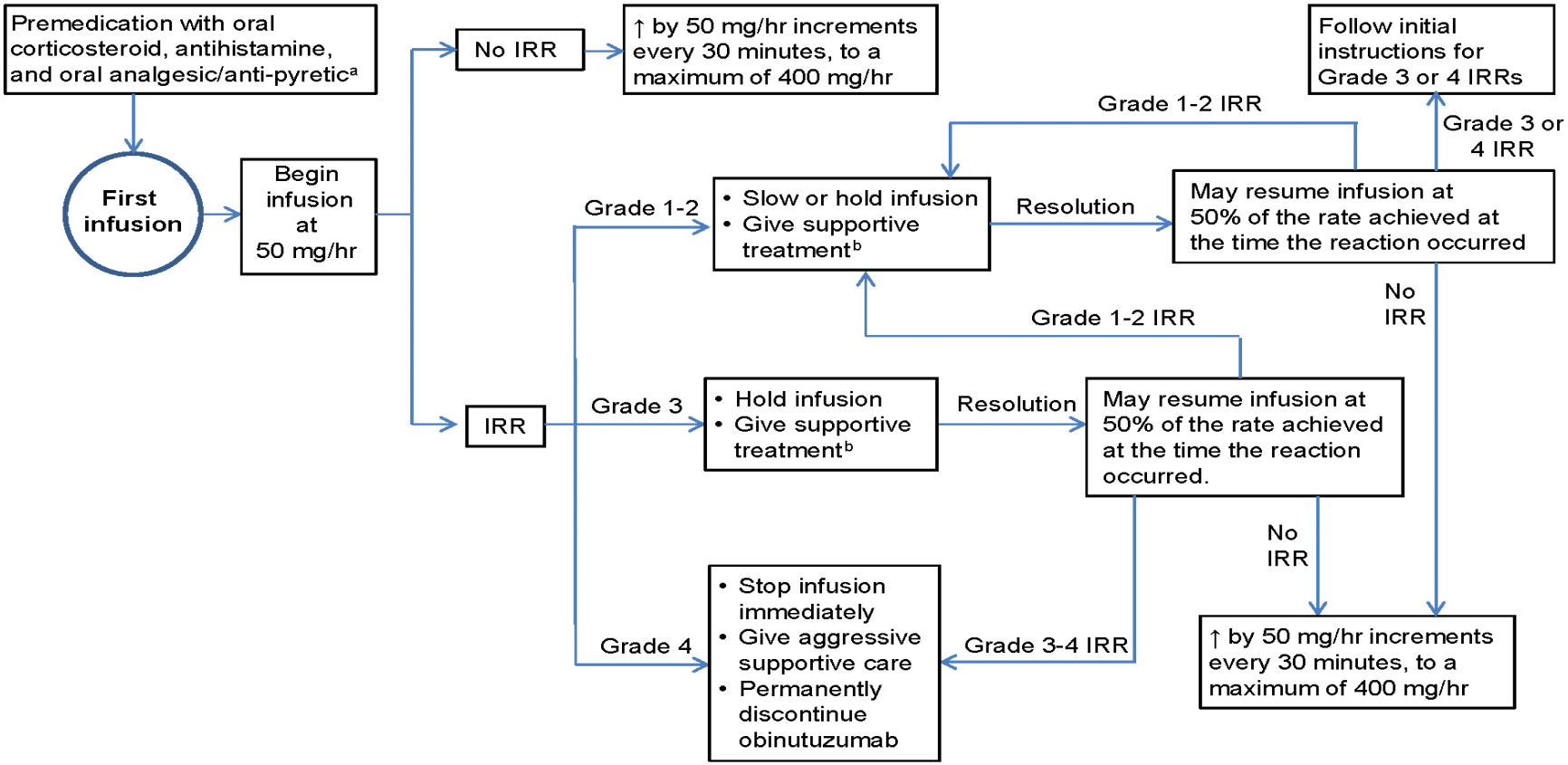
Obinutuzumab will be administered by IV infusion at an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of the first cycle and on Day 1 of each subsequent cycle during induction treatment, and on Day 1 of every other month (i.e., every 2 months) during maintenance treatment (eligible patients with 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 health care provider. Obinutuzumab infusions will be administered according to the instructions outlined in Figure 6 and Figure 7. 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 modifications for obinutuzumab are allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.

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 9.

Figure 6 Guidelines for Obinutuzumab Infusions: First Infusion

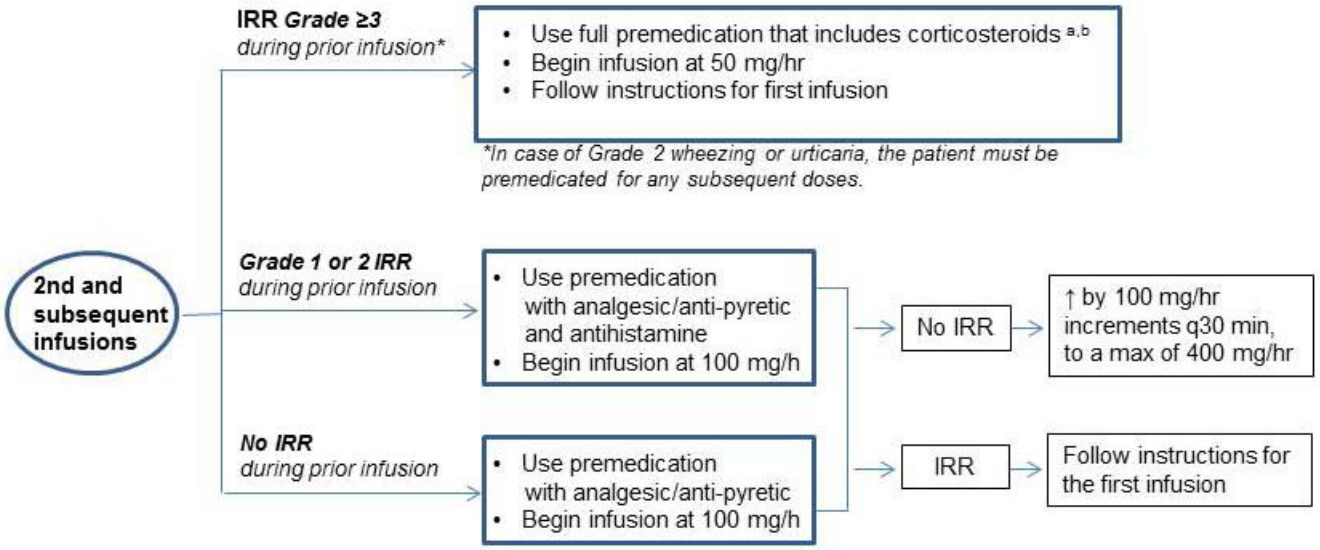


IRR = infusion-related reaction; IV = intravenous.

[a] All patients should receive full premedication with an oral corticosteroid, antihistamine, and oral analgesic/anti-pyretic 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. IV 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 9.

Figure 7 Guidelines for Obinutuzumab Infusions: Second and Subsequent Infusions



IRR = infusion-related reaction.

[a] Patients should receive full premedication with an oral corticosteroid, antihistamine, and oral analgesic/anti-pyretic prior to the obinutuzumab infusion. Refer to Section 4.3.2.5 for details. 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. *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. If a patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as a rapid infusion (over 60–90 minutes) in accordance with local institutional guidelines.

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 9.

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 (Day −28 to Day −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 that contain isotonic sodium chloride solution (0.9% NaCl), polatuzumab vedotin will be administered by IV infusion using a dedicated standard administration set with 0.2-µm 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 who experience 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.

There will be no dose reductions of polatuzumab vedotin for any toxicity except neurotoxicity (see Table 21 in Section 5.1.7.3).

4.3.2.4 Venetoclax

During the dose-escalation phase, the dose of venetoclax for each patient will depend on dose assignment (200, 400, 600, or 800 mg). During the expansion phase, the dose of venetoclax for each patient will depend on the RP2D established during the dose-escalation phase. Venetoclax will be taken orally once daily. After completion of induction treatment, patients in both phases will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. However, venetoclax will be discontinued if response assessments at EOI indicate that a patient is not eligible for post-induction treatment. Eligible patients will continue to take venetoclax at the

designated daily dose for 8 months, as part of the post-induction treatment regimen. Alternative dosing schedules may be explored. Venetoclax should always be given before other agents administered on the same day, if applicable.

All patients who receive venetoclax must receive prophylaxis for TLS (see Section 5.1.6) before the initiation of venetoclax in the G+Pola+V *and* $R+Pola+V$ combination treatment. Patients who receive venetoclax who are at high risk for TLS or with compromised renal function must be hospitalized on the first day of Cycle 1 (see Section 5.1.6.2).

Patients will self-administer venetoclax tablets by mouth once daily. Each dose of venetoclax will be taken orally once daily with approximately 240 mL of water within approximately 30 minutes after the completion of breakfast or the subject's first meal of the day. A meal containing approximately 30% of the total caloric content from fat is recommended to ensure adequate absorption of venetoclax. The Standard American Heart Association Healthy (Low-Fat) Breakfast includes 1 box cereal (30-40 g), skim milk (240 mL), 1 boiled egg, 1 slice of toast, and margarine (10 g) for approximately 520 Kcal with approximately 17 grams of fat.

On days that pre-dose PK sampling is required, the patient's first meal of the day (e.g., breakfast) will be consumed in the morning at the clinic, and venetoclax dosing will occur in the clinic after completion of the meal to facilitate PK sampling.

