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APPLICATION NUMBER:

761121Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Original BLA
Application Number	761121
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Reviewer Names	Yvette Kasamon, M.D. (primary clinical reviewer) R. Angelo de Claro, M.D. (team leader)
Review Completion Date	5/28/2019
Established/Proper Name	Polatuzumab vedotin-piiq (DCDS4501A)
(Proposed) Trade Name	Polivy
Applicant	Genentech, Inc.
Dosage Form	For injection: 140 mg of polatuzumab vedotin-piiq as a lyophilized powder in a single-dose vial
Applicant Proposed Dosing Regimen	1.8 mg/kg IV infusion every 21 days for 6 cycles, in combination with bendamustine (90 mg/m ² /day for 2 days) and rituximab
Applicant Proposed Indication/Population	(b) (4)
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication/Population	In combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies

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Glossary

ADC	antibody-drug conjugate
AR	adverse reaction
ASCT	autologous stem cell transplantation
BR	bendamustine + rituximab
BG	bendamustine + obinutuzumab (Gazyva)
BOR	best objective response
CAR	chimeric antigen receptor
CHP	cyclophosphamide, doxorubicin, prednisone
CR	complete remission
CRF	case report form
CSR	clinical study report
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EOT	end of treatment
FL	follicular lymphoma
G	obinutuzumab (Gazyva)
HSCT	hematopoietic stem cell transplantation
IHC	immunohistochemistry
IPI	International Prognostic Index
IR	information request
IRC	independent review committee
IRR	infusion-related reaction
ISS	integrated summary of safety
ITT	intention-to-treat
IWG	International Working Group
Lyo	lyophilized
MMAE	monomethyl auristatin E
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PN	peripheral neuropathy
Pola, PV	polatuzumab vedotin-piiq
PR	partial remission
PRA	primary response assessment
PT	preferred term
RDI	relative dose intensity
rel/ref	relapsed or refractory
SAE	serious adverse event
SD	stable disease

BLA 761121 Clinical Review

Yvette Kasamon, MD

Polivy (polatuzumab vedotin-piiq)

SMQ	standardized MedDRA (Medical Dictionary for Regulatory Activities) query
SOC	system organ class
SUR	safety update report
TEAE	treatment-emergent adverse event
TINAS	Therapy-Induced Neuropathy Assessment Scale

1. Executive Summary

1.1. Product Introduction

Polatuzumab vedotin-piiq is a CD79b-directed antibody-drug conjugate (ADC) containing a humanized, IgG monoclonal antibody against CD79b conjugated to the anti-mitotic agent, monomethyl auristatin E (MMAE). CD79b is a cell-surface antigen expressed on most mature B-cells, with ubiquitous expression in diffuse large B-cell lymphoma (DLBCL). Antibody bound to CD79b is internalized, and the conjugate is cleaved by lysosomal enzymes to release MMAE, which binds to tubulin, disrupts the microtubule network, and results in inhibited cell division and induction of apoptosis.

The clinical review team recommends accelerated approval of polatuzumab vedotin-piiq in combination with bendamustine and a rituximab product (BR) for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, after at least two prior therapies.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of polatuzumab vedotin-piiq (pola) in combination with BR is based on response rates and duration as determined by an independent review committee (IRC) in a multicenter, open-label clinical trial (Study GO29365). The study randomized 80 patients with relapsed or refractory DLBCL after at least one prior therapy to either pola + BR (N = 40) or BR alone (N = 40) for six cycles. The primary endpoint was complete remission (CR) rate at the end of therapy per IRC. At the end of therapy, the PET CR rate was numerically more than 2-fold higher in the pola + BR arm (40%; 95% CI, 25-57) than in the BR arm (18%; 95% CI, 7-33), representing a 22% higher observed CR rate (95% CI: 3, 41). The best objective response (BOR) rate was likewise more than 2-fold higher in the pola + BR arm (63%, vs. 25% with BR alone). Of the 25 responding patients in the pola + BR arm, 16 (64%) had a DOR of ≥ 6 months, and 12 (48%) had a DOR of ≥ 12 months. In contrast, of the 10 responding patients in the BR arm, 3 had a DOR lasting ≥ 6 months, and 2 had a DOR lasting ≥ 12 months. Progression-free survival (PFS) and overall survival (OS) also tended to be longer in the pola + BR arm; however, there are multiple limitations with those data.

Because of the small sample size, the magnitude of the treatment effect with the addition of pola is uncertain. However, the observed differences between arms in depth of response at end of therapy, overall response, and response duration are clinically meaningful. These response data provide substantial evidence of effectiveness and are the basis for the recommended accelerated approval. Because of the paucity of data in patients with one prior therapy, the recommended indication is restricted to patients with relapsed or refractory DLBCL after at least two prior therapies.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Efficacy: The efficacy of pola is based on IRC-assessed CR rate at end of treatment (EOT), BOR, and DOR in Study GO29365, which included a randomized, open-label, study of 80 patients with relapsed or refractory DLBCL after after least one prior regimen. Patients were randomized 1:1 to receive either pola + BR or BR alone for six 21-day cycles. Eligible patients were not candidates for autologous hematopoietic stem cell transplantation (HSCT) at study entry. The primary endpoint was IRC-assessed CR rate by PET-based criteria at EOT. The median number of prior therapies was 2, with 29% receiving one prior therapy, 25% receiving 2 prior therapies, and 46% receiving 3 or more prior therapies. Eighty percent of patients had refractory disease to last therapy.

Patients in the pola +BR arm received a median of 5 cycles, whereas patients in the BR arm received a median of 3 cycles. The difference in exposure was driven by the higher rate of early treatment discontinuation due to inefficacy in the BR arm. At EOT, the observed objective response rate (ORR) and CR rates per IRC were more than 2-fold higher in the pola + BR arm than in the BR arm. The PET CR rate per IRC was 40% with pola + BR vs. 18% with BR, with overlapping 95% CIs. This represented a 22% higher observed CR rate (95% CI: 3, 41) in the pola arm. The observed rates of objective response and CR at any point were also more than 2-fold higher in the pola + BR arm, with overlapping 95% CIs. A best response of CR or PR per IRC was achieved by 63% of the pola + BR arm and 25% of the BR arm, whereas a best response of CR was achieved by 50% and 23%, respectively.

Responses tended to be more durable in the pola + BR arm. Of the 25 responding patients in the pola + BR arm, 16 (64%) had a DOR of ≥ 6 months, and 12 (48%) had a DOR of ≥ 12 months. Of the 10 responding patients in the BR arm, 3 had a DOR lasting ≥ 6 months, and 2 had a DOR lasting ≥ 12 months. Additionally, the estimated median PFS was > 5 months longer in the pola + BR arm (7.6 months) than in the BR arm (2.4 months), with a corresponding HR of 0.29 (95% CI: 0.16, 0.52). On exploratory analysis, the estimated median OS was > 7 months longer in the pola + BR arm (12.4 vs. 4.7 months), with a corresponding HR of 0.42 (95% CI: 0.24, 0.75).

Safety: In 173 patients with lymphoma treated with pola, bendamustine, and either rituximab or obinutuzumab in Study GO29365, fatal AEs occurred in 4.6% within 90 days of last treatment, with infection as a leading cause. SAEs occurred in 60%, most often from infection. Adverse reactions in $\geq 20\%$ of patients were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting.

Benefit/Risk: Pola + BR has an overall favorable benefit/risk in patients with relapsed or refractory DLBCL after at least 2 prior lines of therapy. There were too few patients with one prior line (11 in the experimental arm) to inform benefit/risk.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	DLBCL is fatal if not cured. In refractory DLBCL, standard salvage regimens produce ORRs of 20-30%, with <15% CR and an estimated median OS of 6 months.	There is a need for more effective yet tolerable salvage therapies for DLBCL.
Current Treatment Options	- Widely used salvage regimens for DLBCL include platinum, etoposide, and/or cytarabine-based combination regimens with rituximab, while less intensive regimens include gemcitabine and bendamustine. - Axicabtagene ciloleucel and tisagenlecleucel have regular approval for relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. There is no FDA-approved therapy for patients with DLBCL after failure of one prior therapy or for patients who are unable to receive, or who have relapse despite, CAR-T therapy.	Patients with relapsed or refractory DLBCL have unmet medical needs.
Benefit	- An open-label phase 2 study (GO29365) randomized 80 patients with DLBCL after at least 1 prior therapy to pola + BR or BR alone for 6 cycles. The observed ORR and CR rate per IRC were numerically more than 2-fold higher in the pola + BR arm than in the BR arm, both at EOT and at the time of best response. - At EOT, the PET CR rate was 40% with pola + BR vs. 18% with BR, with overlapping 95% CIs. This represented a 22% higher observed CR rate (95% CI: 3, 41) in the experimental arm. - A best response of CR or PR per IRC was achieved by 63% of the pola + BR arm and 25% of the BR arm, whereas a best response of CR was achieved by 50% and 23%, respectively. - Responses tended to be longer in the pola + BR arm, as did PFS per IRC and OS.	Based on CR rate at EOT, BOR, and DOR per IRC in a randomized phase 2 study, pola + BV has clinically meaningful activity in patients with relapsed or refractory DLBCL. Despite the limitations of the study, there is a strong indication of a positive treatment effect with the addition of pola to BR in the intended population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In 173 patients with lymphoma treated with pola, bendamustine, and either rituximab or obinutuzumab in Study GO29365, – Fatal AEs occurred in 4.6% within 90 days of last treatment, with infection as a leading cause. – SAEs occurred in 60%, most often from infection. – Adverse reactions in $\geq 20\%$ were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting.	• Pola + BV has an acceptable safety profile in the intended population. • Peripheral neuropathy, infusion-related reaction, myelosuppression, and serious or opportunistic infections should be included in the Warnings and Precautions.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