If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be provided. If tablets are not identified, or if any are not intact, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible and ensure that the dose is taken with food within 8 hours after the scheduled time of the missed dose. Otherwise, the missed dose should not be taken.

Patient compliance with the assigned daily dose of venetoclax will be assessed by standard pill counts. Bottles that contain venetoclax tablets will be given to patients at regular scheduled visits. Previously distributed bottles will be returned to the clinic, and tablets will be counted. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

Guidelines for venetoclax dosage modification and treatment interruption or discontinuation are provided in Section 5.1.7.1.

4.3.2.5 Premedication

Patients should receive premedication as outlined in Table 13.

Table 13 Premedication

Timepoint	Patients who Require 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/ anti-pyretic [c]	Administer ≥30 minutes prior to obinutuzumab *or rituximab* infusion.
	• All patients	• Allopurinol or suitable alternative such as rasburicase, along with adequate hydration	Administer prior to venetoclax.
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 ≥30 minutes prior to obinutuzumab infusion. *For patients receiving rituximab, premedicaion may be omitted at the investigator's discretion.*
	• *Patients with Grade 1 or 2 IRR during the previous infusion*	• *Antihistamine drug [b]* • *Oral analgesic/ anti-pyretic [c]*	*Administer ≥30 minutes prior to obinutuzumab or rituximab infusion.*
	• Patients with Grade 3 IRR, wheezing, *urticaria*, 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/ anti-pyretic [c]	Administer ≥30 minutes prior to obinutuzumab *or rituximab* infusion.

Timepoint	Patients who Require Premedication	Premedication	Administration
	• Patients still at risk for tumor lysis syndrome	• Allopurinol or suitable alternative such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab *or rituximab* infusion.

IRR = infusion-related reaction.

[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 venetoclax) 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.

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 Venetoclax

Currently, the Sponsor does not have any plans to provide obinutuzumab, *rituximab,* polatuzumab vedotin, venetoclax, or any other study treatments or interventions to patients who have completed the study. The Sponsor will evaluate whether to continue to provide obinutuzumab*, rituximab*, polatuzumab vedotin, and venetoclax 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, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

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

Premedication is permitted as described in Section 4.3.2.5:

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

Patients who receive concomitant medication that could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding. Replace prior vitamin K antagonist therapy with low-molecular-weight heparin (LMWH) prior to Day 1 of Cycle 1.

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.

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 and Cautionary Therapy for Concomitant Medications

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

- Any anti-cancer therapy, approved or investigational, other than intrathecal CNS 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

Use of the following concomitant medications is prohibited within 7 days before the first dose and during the study:

- Steroid therapy for antineoplastic intent
- Strong and moderate CYP3A inhibitors such as fluconazole, ketoconazole, and clarithromycin (see Appendix 10 for examples)
- Strong and moderate CYP3A inducers such as rifampin, carbamazepine, phenytoin, and St. John's wort (see Appendix 10 for examples)

Concomitant medications that fall into the categories below could potentially lead to adverse reaction(s) and should be considered cautionary (except where noted). If a potential study patient is taking any of the medications in the categories described below, the investigator will assess and document the use of medications known or suspected to fall in the following medication categories:

- Weak CYP3A inducers
- Weak CYP3A inhibitors
- P-gp substrates
- BCRP substrates

- OATP1B1/1B3 substrates
- P-gp inhibitors
- BCRP inhibitors
- OATP1B1/B3 inhibitors
- Warfarin should be used with caution during the study. The investigator should discuss the use of other anticoagulation therapies, such as systemic or low molecular weight heparin, with the Medical Monitor.

A sample list of excluded medications and cautionary medications that fall into the categories within this section can be found in Appendix 10. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label.

4.4.3 Prohibited Food

Use of the following foods is prohibited during the study and for at least 3 days before initiation of study treatment:

- Grapefruit
- Grapefruit juice
- Products that contain grapefruit
- Seville oranges (including marmalade that contains Seville oranges)
- Star fruit

4.5 STUDY ASSESSMENTS

Please see Appendix 1 and Appendix 2 for the schedule 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 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 (seeAppendix 6)
- B symptoms (unexplained fever $>$38°C, night sweats, unexplained weight loss $>$10% of body weight over 6 months)
- Ann Arbor staging (see Appendix 7)
- For patients with FL: Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI2 (see Appendix 8)
- For patients with DLBCL: IPI (see Appendix 8)
- 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.

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 physical examinations (see Section 4.5.3) and PET and CT scans using the Lugano 2014 criteria (see Appendix 5), 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 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. Diagnostic CT scans obtained as a part of a combined PET-CT scans are allowable as long as they are acquired according to the standardized imaging manual.

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, 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 CrCl, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, uric acid, phosphate, 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.
- β_2 microglobulin
- Coagulation: INR, aPTT (or PTT), PT
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening (within 7 days of Day 1 of Cycle 1).

- Viral serology

  Hepatitis B testing includes HBsAg and total HBcAb.

  Hepatitis C testing includes HCV antibody.

  HIV (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 assessment of PK of polatuzumab vedotin and relevant analytes using a validated assay
- Plasma samples for venetoclax PK analysis using a validated assay. If appropriate, pharmacokinetics of other relevant metabolites may also be evaluated.
- Serum samples for assessment of obinutuzumab HAHAs using a validated assay
- Serum samples for assessment of ATAs to polatuzumab vedotin using a validated assay
- Tumor tissue samples 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 patient has had anti-lymphoma treatment between the time of the prior biopsy and the time of study treatment initiation, a core-needle biopsy is 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 tissue samples obtained at the time of progression (unless no adequate tumor site is accessible) for exploratory research on candidate biomarkers (see Table 14)
- Whole blood samples for isolation of peripheral blood mononuclear cells and plasma for exploratory research on candidate biomarkers (see Table 14)
- Whole blood samples for lymphocyte immunophenotyping (see Table 14)

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 14. Results from exploratory biomarker research will not be shared with investigators or study participants, unless required by law, given the complexity and exploratory nature of these analyses.

Table 14 Proposed Non-Inherited Biomarkers

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Archival or fresh pre-treatment, and progression tumor tissue	Prior to study (archival) or baseline (fresh); 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 • Lymphoma-related genetic changes (DNA) and gene expression (mRNA) or protein expression (IHC) associated with response or potential resistance • Lymphoma index clone in MRD
Peripheral blood mononuclear cells and plasma isolated from whole blood	Baseline, subsequent timepoints during treatment	• 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)

ABC = activated B cell–like; DBLCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; GCB = germinal-center B cell–like; IHC = immunohistochemistry; MRD = minimum residual disease; mRNA = messenger RNA; NK = natural killer.

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 PK 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.

4.5.7.1 Multigated Acquisition Scan/Echocardiogram

MUGA scans will be obtained prior to treatment to assess left ventricular ejection fraction (LVEF; see Appendix 1). Echocardiogram may be used if MUGA is not available. Any clinically significant changes in cardiac function must be reported within 7 days.

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 or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (see 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, venetoclax, 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, PBMCs, plasma, and serum)

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. 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 Roche Clinical Repository 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 GO29833 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 GO29833.

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 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
- Disease progression
- Pregnancy

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 completion of the DLT assessment window for reasons other than a DLT will be replaced by an additional patient at that same dose level.
- Patients who discontinue before having received 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 Conference on 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

*P*olatuzumab vedotin *is* not *a* marketed product, and *venetoclax* is not approved for R/R FL or DLBCL. *Obinutuzumab is only approved in combination with bendamustine for the treatment of R/R FL and rituximab is not approved for the treatment of 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 venetoclax

in completed and ongoing studies. The anticipated important safety risks of obinutuzumab, *rituximab,* polatuzumab vedotin, and venetoclax are outlined below. Please refer to the Obinutuzumab*, Rituximab*, Polatuzumab Vedotin, and Venetoclax Investigator's Brochures 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 anti-hypertensive 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 anti-hypertensive medication.

Patients who have preexisting cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the postinfusion period.

Guidelines for medical management of IRRs and anaphylaxis are provided in Section 4.3.2.1 and Appendix 9.

5.1.1.2 Tumor Lysis Syndrome

TLS, including fatal events, has been reported with obinutuzumab administration. Patients should receive adequate hydration and premedication with allopurinol or an alternative uricostatic as indicated in Section 4.3.2.5 (see Table 13). Additional guidelines for management of TLS in this study are provided in Section 5.1.6.

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 5.1.7.2.

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 CLL patients exposed to obinutuzumab, fatal hemorrhagic events have also been reported during Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients who receive concomitant medication that could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding. Replace prior vitamin K antagonist therapy with LMWH prior to Day 1 of Cycle 1. Use of all concomitant therapies, which could possibly worsen thrombocytopenia-related events such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle. 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. Particular attention should be given to patients who have previously received highly immunosuppressive treatment, such as high-dose chemotherapy and SCT. Patients positive for HBsAg or HBcAb are not eligible for this study.

John Cunningham virus (JCV) infection that results in PML has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient who presents 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 JCV DNA). Additional guidelines for medical management of PML in this study are provided in Section 5.1.7.2.

5.1.1.6 *Impaired* Immunization *Response*

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

Gastrointestinal perforation has been reported in patients with NHL treated with obinutuzumab, including fatal events. Patients with gastrointestinal involvement should be monitored for signs of gastrointestinal 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/toxic epidermal necrolysis), 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 (Grade 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, which 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 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, since 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 1 to 13 weeks following rituximab exposure. The majority of the Stevens-Johnson syndrome and toxic epidermal necrolysis 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 Stevens-Johnson syndrome and toxic epidermal necrolysis.