X	Patient experience data that were submitted as part of the application include:	Section where discussed
	X Clinical outcome assessment (COA) data, such as	
	X Patient reported outcome (PRO)	Section 6.1.2.4
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
	□ Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
	□ Patient experience data were not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Although standard chemoimmunotherapy (R-CHOP) is considered curative for more than half of patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL), an estimated 20-30% relapse after an initial remission and an estimated 10% have primary refractory disease.^{1,2} For first relapse, high-dose chemotherapy with autologous HSCT is the usual standard provided that the relapse is chemosensitive. However, over 50% of such relapses can be resistant to second-line therapy,³ typically precluding HSCT, and comorbidities may also preclude HSCT. Outcomes tend to be poor with DLBCL that is refractory or relapses early after autologous HSCT.⁴⁻⁶ In a meta-analysis of over 500 such patients, ORRs to subsequent therapy were 20-30%, CR rates were $\leq$ 15%, and the median OS was 6 months.⁴

2.2. Analysis of Current Treatment Options

There is no one universal standard for patients with DLBCL who are ineligible for, or who relapse despite, HSCT.^{1,7,8} Allogeneic HSCT can produce durable remissions, if not cure, in a subset of patients despite failure of autologous HSCT. However, patients unable to achieve sufficient disease control with salvage therapy are generally not considered for allogeneic HSCT, given the high relapse risk.

Widely used salvage regimens for large B-cell lymphoma include platinum, etoposide, and/or cytarabine-based combination regimens (ICE, ESHAP, DHAP) with rituximab. These intensive regimens are not definitive and typically serve as a bridge to HSCT. Less intensive regimens include gemcitabine, gemcitabine-oxaliplatin, and bendamustine. Two CD19-directed, chimeric antigen receptor (CAR) T cell therapies, axicabtagene ciloleucel and tisagenlecleucel, have regular approval for the treatment of adult patients with relapsed or refractory (rel/ref) large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma (FL), and (for axicabtagene ciloleucel) primary mediastinal large B-cell lymphoma.

Although these CAR-T cell therapies can produce durable CRs, their use has limitations in the general rel/ref DLBCL population because of the toxicity profile, which requires rigorous selection criteria, and restricted availability. In addition, the waiting period associated with CAR-T manufacture may be prohibitive in patients with symptomatic or rapidly progressing disease.

There is no FDA-approved therapy for patients with DLBCL after failure of one prior therapy, or for patients who are unable to receive, or who have relapse despite, CAR-T therapy.

To place the results of Study GO29365 in context, Table 1 summarizes the literature on BR alone in patients with rel/ref DLBCL. BR has modest activity in this setting, with ORRs of 50-63%, CR rates of 15-39%, and generally short-lived responses.

Table 1: Studies of BR in Relapsed or Refractory DLBCL

Study	DLBCL Population	N	Median age	Benda dose, mg/m ² /d for 2 d	ORR	CR rate	Median cycles (% with 6)
Prospective							
Ohmachi et al 2013 ⁹	1-3 prior lines (64% with 1; 14% with 3), ASCT ineligible (14% post ASCT)	59	67	120	63%	37%	4 (27%)
Vacirca et al 2014 ¹⁰	1+ prior lines (median 1; 28% with ≥ 3), ASCT ineligible (8% post ASCT)	59	74	120 in 97%	46%	15%	4 (6%)
Retrospective							
Hong et al 2018 ¹¹	1+ prior lines (40% with ≥3), ASCT ineligible (22% post ASCT)	58	69	120 or 90	55%	31%	2.5 (17%)
Arcari et al 2016 ¹²	1+ (53% with 1, 20% with ≥ 3), completed ≥ 2 BR cycles, ASCT ineligible (7% post ASCT)	55	76	90 or 70	50%	28%	4 (29%)
Merchionne et al 2014 ¹³	1-5 prior lines (median 2), 25% post ASCT	28	71	120 or 90	50%	39%	5 (57%)

Source: FDA analysis

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

None. Polatuzumab vedotin-piiq is a new molecular entity.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant initially submitted IND 109409 on January 7, 2011.

Under IND 109409, (b) (4) polatuzumab vedotin was placed on partial clinical hold in 9/2014 due to concerns for excess toxicity, with that hold continuing. Clinical development proceeded with fixed duration, 1.8 mg/kg dosing.

Polatuzumab vedotin received orphan drug designation for treatment of DLBCL in 12/2016. Breakthrough Therapy Designation was granted in 9/2017 for polatuzumab in combination with rituximab and bendamustine for the treatment of adult patients with relapsed or refractory DLBCL who are not candidates for HSCT. A pre-BLA meeting was held in 3/2018 to align content and format of this BLA. This included expectations for PK bridging between the original liquid formulation and the lyophilized formulation intended for marketing, through evaluation of a new-formulation cohort in Study G029365.