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 Phase 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. Refer also to the current version of Investigator's Brochure for complete and updated details.

5.1.3.1 *Identified Risks*

Based on clinical experience with polatuzumab vedotin in patients treated in the current Phase I and Phase 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). Adequate hematologic function should be confirmed before initiation of study treatment. Patients who receive 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 5.1.7.2. The use of G-CSF for neutropenia is described in Section 5.1.7.2.

Peripheral Neuropathy

Patients who receive 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 who experience new or worsening peripheral neuropathy may require a dose delay or discontinuation of treatment and should be managed according to the protocol.

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. The reported incidence of infection in chemotherapy courses for B-cell lymphoma associated with <500 granulocytes/μL was higher than those with ≥ 500 granulocytes/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 JCV by polymerase chain reaction 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. Precautions for suspected anaphylactic reaction during study drug infusions are provided in Section 4.3.2.5. 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 4.3.2.5). Significant issues with polatuzumab vedotin IRRs have not been observed.

Similar considerations regarding infusion reactions are applicable for obinutuzumab. Refer to Section 4.3.2.5 for additional information.

Tumor Lysis Syndrome

There is a potential risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. Patients will receive tumor lysis prophylaxis (e.g., allopurinol ≥ 300 mg/day orally or a suitable alternative treatment [according to institutional practice] starting prior to study treatment) and must be well hydrated before the initiation of study treatment at Cycle 1 Day 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 Grade 3 laboratory TLS was reported in this ongoing study. 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 patient was asymptomatic. The TLS event was considered related to all 3 study treatments and resolved in 4 days with supportive care. One case of TLS attributed to polatuzumab vedotin has been reported (GO27834); however, the laboratory elevations did not meet the Howard criteria for TLS (see Appendix 13). The suspected TLS event resolved after 3 days of supportive care (see polatuzumab vedotin IB for case details).

Bone Marrow Toxicity

Patients with inadequate hematologic function will be excluded from this study (see Section 4.1.2). Patients who receive 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 5.1.7.2.

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 Phase 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 who received polatuzumab vedotin and have ranged in intensity from Grades 1 to 3. These elevations have been reversible with and without dose modification.

5.1.4 Risks Associated with Venetoclax

Phase I experience with venetoclax has demonstrated that it is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible; see the Venetoclax Investigator's Brochure for more information.

On the basis of clinical data to date, the following known and suspected risks with venetoclax are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.7.1, Table 16, and Table 17.

5.1.4.1 Tumor Lysis Syndrome

To date, the principal adverse reaction associated with venetoclax in the ongoing single-agent Phase I dose-escalation study M12-175 has been TLS (primarily, but not exclusively, related to the first dose). TLS, including cases that have led to clinical sequelae and death, has been observed in patients with CLL at venetoclax doses of $\geq$50 mg. Clinically relevant TLS has been observed only in patients with CLL (highest risk in patients with nodes $\geq$10 cm in size or absolute lymphocyte count $\geq 25 \times 10^9$/L if nodes size is $\geq$5 cm) and not in NHL (other than MCL) patients to date. Very few cases of non-clinically relevant electrolyte changes (e.g., elevated phosphate levels marginally above the ULN and 25% changes from baseline in uric acid levels that remained within the normal reference range) have been observed in NHL patients to date. However, TLS is a risk for patients with NHL who are treated with high cell–killing agents. The risk is greatest for those with bulky disease, elevated pretreatment LDH levels, elevated leukocyte count, and dehydration. Patients with bulky disease, defined as any lymph node $\geq$10 cm on the screening CT scan, are considered at higher risk of TLS. In light of potential synergy between venetoclax, obinutuzumab, and polatuzumab vedotin, rigorous TLS monitoring and prophylaxis will be instituted in this study (see Section 5.1.6).

5.1.4.2 Cytopenia

Effects on lymphocyte numbers are expected on the basis of the mechanism of action, and modest reductions in neutrophils have been observed with venetoclax therapy in patients. Thrombocytopenia and anemia have been reported with venetoclax in the ongoing Phase I, single-agent, dose-escalation study M12-175 that is being conducted in heavily pretreated patients with CLL and NHL. In most cases, the condition was preexisting. Adverse events of neutropenia and thrombocytopenia, including Grade $\geq$3 events, have been reported in the oncology studies, with a slightly higher frequency in

studies in which venetoclax was combined with other chemotherapeutic agents. In this study, blood counts will be monitored closely throughout treatment (see the schedules of assessments in Appendix 1 and Appendix 2). Growth factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infections. Dose interruptions or reductions will be allowed on the basis of toxicity.

5.1.4.3 Infectious Complications

Infections of various types have occurred in patients in the ongoing, Phase I, single-agent dose-escalation study M12-175. NHL can be associated with impaired immune function and increased infections; it is unclear whether or how much the incidence could be further increased because of obinutuzumab, polatuzumab vedotin and venetoclax treatment. Patients in this study will be closely monitored for infections, and prompt therapy will be instituted as necessary. Patients are allowed to receive concomitant prophylactic anti-infective therapy at the investigator's discretion.

5.1.4.4 Effects on Cardiac Function

Nonclinical studies demonstrated decreases in cardiac function of approximately 20% in healthy laboratory animals. No patterns of adverse events indicating changes in cardiac function have been reported in clinical studies to date. However, the number of patients exposed and the duration of exposure are still relatively low. Patients enrolled in this study are required to have ECGs and assessments of left ventricular ejection fraction at screening and as clinically indicated afterwards.

5.1.4.5 Effects on Fertility

There is a potential for decreased spermatogenesis. Male patients who are considering preservation of fertility should bank sperm before treatment with venetoclax. Long-term effects of venetoclax on either male or female reproductive potential are unknown.

5.1.4.6 Drug Interactions

DDIs may occur with venetoclax. See Section 4.4 and Appendix 10 for a list of medications that are to be excluded or used with caution in patients who receive venetoclax.

5.1.5 Risks of Overlapping Toxicities

The overlapping toxicities from the combined administration of obinutuzumab *or rituximab*, polatuzumab vedotin, and venetoclax are anticipated in this clinical trial and will be closely monitored and managed 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 NHL, obinutuzumab was associated with a 5% incidence of Grade 3–4 neutropenia. Because obinutuzumab is expected to have an incidence of neutropenia that is higher than 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. Any applicable findings from this study that affect patient safety will be applied to this study.

Venetoclax has also been associated with hematologic adverse events, including neutropenia. Therefore, the combination of obinutuzumab *or rituximab*, polatuzumab vedotin, and venetoclax is anticipated to have overlapping hematologic toxicity and will be closely monitored. Guidelines for management of patients who develop hematologic toxicities are provided in Section 5.1.6. In addition to the standard hematologic monitoring, patients enrolled in this study will be closely monitored for evidence of infections.

There is the identified risk of TLS if treatment with obinutuzumab *or rituximab* or venetoclax and a theoretical risk for polatuzumab vedotin since 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 Section 5.1.6.

5.1.6 Prophylaxis and Monitoring for Tumor Lysis Syndrome

TLS is a risk for patients with NHL who are treated with high cell–killing agents. Risk is highest for those with bulky disease, circulating lymphoma cells, elevated pretreatment LDH levels, elevated leukocyte count, impaired renal function, and dehydration. Patients with bulky disease, defined as any lymph node ≥10 cm on the screening CT scan, are considered to potentially be at higher risk of TLS and must be hospitalized for more intensive monitoring during the initial dose of venetoclax. Patients who do not meet these criteria may be considered at high risk for TLS and may be hospitalized per discussion with the investigator and Medical Monitor.

5.1.6.1 Prophylaxis and Monitoring for All Patients

All patients must receive prophylaxis for TLS before the initiation of the first dose of G+Pola+V, as outlined in Table 15.

Table 15 Prophylaxis and Assessments for Tumor Lysis Syndrome

	High Risk	Regular Risk
Definition	• Bulky disease, defined as: ○ Any lymph node ≥ 10 cm on the screening CT scan • Circulating lymphoma cells • Other characteristics deemed by the investigator to confer high risk of TLS	• All other patients not meeting definition of high risk
Hospitalization	Required for intensive monitoring during initial dose of venetoclax (See Hospitalization section below).	Not required, but may be hospitalized per discussion with the investigator and Medical Monitor
TLS prophylaxis	**All patients must receive prophylaxis for TLS, which will include:** • Appropriate hydration, which consists of a fluid intake of approximately 2–3 L/day starting 24–48 hours before the start of treatment, which can occur as oral intake or intravenous fluids • Administration of an agent to reduce uric acid (such as allopurinol 300 mg/day orally beginning 72 hours before dose and continuing for 3–7 days afterward) or rasburicase IV (for high-risk patients with elevated uric acid levels before treatment, or when otherwise judged to be appropriate by the investigator) until normalization of serum uric acid and other laboratory evidence of TLS (e.g., elevated serum LDH levels). • Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities before the first dose of venetoclax, or the patient should receive additional prophylactic treatment and hydration before the initiation of dosing.	
Assessments	On the day of the initial visit with administration of venetoclax (Cycle 1, Day 1): • Serial vital signs will be recorded • Chemistry and hematology samples will be drawn (see Appendix 1 and Appendix 2): – Before the dose (0–4 hours before venetoclax administration). Predose laboratory samples should be drawn within 0–4 hours before venetoclax administration. These samples are to be sent immediately to the laboratory and the investigator or designee must review the results promptly. If laboratory values from within 24 hours have demonstrated no clinically significant abnormalities, the chemistry and hematologic values drawn on the day of initial venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0–4 hours) labs should still be drawn and these values will serve a baseline for later laboratory values in the assessment of laboratory evidence of TLS. – 8 hours following the dose – 12 hours following the dose (only for hospitalized patients) – 24 hours following the dose Laboratory results 24 hours postdose must be reviewed before the patient receives the dose of venetoclax for that day (i.e., Day 2). Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring as outlined in Appendix 9. Patients still at risk of TLS before the subsequent dose should receive adequate prophylaxis and monitoring.	