Two randomized, phase 3 trials of polatuzumab vedotin are either ongoing or proposed:

- Study GO39942 (POLARIX; NCT03274492), “A phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP versus R-CHOP in previously untreated patients with DLBCL,” opened 9/2017 after alignment with FDA.
- Protocol MO40598, “A Phase III, Open-label, Multicenter, Randomized Study Evaluating the Safety and Efficacy of Polatuzumab Vedotin in Combination with Rituximab plus Gemcitabine plus Oxaliplatin (R-GemOx) Versus R-Gemox Alone in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma” was submitted 2/2019 with potential deficiencies communicated 3/2019.

3.3. Foreign Regulatory Actions and Marketing History

Polatuzumab vedotin has not been marketed outside of the US.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI inspected the Applicant and a single clinical site (#272994) with regard to the randomized phase 2 study in DLBCL (the basis of efficacy in Study GO29365). The clinical review team selected the site because of its relatively high accrual and disclosed financial interests (see Appendix, Section 13.2). The preliminary regulatory compliance classification for both the Applicant and the clinical site was No Action Indicated.

4.2. Product Quality

None as of the midcycle meeting.

4.3. Nonclinical Pharmacology/Toxicology

None

4.4. Clinical Pharmacology

In a subset of Arm G (Study GO29365), a population PK model was used to evaluate differences in PK due to change from the liquid to lyophilized formulation of pola. Based on model-derived exposure comparisons, the lyophilized formulation was associated with:

- Lower ADC exposure (5% AUC, 6% C_{max})
- Lower MMAE exposure (15% AUC, 17% C_{max}), with wide confidence intervals for MMAE due to high interpatient variability

The clinical pharmacology reviewers concluded that there were no meaningful differences in PK between the two formulations.

The safety of pola has not been characterized in patients with moderate or severe hepatic

impairment. Evaluation of the impact of strong CYP3A inhibition on MMAE levels was ongoing at the time of the midcycle meeting.

4.5. **Devices and Companion Diagnostic Issues**

High CD79b prevalence assessed by immunohistochemistry (IHC) was observed in rel/ref DLBCL cases in GO29365 (96%, 80/83), where positive is defined as an H-score > 0. This finding is consistent with the combined 98% (198/202) prevalence of detectable CD79b by IHC in DLBCL tumor samples from two other studies: GO27834 (n = 75, rel/ref DLBCL) and GO29044 (n = 44, front-line DLBCL)(source: biomarker report for GO29365). Of the 3/83 CD79b negative cases by IHC in GO29365, measurements of CD79b mRNA by gene expression analysis suggested its expression. Of 100 FL samples in GO29365 and GO27834 combined, 97% had CD79b detected by IHC (source: biomarker report).

The Applicant indicated that these results are consistent with the high expression of CD79b described in the literature in normal mature B-cells and in mature B-cell malignancies such as DLBCL and FL.¹⁴⁻¹⁷ In a study involving clinical samples,¹⁷ surface CD79b was detected by flow cytometry in most cases of DLBCL and FL in the front line and rel/ref setting (Appendix).

The Applicant did not provide any analytical validation studies in the biomarker report to enable the assessment of the operating characteristics of the IHC assay. Therefore, CDRH could not comment on the reliability of the CD79b IHC test. Nonetheless, existing literature supports the high prevalence of CD79b expression reported in the Applicant's trials (98%). Based on a prevalence >95% in DLBCL, CDRH suggested that a companion diagnostic is not necessary.

Reviewer comment:

- **The clinical review team agrees that a companion diagnostic for CD79b expression is not necessary for the intended population.**

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study GO29365 is the basis of the BLA. All studies summarized in Table 2 were conducted using the 100 mg liquid drug product, with the exception of additional cohorts (Arms G and H) in Study GO29365 that use the new formulation, 140 mg lyophilized (LYO) drug product. All references to polatuzumab vedotin-piiq (“pola”) pertain to the original liquid formulation unless otherwise noted; the new formulation is referred to as “LYO pola.”

Table 2: Clinical Studies in BLA 761121

Trial	Population	Design	Regimen	Relevant populations
Controlled studies of efficacy and safety				
GO29365 (primary); NCT02257567	rel/ref FL or DLBCL	Phase 1b/2, open-label multicenter study – safety run-in – randomized p 2 (pola + BR vs BR) with primary endpoint of CR at EOT per IRC, separately for DLBCL and FL – single-arm expansion (pola + BG) – single-arm DLBCL cohort (Arm G) of new formulation (LYO pola + BR)	DLBCL: Pola 1.8 mg/kg + BR/BG q 21 days x 6 cycles FL: Pola 1.8 mg/kg + BR/BG q 28 days x 6 cycles	<u>Efficacy</u> in DLBCL: 80 pts randomized to pola + BR (n = 40) vs BR (n = 40) <u>Safety</u> : 141 pts treated with original-formulation pola 1.8 mg/kg + BR/BG including: Pola + BR: 89 treated – 45 with DLBCL (39 from randomized cohort), 44 with FL Pola + BG: 52 treated – 26 with DLBCL, 26 with FL Pola + BR/BG, q 21 day schedule: 71 (all DLBCL) BR alone: 80 treated (39 with DLBCL, 41 with FL) <u>New formulation (Arm G)</u> 32 evaluated
Primary data cutoff: 30 Apr 2018 (Arms A-F), 15 Nov 2018 (Arm G efficacy)				
Safety update and Arm G safety: 11 Oct 2018				

Table 2: Clinical Studies in BLA 761121

Trial	Population	Design	Regimen	Relevant populations
Supportive studies				
DCS4968g (safety, efficacy); NCT01290549 Data cutoff: 18 Nov 2014	rel/ref B-NHL or CLL	Phase 2, open-label, multicenter study of pola +/- R	Pola monotherapy (0.1 – 2.4 mg/kg) q 21 days indefinitely Pola 2.4 mg/kg + R, q 21 days indefinitely	Total treated: 95 ^a Pola < 1.8 mg/kg: 30 Pola 1.8 mg/kg: 11 (4 DLBCL) Pola 2.4 mg/kg: 45 (27 DLBCL) Pola 2.4 mg/kg + R: 9
GO27834 (safety, efficacy); NCT01691898 Data cutoff: 19 Apr 2017	rel/ref FL or DLBCL	Phase 2, open-label, multicenter study of pola + G or R	Pola 1.8 mg/kg + G, q 21 days x 8 cycles Pola 1.8 mg/kg or 2.4 mg/kg + R, q 21 days for up to 1 y	Total treated: 163 Pola 1.8 mg/kg + R: 20 (0 DLBCL) Pola 1.8 mg/kg + G: 84 (43 DLBCL) Pola 2.4 mg/kg + R: 59 (39 DLBCL)
GO29044 (safety); NCT01992653 Data cutoff: 29 Dec 2017	Untreated or rel/ref B-NHL	Phase 1b/2, open-label, multicenter, dose escalation and expansion study of pola + chemo	Pola 1.0 – 1.8 mg/g + R-CHP or G-CHP, q 21 days for 6 – 8 cycles	Includes 69 treated with pola 1.8 mg/kg + R/G-CHP (66 for 1L DLBCL)

Source: SCS Table 1 and FDA analysis.

B = bendamustine, G = obinutuzumab (Gazyva), R = rituximab

^a 40 DLBCL patients treated, 39 with pola monotherapy

Two supportive studies evaluated pola alone (DCS4958g) or in combination with a CD20-directed monoclonal antibody (GO27834). Study GO29044 informed the dose of pola to combine with chemotherapy, and is not considered further in this safety review due to the single-arm design and chemotherapy backbone.

5.2. Review Strategy

The clinical review is primarily based on the randomized phase 2 portion of Study G029365 in patients with rel/ref DLBCL, with supportive safety data from all 173 recipients of pola or LYO pola + BR/BG in that study. The safety review strategy is described in Section 8.1.

Adjudication of Efficacy

The clinical reviewer adjudicated all key efficacy analyses per IRC (ORR at EOT, BOR, DOR, and PFS in the randomized phase 2 portion; ORR at EOT and BOR in Arm G) by reviewing efficacy narratives, supplemented by radiology reports and the IRC electronic case report forms (eCRFs). The originally submitted eCRFs contained only investigator assessments of efficacy and did not include primary source data. To evaluate the accuracy of the reported efficacy outcomes, multiple IRs were required and included:

- Clarifications regarding the algorithms used for prioritizing and integrating the results of PET-CT vs. CT scans.
- Efficacy narratives and radiology reports for all patients in the primary efficacy population and Arm G
- eCRFs from the IRC review
- Reasons for patients being NE for efficacy, which had not been captured.
- Additional datasets that provided tumor measurements per IRC; the response determinations of all IRC reviewers (radiologist 1, radiologist 2, adjudicating radiologist if needed, and the medical oncologist's final overall response designation); Deauville scores; and waterfall and swimmer's plots.

There were multiple discordances between the adjudicated results and the results reported by the Applicant. Discordances were mainly due to how PET-CT vs. CT results were integrated, and whether clinical (nonradiographic) progressive disease (PD) per INV was considered in the overall assessment of disease status per IRC. Table 3 summarizes the key differences between FDA's and the Applicant's approach. For the endpoints affected, refer to Section 6.1.2.3.