LDH = lactate dehydrogenase; TLS = tumor lysis syndrome.

5.1.6.2 Hospitalization for Patients at Higher Risk for Tumor Lysis Syndrome

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

- Any lymph node $\geq$10 cm on the screening CT scan
- Circulating lymphoma cells, defined by out of range (high) Absolute Lymphocyte Count (ALC) or the presence of abnormal cells in the peripheral blood differential

In addition to characteristics requiring mandatory hospitalization, other patient characteristics may suggest an increased risk of TLS. These include, but are not limited to, the following:

- Overall disease burden (e.g. several enlarged lymph nodes, even if none reaching 10 cm)
- Elevated LDH levels
- Impaired renal function (CrCl $<$80 mL/min)
- Extensive bone marrow involvement
- Dehydration

Hospitalization is not mandatory for patients exhibiting above characteristics, but these and any other factors considered relevant to TLS should be considered in an overall assessment of the patient's state and their risk of TLS. Investigators should use their judgment in assessing TLS risk for their patients. Any patient that an investigator or other clinical provider considers to be at risk for TLS for the first dose of venetoclax, may be hospitalized and should be discussed with the Medical Monitor.

Hospitalization Procedures

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

Serial vital signs and TLS laboratory samples will be drawn (serum chemistry as defined in Section 4.5.6) before the first dose of venetoclax and at 8-, 12-, and 24-hours

postdose; additionally, hematologic samples will be drawn at 8- and 24-hours postdose (see Appendix 1 and Appendix 2). These samples are to be sent STAT to the laboratory and the investigator or designee must review the results promptly. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results from 24-hours postdose must be reviewed before the patient receives the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 11, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome.

Patients determined by the investigator to be at particularly high risk for TLS may, in addition to hospitalization, delay the start of venetoclax to Day 8 in Cycle 1 following discussion with the Medical Monitor.

5.1.7 Management of Specific Adverse Events

Patients should be assessed clinically before each study treatment administration. Guidelines for management of toxicities are based on laboratory values obtained within 72 hours prior to Day 1 of each cycle during induction or each month during maintenance (FL) or consolidation (DLBCL) or within 24 hours prior to Days 8 and 15 of Cycle 1 *for patients receiving obinutuzumab*. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.

There will be no dose reductions of obinutuzumab *or rituximab*. There will be no dose reductions of polatuzumab vedotin for any toxicity except neurotoxicity (see Section 5.1.7.2). *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.* Study treatment may be delayed for toxicity for a maximum amount of time (e.g., 21 days), as specified in the tables below. If study treatment is delayed for longer than the specified maximum, study treatment will be permanently discontinued. When a treatment cycle is delayed because of toxicity resulting from any component of the regimen, all study treatments 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 any of the study treatment components. Depending on causality, toxicities that occur during the cycle and subside prior to the next cycle may not trigger the suggested dose modifications.

Guidelines for management of toxicities during induction treatment are provided in Section 5.1.7.2. Guidelines for management of toxicities during consolidation or maintenance treatment are provided in Section 5.1.7.3.

5.1.7.1 Venetoclax Dose Reduction and Re-Escalation Steps

The dose of venetoclax may be reduced according to the following dose reduction steps based on the starting dose. Re-escalation is permitted by investigator after discussion with the Medical Monitor if toxicity improves to Grade ≤1.

Table 16 Venetoclax Dose Reduction Steps during Induction

	Dose Reduction	
Starting Dose	Step 1	Step 2
800 mg	600 mg	400 mg
600 mg	400 mg	200 mg
400 mg	200 mg	100 mg
200 mg	100 mg	none

Table 17 Venetoclax Dose Reduction Steps during Maintenance

	Dose Reduction			
Starting Dose	Step 1	Step 2	Step 3	Step 4
800 mg	600 mg	400 mg	200 mg	100 mg
600 mg	400 mg	200 mg	100 mg	none
400 mg	200 mg	100 mg	none	none
200 mg	100 mg	none	none	none

5.1.7.2 Toxicities during Induction Treatment

Hematologic Toxicities during Induction Treatment

Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia is not considered hematologic toxicity but an expected outcome of therapy. Table 18 provides guidelines for management of hematologic toxicities that occur during induction treatment, with the exception of Days 8 and 15 of Cycle 1555. Table 19 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 18 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 who have had one or no prior venetoclax 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. • If improvement to Grade $\leq$2 or baseline occurs within 7 days after the scheduled date for the next cycle, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume venetoclax at current dose. • If improvement to Grade $\leq$2 or baseline occurs within 8–14 days after the scheduled date for the next cycle, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume venetoclax at a reduced dose [a,b] for current and subsequent cycles per guidelines in Table 16. No more than 2 dose *level* reductions *from the original dose* of venetoclax are allowed *during induction*. • If study treatment is withheld for $>$21 days, permanently discontinue study treatment. **For patients who have had two prior venetoclax dose reductions:** • Permanently discontinue study treatment.

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 venetoclax dose.

Table 19 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 infection	• Withhold obinutuzumab *and venetoclax* until resolution of fever and infection (as applicable). • If the event is ongoing at Day 1 Cycle 2, follow instructions in Table 20. Note: Obinutuzumab *and venetoclax* should not be withheld for asymptomatic neutropenia.
Severe thrombocytopenia [a] or bleeding	• Withhold obinutuzumab *and venetoclax* until platelet count ≥ 50,000/μL and 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 Cycle 2, follow instructions in Table 18.

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 20 provides guidelines for management of non-hematologic toxicities that occur during induction treatment.

Table 20 Guidelines for Management of Non-Hematologic Toxicities That Occur 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.
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.* Anaphylaxis precautions are provided in Appendix 9.
TLS	• Withhold study treatment. [a] • Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. • If symptoms have resolved completely, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume venetoclax at current dose.
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* and polatuzumab vedotin at full dose and resume venetoclax 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. [a] • If improvement to Grade ≤ 1, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume venetoclax at next lower dose [a] for current and subsequent cycles per guidelines in Table 16. No more than 2 dose *level* reductions *from original dose* of venetoclax are allowed during induction. Patients who have had two prior dose reductions should be permanently discontinued. • Permanently discontinue study treatment for life-threatening liver toxicity.

Table 20 Guidelines for Management of Non-Hematologic Toxicities That Occur During Induction (cont.)

Event	Grade	Action to Be Taken
Neurotoxicity	Grade 4	• Permanently discontinue polatuzumab vedotin and all other study treatment.
	Grade 2 or 3	• Withhold study treatment. [a] • If improvement to Grade ≤ 1 within 21 days, resume study treatment for current and subsequent cycles as follows: – Resume obinutuzumab *or rituximab* at full dose – Resume venetoclax at current dose[a] – For patients who started at 1.8 mg/kg, resume polatuzumab vedotin at the permanently reduced dose of 1.4 mg/kg; for patients who started at 1.4 mg/kg, permanently discontinue polatuzumab vedotin [a]
Other non-hematologic toxicities (i.e., not described above), excluding alopecia, nausea, and vomiting	Grade 3 or 4	**For patients who have had no prior dose reductions:** • Withhold study treatment. [a] • If improvement to Grade ≤ 1 or baseline, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume venetoclax at next lower dose [a] for current and subsequent cycles per guidelines in Table 16. **For patients who have had one prior dose reduction:** Grade 4 events • Permanently discontinue study treatment. Grade 3 events • Withhold study treatment. [a] • If improvement to Grade ≤ 1 or baseline, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume venetoclax at next lower dose [a] for subsequent cycles per guidelines in Table 16. No more than two dose *level* reductions *from the original dose* of venetoclax are allowed *during induction*. **For patients who have had two prior dose reductions:** • Permanently discontinue study treatment.
	Grade 2	• Withhold study treatment.[a] • If improvement to Grade ≤ 1 or baseline, resume obinutuzumab *or rituximab* and polatuzumab vedotin at full dose and resume venetoclax at current dose.

IRR = infusion-related reaction; PML = progressive multifocal leukoencephalopathy; TLS = tumor lysis syndrome; ULN = upper limit normal.

[a] Treatment delays apply to all events; dose modifications apply only to events 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.

5.1.7.3 Toxicities during Consolidation or Maintenance Treatment

Table 21 provides guidelines for management of toxicities that occur during consolidation or maintenance treatment.

Table 21 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 venetoclax. • Administer G-CSF for neutropenia per institutional guidelines. • Administer RBCs or platelets as required. • If improvement to Grade ≤ 2, resume obinutuzumab *or rituximab* at full dose and resume venetoclax at next lower dose [a] for subsequent cycles per guidelines in Table 16. Patients who are not eligible for further venetoclax dose reductions per Table 17 should be permanently discontinued." • If study treatment is withheld for > 42 days, permanently discontinue study treatment.
Non-hematologic toxicity: Grade ≥ 2	• Withhold obinutuzumab *or rituximab* and venetoclax. • If improvement to Grade ≤ 1 or baseline, resume obinutuzumab *or rituximab* at full dose and resume venetoclax at next lower dose [a] for subsequent cycles per guidelines in Table 16. Patients who are not eligible for further venetoclax dose reductions per Table 17 should be permanently discontinued. • 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 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; 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
- Grade 4 thrombocytopenia
- Grade $\geq$ 3 infection
- *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 that occur 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 ≥ 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 FL patients receiving obinutuzumab, 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 (v4.0) will be used for assessing adverse event severity. Table 22 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 22 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 (v4.0), 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 who receive 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 increases 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 if 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 an 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)

  This includes planned hospitalization for TLS prophylaxis and monitoring (i.e., Cycle 1 Day 1 hospitalization)

- 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 Drug 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. Additionally, 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 venetoclax 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: [redacted], Pharm.D. (primary)
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

Medical Monitor: [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 Monitor 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 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).* An exception is *for FL patients receiving obinutuzumab, where* Grade 3 and 4 infections (both related and unrelated) should be reported until up to 2 years after the last dose of *obinutuzumab*. 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 3 months after the last dose for obinutuzumab *or rituximab, 30 days after the last dose of* venetoclax, and 5 months after last dose of polatuzumab vedotin. 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 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).

5.4.3.4 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 trial-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, 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 FL 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 *obinutuzumab.*

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 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 documents:

- Obinutuzumab Investigator's Brochure
- *Rituximab Investigator's Brochure*
- Polatuzumab Vedotin Investigator's Brochure
- Venetoclax in combination with Obinutuzumab Investigator's Brochure

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 is a Phase Ib/II, open-label, multicenter, non-randomized study of obinutuzumab in combination with polatuzumab vedotin and venetoclax (G+Pola+V) in patients with R/R FL *and rituximab in combination with polatuzumab vedotin and venetoclax (R +Pola +V) in patients with R/R* DLBCL.

The dose-escalation phase *in patients with FL* is designed to determine the RP2D for *both* polatuzumab vedotin and venetoclax when combined with fixed doses of obinutuzumab *(1000 mg).* The dose-escalation phase *in patients with DLBCL is designed to determine the RP2D of venetoclax when combined with fixed doses of polatuzumab vedotin (1.8 mg/kg) and rituximab (375 mg/m²).* The expansion phase is designed to assess the safety and efficacy of polatuzumab vedotin and venetoclax 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 histological 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 6 cohorts of 3–6 patients each, for a total of *21–36* patients, will be required to establish the RP2D during the dose-escalation phase *for patients with R/R FL. There are 3 possible cohorts of 3–6 patients each, for a total of 12–18 patients with replapsed or refractory DLBCL.*

Approximately 80 patients (40 patients with FL and 40 patients with DLBCL) will be enrolled during the expansion phase. Overall, approximately *113–134* patients will be enrolled in this study.

The primary analysis will be 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 around 40% for R/R FL and DLBCL.

Table 23 provides 90% Clopper-Pearson exact CIs for the probability of achieving an EOI PET-CT–defined CR for a range of observed proportions based on a sample of 40 patients. 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 23 Potential 90% CI Estimates 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 for True Population PET-CT–Defined CR
0.50	(0.36, 0.64)
0.55	(0.41, 0.68)
0.60	(0.46, 0.73)
0.65	(0.51, 0.77)
0.70	(0.56, 0.82)
0.75	(0.61, 0.86)

CR=complete response; CT=computed tomography; EOI=end of induction; PET=positron emission tomography.
Note that lower limit of two-sided 90% CI is equivalent to one-sided 95% CI.

6.2 SUMMARIES OF PATIENT CHARACTERISTICS

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 the 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 study treatment will be summarized using descriptive statistics (mean, standard deviation, median, and range).

6.3 DEFINITION OF ANALYSIS POPULATIONS

The following population*s are defined:*

- *The primary safety and efficacy populations* will include patients who receive at least one dose of *any* component of the combination.

- The *intent-to-treat* population will include all patients enrolled in the study.

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). Patients in the dose-escalation phase will be summarized by cohort *and histology type*, and patients in the expansion phase will be summarized by histology type (FL or DLBCL).

Safety will be assessed through summaries of adverse events and changes from baseline 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 v4.0 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 venetoclax 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 endpoint is the proportion of patients achieving a CR at EOI, as determined by the IRC on the basis of PET-CT scans according to Lugano 2014. Point estimates will be presented, along with the corresponding 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 pro portion of patients who achieve 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 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

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 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

The PK population for analysis will include all patients who have at least one evaluable PK sample post dose for at least one analyte.

Serum or plasma concentrations of obinutuzumab, *rituximab*, polatuzumab vedotin and relevant analytes, and venetoclax will be tabulated and plotted over time after appropriate grouping. Summary statistics of concentration data will be computed for each scheduled sampling time for each analyte after appropriate grouping. Interpatient variability and drug accumulation after multiple doses will be evaluated as appropriate. Compartmental, non-compartmental, and/or population approaches will be considered as appropriate. Potential correlations between PK variability and pharmacodynamic, efficacy, and safety endpoints may be explored by exploratory graphical analysis and PK-pharmacodynamic modeling. The exploratory analyses may be reported separately from the CSR.

The assessment of PK parameters and related analyses will be performed per the Sponsor's discretion, taking into consideration the appropriateness of the PK data collected and the trial outcome. At the discretion of the Sponsor, all analyses may be

extended to include relevant biotransformation products of venetoclax or polatuzumab vedotin.

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one predose and one postdose *HAHA or* ATA assessment, with patients grouped according to histology.

The numbers and proportions of *HAHA- or* ATA-positive patients and *HAHA- or* ATA-negative patients during both the treatment and follow-up periods will be summarized by histology group. Patients are considered to be *HAHA- or* ATA-positive if they are *HAHA- or* ATA-negative at baseline but develop an *HAHA or* ATA response following study drug administration (treatment-induced *HAHA or* ATA response), or if they are *HAHA- or* ATA-positive at baseline and the titer of 1 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 *HAHA or* ATA response). Patients are considered to be *HAHA- or* ATA-negative if they are *HAHA- or* ATA-negative at baseline and all post-baseline samples are negative, or if they are *HAHA- or* 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* ATA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses. *Considering the historically low immunogenicity rate of rituximab in NHL patients, human anti-chimeric antibodies against rituximab will not be monitored in this study.*

6.9 BIOMARKER ANALYSES

Exploratory analyses of biomarkers related to tumor biology and study treatment mechanisms of action will be conducted. Analyses will assess the prognostic and/or predictive value of candidate biomarker for each histological subtype with respect to both IRC- and investigator-assessed outcomes. Specifically, the association between candidate biomarkers and PET-CT–defined CR rate and OR 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 one interim analysis will be conducted during the expansion phase of the study, when at least 15 patients *in each treatment group* have been evaluated for PET-CT–defined CR at the 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 expansion cohort with that in historical controls. *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 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 cohort because of futility.

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 GCP 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. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) 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 (HIPAA) of 1996. 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. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

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.

EDC 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.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.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

Assessment/Procedure	Screening [a]		Induction (21-day cycles)					EOI	Maint. (24 months)		EOM [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
	D –28 to D –1	D –14 to D –1	Cycle 1 (± 1 d)			Cycle 2 (± 2 d)	Cycles 3–6 (± 2 d)	After last induction dose [b]	Monthly (±3 d)	Every 2 months (± 1 wk)	35 days after last dose		
			D1	D8	D15	D1	D1		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			x		
Height	x												
Weight	x												
12-lead ECG [g]	x							x [h]			x		
MUGA/echocardiogram [g]	x												
Complete physical examination [i,j]	x												
Targeted physical examination [j,k]						Cycles 2 and 4		x		x	x	x	
Ann Arbor, FLIPI, and FLIPI2	x												
B symptoms [l]	x												
β_2 microglobulin			x [o]										
Hematology [m]		x	x [n,o]	x [o]	x [o]	x [o]	x [o]	x [h]	x [o]		x		
Chemistry panel (serum or plasma) [p]		x	x [n,o]	x [o]	x [o]	x [o]	x [o]	x [h]	x [o]		x		

Appendix 1 Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

Assessment/Procedure	Screening [a]		Induction (21-day cycles)					EOI	Maint. (24 months)		EOM [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
	D –28 to D –1	D –14 to D –1	Cycle 1 (± 1 d)			Cycle 2 (± 2 d)	Cycles 3–6 (± 2 d)	After last induction dose [b]	Monthly (±3 d)	Every 2 months (± 1 wk)	35 days after last dose		
			D1	D8	D15	D1	D1		D1	D1			
Coagulation (INR, aPTT [or PTT], and PT)		x											
Pregnancy test [q]		x				x	x	x			x		
Hepatitis B and C testing [r]	x												
Quantitative IgA, IgG, IgM			x [o]					x	x [s]		x	x [t]	
HAHA sample for obinutuzumab			x [u] (See Appendix 3)										
ATA sample for polatuzumab vedotin			x [u] (See Appendix 3)										
PK sample for obinutuzumab			x [u] (See Appendix 3)										
PK sample for polatuzumab vedotin			x [u] (See Appendix 3)										
PK sample for venetoclax			x [u] (See Appendix 3)										
Whole blood for MRD [v]			x [o]					x	x [s]				
Whole blood for lymphocyte immunophenotyping [w]			x [o]		x [o]	x [o]	x [o]	x	x [s]		x	x [t]	