Table 3: Differences between FDA and Applicant Analysis of Efficacy per IRC

Setting	Difference in approach	Comment
Nonradiographic PD	FDA counts clinical progression events per INV as DOR/PFS failure, rather than discounting such events.	The IRC assessments, which per the charter were to consider both radiographic and clinical data, did not count most clinical (nonradiographic) progression events as PD. The Applicant instead classified patients with non-radiographic progression as NE for efficacy per IRC, missing multiple progression events.
DOR, PFS	If NE by PET and CT shows PD, FDA views as PD and thus a DOR/PFS failure, rather than NE.	The Applicant's algorithm differed for IRC vs INV for overall response (including BOR), DOR, and PFS. In contrast to response per INV, for response per IRC, only the PET result was considered in most cases, ^c even if PET was not performed and the CT showed PD. Thus, cases where CT showed PD, but no PET was performed, were inappropriately reported as failure-free per IRC.
DOR, PFS	After PET CR, if follow-up PET has SD, FDA views as PD and thus DOR/PFS failure, rather than regarding as SD and failure-free. After PET PR, if follow-up PET has SD and CT shows PD, FDA views as PD, rather than SD.	The Applicant's algorithm for reporting outcomes per IRC prioritized the PET result, in most cases discounting the CT result. As a result, patients who had responded, then had PET showing SD (thus no molecular response) were inappropriately reported as NE for that time point, even if the CT showed PD, leading to overestimation of DOR and PFS.
Response	FDA views SD (no molecular response) by PET, with PD by CT, as PD, rather than SD.	For efficacy per IRC, the Applicant's algorithm discounted the CT result in cases where PET was not performed, instead calling all such cases NE. The Applicant later proposed that PR by CT, without PET imaging, be viewed as PR rather than NE. This was acceptable and in keeping with 2007 IWG criteria. ^{a,b}
NALT (including HSCT) in absence of PD	FDA censors DOR and PFS at date of last radiographic disease assessment prior to NALT, rather than not censoring. ^c	

NALT = new anti-lymphoma therapy; NE = nonevaluable; IWG, International Working Group

^a PET-CT remained required for first CR resignation.

^b No molecular response by PET-CT, with PR by CT, was viewed as SD. For response at PRA using PET-CT criteria, patients were regarded as NE if CT showed SD and PET was not done.

^c For consolidative radiation, patients need not be censored if, at study baseline, they also had radiographically evaluable disease outside of the radiation field.

BLA 761121 Clinical Review
Yvette Kasamon, MD
Polivy (polatuzumab vedotin-piiq)

Safety Review

Refer to Section 8.1 for the approach to safety. The clinical reviewer verified or reworked the major safety analyses and requested ISS analysis datasets for supportive safety data. Output was generated with JMP 13.0 (b) (4) using analysis datasets.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. G029365

A Phase Ib/II study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab (R) or obinutuzumab (G) plus bendamustine (B) in relapsed or refractory follicular or diffuse large B-cell lymphoma

First patient entered: 15 Oct 2014

Last patient entered, Arms A-F: 13 Sept 2016

Status: ongoing; new-formulation cohorts accruing

Sites: 54 (12 US)

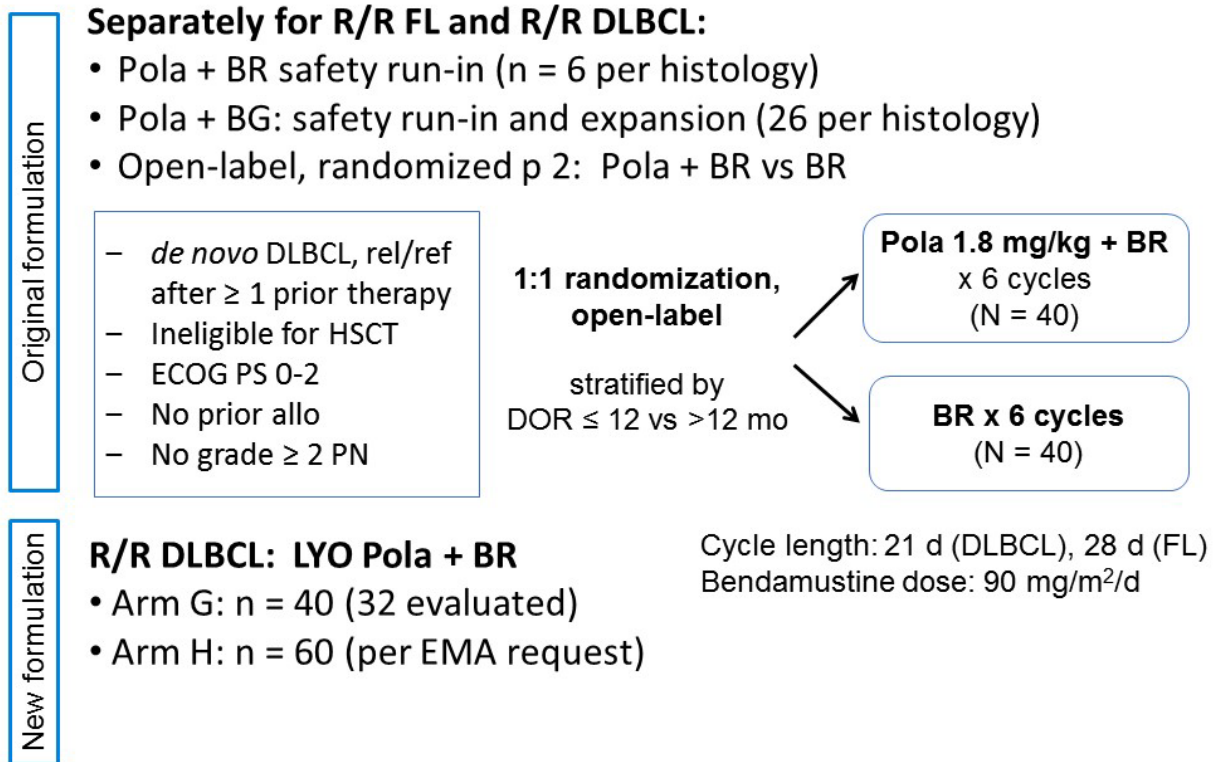
Primary data cutoff: 30 Apr 2018 (Arms A-F), 15 Nov 2018 (Arm G efficacy)