Appendix 1 Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

Assessment/Procedure		Screening [a]		Induction (21-day cycles)					EOI	Maint. (24 months)		EOM [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
		D −28 to D −1	D −14 to D −1	Cycle 1 (± 1 d)			Cycle 2 (± 2 d)	Cycles 3–6 (± 2 d)	After last induction dose [b]	Monthly (±3 d)	Every 2 months (± 1 wk)	35 days after last dose		
				D1	D8	D15	D1	D1		D1	D1			
Optional peripheral blood sample for RCR [x]				(x)										
Tumor tissue specimen		x [y]							(x [z])					
Concomitant medications [aa]		x		To be recorded continually until end of treatment [aa]										
Adverse events [bb]		x		To be assessed continually [bb]										
PET-CT scan		x [cc]							x [dd]	x [ee]				
CT scan [ff]		x [ff]					x [gg]		x [dd]	x [s]		x [hh]	x [ii]	
Bone marrow biopsy and aspirate		x [jj]							x [dd,kk]	x [kk]		x [hh,kk]		
Study treatment administration	Obinutuzumab [ll]			x	x	x	x	x			x			
	Polatuzumab vedotin [ll]			x			x	x						
	Venetoclax [ll]			x (daily)						x (daily)				
New anti-lymphoma treatment													x	x
Survival follow-up														x

ATA = anti-therapeutic antibody; CT = computed tomography; D = day; Discont. = discontinuation; 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; Maint. = maintenance; MRD = minimal residual disease; MRI = magnetic resonance imaging; NK = natural killer; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; PK = pharmacokinetic; q3m = every 3 months; RCR = Roche Clinical Repository; wk = week; (x) = conditional/optional.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 1 Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

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] 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.

[c] Patients who complete maintenance treatment or discontinue maintenance treatment prematurely will undergo assessments at EOM.

[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 FL patients have completed or discontinued study treatment and all enrolled DLBCL patients have been followed for at least 1 year after they 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 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] Note that ECGs and ECHO/MUGA scans will be performed at other timepoints as needed.

[h] Perform only in patients who will not be receiving maintenance treatment.

[i] 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.

[j] 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.

[k] 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.

[l] Unexplained fever $>38°C$, night sweats, unexplained weight loss $>10\%$ of body weight over 6 months.

[m] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[n] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 24 hours prior to Day 1 of Cycle 1. Additional hematology and chemistry samples must be drawn 0–4 hours predose and 8 and 24 hours postdose on Day 1 of Cycle 1 to monitor for TLS, with an additional chemistry sample at 12 hours after venetoclax dose for hospitalized patients. Note that the sample at 24 hours postdose will actually be obtained on Day 2 of Cycle 1.

[o] 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 Days 8 and 15 of Cycle 1. *For β_2 microglobulin and quantitative IgA, IgG, IgM: C1D1 requires predose collection.* Samples for exploratory biomarker research should be collected at the same time as hematology and chemistry samples, but test results are not required prior to treatment administration.

[p] Chemistry panel includes sodium, potassium, glucose, BUN or urea, creatinine, calculated CrCl, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, uric acid, phosphate, 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.

[q] All women of childbearing potential will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1. In addition a serum or urine pregnancy test must be performed prior to Day 1 of each subsequent cycle of study treatment (laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

[r] 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.

[s] Perform at 12, 18, and 24 months after initiation of induction treatment, within 14 days prior to treatment administration.

[t] 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.

[u] See Appendix 3 for detailed schedule.

[v] Includes circulating lymphoma cells and/or cell-free circulating tumor DNA.

[w] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK cell counts (CD16 and CD56).

[x] Requires separate patient consent for RCR participation. Not applicable for a site that has not been granted approval for RCR sampling.

[y] 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).

[z] A sample will be collected at the time of progression unless no adequate tumor site is accessible.

[aa] 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 until the EOI or EOM visit, whichever occurs later.

[bb] 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 Grade 3 or 4 infections (both 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.

[cc] The screening PET-CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[dd] Perform only for patients who have received at least 2 cycles of induction treatment.

[ee] If PET-CT scan is positive at EOI, perform at 12 months after initiation of induction treatment, within 14 days prior to treatment administration.

[ff] 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. Screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[gg] Perform within 7 days prior to Day 1 of Cycle 3.

[hh] Perform only if not done within previous 3 months.

[ii] Perform every 6 months.

[jj] Bone marrow biopsy and aspirate must be performed within approximately 3 months prior to Day 1 of Cycle 1.

[kk] 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).

[ll] Refer to Section 4.3.2 for details on dosing and schedule.

Appendix 2 Schedule of Assessments for Patients with DLBCL

Assessment/Procedure	Screening [a]		Induction (21-day cycles)					EOI	Consolidation (28-day cycles)	EOC [c]		
	D −28 to D −1	D −14 to D −1	Cycle 1 (±1 d)			Cycle 2 (±2 d)	Cycles 3–6 (±2 d)	After last induction dose [b]	Cycles 7–14 Months 1-8 (± 3 days)	35 days after last dose	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
			D1	D8	D15	D1	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											
12-lead ECG [g]	x							x [h]		x		
MUGA/echocardiogram [g]	x											
Complete physical examination [i,j]	x											
Targeted physical examination [j,k]			Cycles 2 and 4					x	Every 2 cycles	x	x	
Ann Arbor staging, IPI	x											
B symptoms [l]	x											
β_2 microglobulin			x [o]									

Appendix 2 Schedule of Assessments for Patients with DLBCL (cont.)

Assessment/Procedure	Screening [a]		Induction (21-day cycles)					EOI	Consolidation (28-day cycles)	EOC [c]		
	D –28 to D –1	D –1 4 to D –1	Cycle 1 (± 1 d)			Cycle 2 (± 2 d)	Cycles 3–6 (± 2 d)	After last induction dose [b]	Cycles 7–14 Months 1-8 (± 3 days)	35 days after last dose	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
			D1	D 8	D15	D1	D1		D1			
Hematology [m]		x	x [n,o]		x [o]	x [o]	x [o]	x [h]	x [o]	x		
Chemistry panel (serum or plasma) [p]		x	x [n,o]		x [o]	x [o]	x [o]	x [h]	x [o]	x		
Coagulation (INR, aPTT [or PTT], and PT)		x										
Pregnancy test [q]		x				x	x	x		x		
Hepatitis B and C testing [r]	x											
Quantitative IgA, IgG, IgM			x [o]					x		x	x	
ATA sample for polatuzumab vedotin			x [s] (see Appendix 4)									
PK sample for *rituximab*			x [s] (see Appendix 4)									
PK sample for polatuzumab vedotin			x [s] (see Appendix 4)									
PK sample for venetoclax			x [s] (see Appendix 4)									
Whole blood for MRD [t]			x [o]					x	x (at end of C10)	x		
Whole blood for lymphocyte immunophenotyping [u]			x [o]		x [o]	x [o]	x [o]	x	x (at end of C10)	x	x	

Appendix 2 Schedule of Assessments for Patients with DLBCL (cont.)

Assessment/Procedure		Screening [a]		Induction (21-day cycles)					EOI	Consolidation (28-day cycles)	EOC [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
		D −28 to D −1	D −14 to D −1	Cycle 1 (± 1 d)			Cycle 2 (± 2 d)	Cycles 3–6 (± 2 d)	After last induction dose [b]	Cycles 7–14 Months 1-8 (± 3 days)	35 days after last dose		
				D1	D8	D15	D1	D1		D1			
Optional peripheral blood sample for RCR [v]				x									
Tumor tissue specimen		x [w]							(x [x])				
Concomitant medications [y]		x		To be recorded continually until end of treatment [y]									
Adverse events [z]		x		To be recorded continually [z]									
PET-CT scan		x [aa]							x [bb]		x [cc]		
CT scan [dd]		x [dd]					x [ee]		x [bb]	At end of C10	x [ff]	x [gg]	
Bone marrow biopsy and aspirate		x [hh]							x [bb,ii]	x [ii]	x [ff,ii]		
Study treatment administration	*Rituximab* [jj]			x			x	x		*x*			
	Polatuzumab vedotin [jj]			x			x	x					
	Venetoclax [jj]			x (daily)						x (daily)			
New anti-lymphoma treatment												x	x
Survival follow-up													x

Abbreviations: ATA = anti-therapeutic antibody; C = cycle; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CT = computed tomography; D = day; Discont. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOC = end of consolidation; EOI = end of induction; FU = follow-up; IPI = International Prognostic Index; LVEF = left ventricular ejection fraction; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NK = natural killer; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; PK = pharmacokinetic; q3m = every 3 months; RCR = Roche Clinical Repository; wk = week.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 2 Schedule of Assessments for Patients with DLBCL (cont.)

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] 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.

[c] Patients who complete consolidation treatment or discontinue consolidation treatment prematurely will undergo assessments at EOC.

[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 FL patients have completed or discontinued study treatment and all enrolled DLBCL patients have been followed for at least 1 year after they 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] Note that ECGs and ECHO/MUGA scans will be performed at other timepoints as needed.

[h] Perform only in patients who will not be receiving consolidation treatment.

[i] 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.

[j] 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.

[k] 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.

[l] Unexplained fever >38°C, night sweats, unexplained weight loss >10% of body weight over 6 months.

[m] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[n] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 24 hours prior to Day 1 of Cycle 1. Additional hematology and chemistry samples must be drawn 0–4 hours predose and 8 and 24 hours postdose on Day 1 of Cycle 1 to monitor for TLS with an additional chemistry sample at 12 hours post venetoclax dose for hospitalized patients. Note that the 24-hour sample will actually be obtained on Day 2 of Cycle 1.

[o] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle during induction or each month during consolidation. *For β_2 microglobulin and quantitative IgA, IgG, IgM: C1D1 requires predose collection.* Samples for exploratory biomarker research should be collected at the same time as hematology and chemistry samples, but test results are not required prior to treatment administration.

[p] Chemistry panel includes sodium, potassium, glucose, BUN or urea, creatinine, calculated CrCl, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, uric acid, phosphate, 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.

[q] All women of childbearing potential will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1. In addition, a serum or urine pregnancy test must be performed prior to Day 1 of each subsequent cycle of study treatment (laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

[r] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody. HIV testing should also be performed if required by local regulatory requirements.

[s] See *Appendix 4* for detailed schedule.

[t] Includes circulating lymphoma cells and/or cell-free circulating tumor DNA.

[u] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK-cell counts (CD16 and CD56).

[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 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 until the EOI or EOM visit, whichever occurs later.

[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 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 3–4 infections (related and unrelated), which should be reported until up to 2 years after the last dose of study treatment. 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 2 cycles of induction treatment.

[cc] If PET-CT scan is positive at EOI, perform *repeat PET-CT at EOC.*

[dd] 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. Screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[ee] Perform within 7 days prior to Day 1 of Cycle 3.

[ff] Perform only if not done within the previous 3 months.

[gg] Perform every 6 months.

[hh] Bone marrow biopsy and aspirate must be performed within 3 approximately months prior to Day 1 of Cycle 1.

[ii] 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 and at EOC if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression).

[jj] Refer to Section 4.3.2 for details on dosing and schedule.

Appendix 3 Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab Polatuzumab Vedotin, and Venetoclax in Relapsed or Refractory Follicular Lymphoma 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 Venetoclax PK Sample [a, c]	Serum Obinutuzumab HAHA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Dose-Escalation Phase (FL Patients; 21-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	4 hr post-dose (± 10 min)	Pre-infusion (anytime prior to dose)	Pre-infusion (anytime prior to dose)
	Day 8	–	–	Anytime during visit	–	–	–
	Day 15	–	–	Anytime during visit	–	–	–
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 EOI	Pre-dose (within 1 hr prior to dose), and 2 (± 10 min), 4 (± 10 min), 6 (± 20 min)and 8 hours post-dose (± 30 min)	–	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 EOI	Pre-dose (within 1 hr 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)	Pre-dose *(within 1 hr prior to dose)*	Pre-infusion (within 5 hr prior to dose)	–

Appendix 3 Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab Polatuzumab Vedotin, and Venetoclax in Relapsed or Refractory Follicular Lymphoma 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 Venetoclax PK Sample [a, c]	Serum Obinutuzumab HAHA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Expansion Phase (Induction Treatment; 21-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	4 hr post-dose (± 10 min)	Pre-infusion (anytime prior to dose);	Pre-infusion (anytime prior to dose);
	Day 8	–	–	Anytime during visit	–	–	–
	Day 15	–	–	Anytime during visit	–	–	–
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-dose (within 1 hr prior to dose), and 4 hours post-dose (± 10 min)	–	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-dose (within 1 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)	Pre-dose (within 1 hr prior to dose)	Pre-infusion (within 5 hr prior to dose)	–

Appendix 3 Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab Polatuzumab Vedotin, and Venetoclax in Relapsed or Refractory Follicular Lymphoma 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 Venetoclax PK Sample [a, c]	Serum Obinutuzumab HAHA Sample[a]	Serum Polatuzumab Vedotin ATA Sample [a]
Maintenance Phase (Post-induction for FL Patients; 28-day cycles; 1 month = 28 days)							
Month 2	Day 1	Pre-infusion (within 5 hr prior to dose)	–	–		–	–
Month 8	Day 1	Pre-infusion (within 5 hr prior to dose)	–	–	–	–	–
Month 14	Day 1	Pre-infusion (within 5 hr prior to dose)	–	–	–	–	=
Month 20	Day 1	Pre-infusion (within 5 hr prior to dose)	–	–	–	–	–
Treatment Discontinuation		Anytime during visit	Anytime during visit	–	–	Anytime during visit	Anytime during visit

Appendix 3 Pharmacokinetic and Immunogenicity Sampling Schedule *for Obinutuzumab Polatuzumab Vedotin, and Venetoclax in Relapsed or Refractory Follicular Lymphoma 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 Venetoclax PK Sample [a, c]	Serum Obinutuzumab HAHA Sample[a]	Serum Polatuzumab Vedotin ATA Sample [a]
120 ± 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)

ATA = anti-therapeutic antibody; DLBCL = diffuse large B-cell lymphoma; EOI=end of infusion; FL = follicular lymphoma; HAHA = human anti-human antibody; hr = hour; min = minute; MMAE = mono-methyl auristatin E; " – "=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 venetoclax PK sampling visits, the venetoclax 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 Venetoclax 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 Venetoclax PK Sample* [a,c]	*Serum Polatuzumab Vedotin ATA Sample* [a]
Dose-Escalation Phase (DLBCL Patients Induction Treatment; 21-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*	*4 hr post-dose (± 10 min)*	*Pre-infusion (anytime prior to dose)*
	Day 8	–	–	*Anytime during visit*	–	–
	Day 15	–	–	*Anytime during visit*	–	–
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-dose (within 1 hr prior to dose), and 2 (± 10 min), 4 (± 10 min), 6 (± 20 min)and 8 hr post-dose (± 30 min)*	*Pre-infusion (within 5 hr prior to dose)*
Cycle 4	*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-dose (within 1 hr prior to dose)*	*Pre-infusion (within 5 hr prior to dose)*

Appendix 4 *Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Polatuzumab Vedotin, and Venetoclax 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 Venetoclax PK Sample [a,c]	Serum Polatuzumab Vedotin ATA Sample [a]
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)	Pre-dose (within 1 hr prior to dose)	–
Expansion Phase (DLBCL Patients Induction Treatment; 21-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	4 hr post-dose (± 10 min)	Pre-infusion (anytime prior to dose);
	Day 8	–	–	Anytime during visit	–	–
	Day 15	–	–	Anytime during visit	–	–
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-dose (within 1 hr prior to dose), and 4 hr post-dose (± 10 min)	Pre-infusion (within 5 hr prior to dose)

Appendix 4 *Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Polatuzumab Vedotin, and Venetoclax 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 Venetoclax PK Sample [a,c]	Serum Polatuzumab Vedotin ATA Sample [a]
Cycle 4	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-dose (within 1 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)	Pre-dose (within 1 hr prior to dose)	–
Consolidation Phase (Post-induction for DLBCL Patients; 28-day cycles; 1 month = 28 days)						
Treatment Discontinuation		–	Anytime during visit		–	Anytime during visit
120 days after last dose of polatuzumab		–	Anytime during visit	–	–	Anytime during visit
1–2 years after last dose of polatuzumab		–	Anytime during visit	–	–	Anytime during visit

Appendix 4 *Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Polatuzumab Vedotin, and Venetoclax in Relapsed or Refractory DLBCL Patients* (cont.)

ATA =anti-therapeutic antibody; DLBCL =diffuse large B-cell lymphoma; EOI =end of infusion; hr =hour; min =minute; MMAE =mono-methyl auristatin E; "–" =not applicable; PK =pharmacokinetic.

[a] *Sample collection timing is relative to specified drug.*

[b] *Samples collected for PK and ATA analysis may be used for additional PK and ATA assay development and validation and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.*

[c] *On venetoclax PK sampling visits, the venetoclax dose will be taken at the clinic appointment.*

[d] *If the Cycle 1 Day 1 dose of rituximab is split over 2 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 ≤ 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 $\geq$ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions $\leq$ 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
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

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
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 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 8 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 or 1
Intermediate	2
High	3 to 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 8 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	
β_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 or 2
High	3 to 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 8 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 $>1\times$ 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 9 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 10 Sample List of Excluded and Cautionary Medications

Prohibited within 7 days before the first dose and during the study:
Strong CYP3A inducers: Avasimibe, carbamazepine, *cyproterone, enzalutamine, hyperforin, mitotane , nevirapine, oxcarbazepine,* phenobarbital, phenytoin, rifampin, St. John's wort **Moderate CYP3A inducers:** Bosentan, efavirenz, etravirine, modafinil, nafcillin, **Strong CYP3A inhibitors:** Boceprevir, clarithromycin, *cobicistat,* conivaptan, *danoprevir/ritonavir, diltiazem, elvitegravir/ritonavir, idelalisib*,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, *paritaprevir/ritonavir combinations,* posaconazole, saquinavir, telaprevir, telithromycin, *tipranavir/ritonavir,* voriconazole **Moderate CYP3A inhibitors:** Amprenavir, aprepitant, atazanavir, *cimetidine,* ciprofloxacin, *clotrimazole,* crizotinib*, *cyclosporine*,* darunavir/ritonavir, *dronedarone,* erythromycin, fluconazole, *fluvoxamine,* fosamprenavir, imatinib*, *isavuconazole, tofisopam,* verapamil
Cautionary throughout the study
Warfarin **Weak CYP3A inducers:** Amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, vemurafenib* **Weak CYP3A inhibitors:** Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide*, cilostazol, *chlorzoxazone ,* fluoxetine, *fosaprepitant,* ginkgo, goldenseal, isoniazid, *istradefylline, ivacaftor, lomitapide,* oral contraceptives, pazopanib*, ranitidine, ranolazine, *tacrolimus,* ticagrelor, zileuton **P-gp substrates:** Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates:** Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates:** *Asunaprevir,* atrasentan, atorvastatin, *bosentan, cerivastatin, danoprevir, docetaxel*,* ezetimibe,-fluvastatin, glyburide, *irinotecan*, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rifampin,* rosuvastatin, simvastatin acid, telmisartan, valsartan, olmesartan **P-gp inhibitors:** Amiodarone, azithromycin, captopril, carvedilol, felodipine, quercetin, *quinidine,* ronalzine, ticagrelor **BCRP inhibitors:** Gefitinib* **OATP1B1/B3 inhibitors:** Gemfibrozil, eltrombopag, tipranavir

Appendix 10 Sample List of Excluded and Cautionary Medications (cont.)