Safety update report (SUR) cutoff: 11 Oct 2018 (Arms A-F update + Arm G safety)

6.1.1. Study Design

This is a multicenter, open-label trial for adults with rel/ref follicular lymphoma (FL), or transplant-ineligible adults with rel/ref, *de novo* DLBCL. Refer to Figure 1 for a schema and Appendix Figure 6 for the description and target accrual of each arm. The study included a randomized open-label phase 2 portion comparing bendamustine-rituximab (BR) with vs. without pola (1.8 mg/kg) for 6 cycles, with FL and DLBCL evaluated in parallel. Randomization (1:1) was stratified by duration of response (DOR) to prior therapy (≤ 12 months vs. >12 months) and, in FL, by tumor burden (low vs. high). The primary endpoint is IRC-assessed CR rate by PET-based criteria at EOT (the primary response assessment [PRA], defined as 6-8 weeks after 6 cycles or last treatment). Arms G and H evaluate BR in combination with the new lyophilized formulation of pola (LYO pola).

Figure 1: Schema of Study GO29365



Source: FDA analysis

BG = bendamustine + obinutuzumab (Gazyva).

Key Eligibility Criteria

- Age ≥ 18 with rel/ref *de novo* DLBCL after ≥ 1 prior therapy and ineligible for SCT; or rel/ref FL after ≥ 1 prior therapy
 - Refractory defined as SD or PD < 6 months from start of prior therapy
- ECOG PS 0, 1, or 2
- Life expectancy ≥ 24 weeks
- Unless from underlying disease,
 - Hgb ≥ 9 g/dL, ANC ≥ 1500/μL, platelets ≥ 75/μL
 - Creatinine ≤ 1.5 x ULN or CrCl ≥ 40 mL/min
 - AST and ALT ≤ 2.5 x ULN, bilirubin < 1.5 x ULN
- No grade ≥ 2 peripheral neuropathy
- No prior allogeneic HSCT
- No active HBV, active HCV, or HIV
- > 1 y response duration to any prior bendamustine
- >30 mg/day prednisone or equivalent permitted for lymphoma symptom control

Reviewer comment:

- **The protocol did not define criteria for transplant ineligibility. Reasons for transplant ineligibility were therefore collected retrospectively.**

Study Treatment

- 6 cycles, with cycle length of 21 days for DLBCL, 28 days for FL
- Rituximab 375 mg/m² IV on Day 1 of each cycle
- After antihistamine and antipyretic premedication, polatuzumab vedotin 1.8 mg/kg IV on Day 2 of Cycle 1 (90 min. infusion), then Day 1 of each subsequent cycle (30 min infusion if tolerated)
- Bendamustine 90 mg/m²/day on Days 2 and 3 of cycle 1, then Days 1 and 2 of each subsequent cycle.

Toxicity management

AE	Dose Delay or Modification
PN Grade 2–3	– Delay all treatment – Hold pola until improvement to Grade ≤ 1. If not recovered to Grade ≤ 1 by Day 14, discontinue pola permanently. – If recovered to Grade ≤ 1 by Day 14, restart pola at a permanently reduced dose of 1.4 mg/kg. If prior dose reduction to 1.4 mg/kg occurred, discontinue pola.
PN Grade 4	Discontinue pola.
Grade 3-4 neutropenia, thrombocytopenia	– If recovery by Day 7 to ANC >1000/μL or platelets >75, resume treatment without modification. – For protracted cytopenias, no dose reductions of pola permitted. Dose reductions of bendamustine to 70 mg/m² then 50 mg/m² were recommended, followed by discontinuation of all treatment.

Source: protocol v 7, Table 7.