Note that this is not an exhaustive list. For an updated list, see the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or Star fruits.
* These are anticancer agents; consult Genentech/*Roche* Medical Monitor before use.

Appendix 11 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Within the first 24 hours after the first dose of venetoclax, if any of the following laboratory criteria are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rising serum potassium level is a medical emergency.

In the event of a suspected anaphylactic reaction during the study treatment infusion, the following procedures should be performed:

- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target: 150 to 200 mL/hr, not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (TLS; e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine immediately (within 1 hour).
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multidisciplinary management will be as per institutional protocols.

Recommendations for initial management of patients with electrolyte imbalances and prevention of TLS are presented in the following table.

Appendix 11 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

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

ECG=electrocardiogram; IV=intravenous; STAT=immediately; ULN=upper limit of normal; WNL=within normal limits.

Appendix 11 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • Recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.

ECG = electrocardiogram; IV = intravenous; STAT = immediately; ULN = upper limit of normal; WNL = within normal limits.

Appendix 11 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (cont.)

Abnormality	Management Recommendations
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus ≥10 mg/dL) • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours STAT.

ECG=electrocardiogram; IV=intravenous; STAT=immediately; ULN=upper limit of normal; WNL=within normal limits.

ONGOING DOSING OF VENETOCLAX

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

- For potassium, admit patient for any increase ≥1.0 mmol/L (1.0 mEq/L), or any level greater than the upper limit of normal.
- Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (see table above).

Appendix 12 Clinical Studies of Study Drugs as Single Treatments and Part of Doublet Treatment Regimens

TREATMENT REGIMENS FOR RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA

	Single Agents			Doublet–Anti-CD20+ Polatuzumab Vedotin	
	Obinutuzumab (Salles et al. 2013b)	Polatuzumab Vedotin (Palanca-Wessels et al. 2015)	Venetoclax (Study M12-175) [a]	R+ Polatuzumab Vedotin (Advani et al. 2015)	G+ Polatuzumab Vedotin (Study GO27834)
N	22 (20 FL, 1 MZL, 1 SLL)	47	105 (all NHL)	20	46 (to be enrolled)
Half-life	29.7 days [b]	5.33 days for acMMAE; 6.35 days for TAb approximately 3–6 days for unconjugated MMAE [c]	17 hours	—	—
Anti-CD20 dose	G: 1600/800 mg	—	—	R: 375 mg/m^2 q3w×8 cycles	G: 1000 mg D1, D8, D15 in C1, then D1 in C2–8
Polatuzumab vedotin dose	—	2.4 mg/kg (n=43) 1.8 mg/kg (n=4)	—	1.8 mg/kg	1.8 mg/kg
Venetoclax dose	—	—	50–1200 mg QD	—	—
ORR	54.5%	52% (DLBCL) 53% (iNHL)	57%	75%	Results not available
CR/CRu	9.1%	10% (DLBCL) 20% (iNHL)	11%	10%	Results not available
DoR	17.2 months	—	—	—	Results not available
PFS	11.9 months	151 days (DLBCL) 264 days (iNHL)	—	Not reached	Results not available

Appendix 12 Clinical Studies of Study Drugs as Single Treatments and Part of Doublet Treatment Regimens (cont.)

	Single Agents			Doublet–Anti-CD20 + Polatuzumab Vedotin	
	Obinutuzumab (Salles et al. 2013b)	Polatuzumab Vedotin (Palanca-Wessels et al. 2015)	Venetoclax (Study M12-175) [a]	R + Polatuzumab Vedotin (Advani et al. 2015)	G + Polatuzumab Vedotin (Study GO27834)
Hematologic toxicity and infection (G3, G4)	Neutropenia (n = 3) FN (n = 1) TCP (n = 1) infection (n = 1)	Neutropenia (n = 5)	Anemia (17.1%) lymphocyte decrease (14.3%)	Neutropenia (35%) FN (10%)	Results not available
Neurotoxicity	NR	G1/2 (42%) G3/4 (10%)	—	G2/3/4 (25%)	Results not available

Abbreviations: acMMAE = antibody conjugate mono methyl auristatin E; C = cycle; CR = complete response; CRu = complete response unconfirmed; D = day; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; FL = follicular lymphoma; FN = febrile neutropenia; G = obinutuzumab; G1/2 = Grade 1 or 2; G3/4 = Grade 3 or 4; G2/3/4 = Grade 2, 3, or 4; G3 = Grade 3; G4 = Grade 4; iNHL = indolent non-Hodgkin's lymphoma; MMAE = mono-methyl auristatin E; MZL = marginal zone lymphoma; NHL = non-Hodgkin's lymphoma; NR = not reported; q3w = every 3 weeks; QD = daily; ORR = objective response rate; PFS = progression-free survival; R = rituximab; SLL = small lymphocytic lymphoma; TAb = total antibody; TCP = thrombocytopenia.

[a] Venetoclax Investigator's Brochure.

[b] Gazyva U.S. Prescribing Information.

[c] Polatuzumab Vedotin Investigator's Brochure.

Appendix 12 Clinical Studies of Study Drugs as Single Treatments and Part of Doublet Treatment Regimens (cont.)

TREATMENT REGIMENS FOR RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

	Single Agents			Doublet–Anti-CD20+ Polatuzumab Vedotin	
	Obinutuzumab (Morschhauser et al. 2013; Salles et al. 2013b)	Polatuzumab Vedotin (Palanca-Wessels et al. 2015)	Venetoclax (Study M12-175)[a]	R+ Polatuzumab Vedotin (Morschhauser et al. 2014)	G+ Polatuzumab Vedotin (Study GO27834)
N	19 15 DLBCL, 4 MCL	47	105 (all NHL)	39	46 (to be enrolled)
Half-life	29.7 days [b]	5.33 days for acMMAE 6.35 days for TAb approximately 3–6 days for unconjugated MMAE[c]	17 hours	—	—
Anti-CD20 dose	G: 1600/800 mg	—	—	R: 375 mg/m^2	G: 1000 mg D1,D8, D15 in C1, then D1 in C2–8
Polatuzumab vedotin dose	—	2.4 mg/kg (n=43) 1.8 mg/kg (n=4)	—	2.4 mg/kg	1.8 mg/kg
Venetoclax dose	—	—	50–1200 mg QD	—	—
ORR	32%	52% (DLBCL) 53% (iNHL)	57%	56%	Results not available
CR/CRu	0%	10% (DLBCL) 20% (iNHL)	11%	15%	Results not available
DoR	9.8 months	—	—	—	Results not available
PFS	2.7 months	151 days (DLBCL) 264 days (iNHL)	—	5.4 months	Results not available

Appendix 12 Clinical Studies of Study Drugs as Single Treatments and Part of Doublet Treatment Regimens (cont.)

	Single Agents			Doublet–Anti-CD20 + Polatuzumab Vedotin	
	Obinutuzumab (Morschhauser et al. 2013; Salles et al. 2013b)	Polatuzumab Vedotin (Palanca-Wessels et al. 2015)	Venetoclax (Study M12-175)[a]	R + Polatuzumab Vedotin (Morschhauser et al. 2014)	G + Polatuzumab Vedotin (Study GO27834)
Hematologic toxicity and infection (G3, G4)	Neutropenia (n = 1)	Neutropenia (n = 5)	Anemia (17.1%) lymphocyte decrease (14.3%)	Neutropenia (24%) FN (10%)	Results not available
Neurotoxicity	NR	G1/2 (42%) G3/4 (10%)	—	Any grade (39%)	Results not available

Abbreviations: acMMAE = antibody conjugate mono methyl auristatin E; C = cycle; CR = complete response; CRu = complete response unconfirmed; D = day; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; FN = febrile neutropenia; G = obinutuzumab; G1/2 = Grade 1 or 2; G3/4 = Grade 3 or 4; G2/3/4 = Grade 2, 3, or 4; G3 = Grade 3; G4 = Grade 4; iNHL = indolent non-Hodgkin's lymphoma; MCL = mantle cell lymphoma; MMAE = mono-methyl auristatin E; NHL = non-Hodgkin's lymphoma; NR = not reported; QD = daily; ORR = objective response rate; PFS = progression-free survival; R = rituximab; TAb = total antibody.

[a] Venetoclax Investigator's Brochure.

[b] Gazyva U.S. Prescribing Information.

[c] Polatuzumab Vedotin Investigator's Brochure.

Appendix 13 Diagnostic Criteria for Tumor Lysis Syndrome

Lab Changes	Lab Value	Lab Value Threshold	
	Uric acid	≥ 476 μmol/L (8 mg/dL)	
	Potassium	≥ 6 mmol/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 Occurs within 3 days before or 7 days after therapy		Laboratory TLS
	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 25% change is not a criteria		Laboratory TLS
	Symptomatic hypocalcemia		Clinical TLS

TLS = Tumor Lysis Syndrome; ULN = upper limit of normal.