Reviewer comments:

- **The protocol called for bendamustine dose reductions to as low as 50 mg/m² for neutropenia, without mention of GCSF prophylaxis, and for thrombocytopenia. No dose reductions of pola were permitted for cytopenias. However, the leading cause of treatment discontinuation was neutropenia and/or thrombocytopenia, raising the question whether continued combination therapy with a lower pola dose would be feasible. Patients should have the option to receive GCSF before dose reducing bendamustine for neutropenia, and to dose reduce pola before discontinuing treatment altogether for cytopenias. The dose modification guidelines in the PI were therefore revised.**

- **The proposed PI recommends administering pola, bendamustine, and rituximab in any order on Day 1 of each cycle (bendamustine Days 1 and 2), whereas in the protocol, cycle 1 pola and bendamustine do not start until day 2. The Applicant provided sufficient justification for this change.**

Supportive care

- Infection prophylaxis:
 - GCSF was optional prior to Amendment 5, which introduced Arm G.
 - Herpesvirus and PJP prophylaxis, during and for ≥ 6 months after treatment, were optional prior to Amendment 5
- Corticosteroids for lymphoma control were permitted.

Response assessment: PET-CT was required at screening, C3 D15, and PRA, with clinical response assessment additionally performed at start of each cycle. Follow-up imaging (PET-CT or CT) was every 3 months until 2 y, then every 6 months.

Study Endpoints (Randomized Phase 2)

Efficacy endpoints

- Primary: CR at primary response assessment (PRA; 6-8 weeks after Cycle 6 Day 1 or last study drug) based on PET-CT, per IRC
- Secondary:
 - CR at PRA per investigator (INV), based on PET-CT
 - Overall response (OR) at PRA, based on PET-CT and CT only (INV and IRC)
 - BOR based on PET-CT and CT only (INV and IRC)
 - For DLBCL: DOR and PFS based on PET-CT or CT per IRC (per INV added in protocol v 7)
- Exploratory: include DOR, PFS, event-free survival, OS

Other endpoints: include safety, PK, PRO analyses of peripheral neuropathy using TINAS (Therapy-Induced Neuropathy Assessment Scale), biomarkers

Reviewer comments:

- **There is overlap in the protocol's stated secondary and exploratory endpoints, and the exploratory endpoints do not specify per INV or per IRC.**
- **Per the Applicant, for the phase 1b, phase 2 expansion, and randomized phase 2 cohorts, DOR and PFS by IRC were secondary objectives, and DOR and PFS per INV were exploratory. For Arms G and H, DOR and PFS by INV and IRC are secondary objectives (source: response to 3/6/19 IR).**

Response designation: Modified Lugano criteria (Cheson et al 2014) were used for the primary endpoint:

- CR criteria by PET-CT were modified to require negative bone marrow biopsy in patients

with positive baseline bone marrow biopsy; otherwise response was downgraded to PR.

- PR criteria by PET-CT were modified to require that CT criteria for PR (i.e. >50% reduction in SPD) also be met. This modification was applied for IRC but not INV assessments due to error.

Investigator assessment was per modified Lugano or 2007 International Working Group (IWG) criteria, with modified Lugano criteria prioritized when available.

Statistical Analysis Plan: Refer to statistical review. For the randomized phase 2 portion, there was no prespecified hypothesis testing. The 95% CIs were provided for various assumed, observed CR rates at PRA. For time-to-event endpoints of PFS and OS, there was similarly no prespecified hypothesis testing or prespecified type I error control.

Protocol Amendments

Of 6 protocol amendments, 4 are considered major.

Protocol version	Notable changes
v2, 4/2016	• Due to partial clinical hold, reduce dose escalation of Phase 1b safety run-in from 2.4 mg/kg to 1.8 mg/kg • Adopt Lugano 2014 response criteria for evaluating PET CR at PRA by IRC
v5, 11/2017	• Add Arm G, a 20-30 patient cohort with rel/ref DLBCL to evaluate NF pola + BR • Add PFS and DOR analysis per IRC for DLBCL cohorts, per FDA request • Mandate GCSF, herpesvirus, and PJP prophylaxis
v6, 5/2018	• Expand Arm G, adding 10 patients with 1 prior line of therapy • Add BOR analysis per IRC for DLBCL cohorts
v7, 10/2018 ^a	• Add new arm (Arm H) of ~60 patients with rel/ref DLBCL also treated with NF pola + BR, with a primary objective of CR rate at PRA per IRC • Update SAP, including a pooled efficacy analysis of ~100 patients (Arms G + H combined) treated with NF pola + BR. • Expand Arm G to ~40 patients

Source: FDA analysis

^a After the clinical cutoff date

6.1.2. Study Results

6.1.2.1 Study Conduct

Compliance with Good Clinical Practices

The Applicant indicated that the study was conducted in accordance with with good clinical practices.

Financial Disclosure

Refer to Appendix.

Data Quality and Integrity

Data integrity appeared acceptable. Issues with the quality of datasets and CRFs were addressed through multiple IRs.

Protocol Violations / Deviations

The numbers of other reported major deviations were generally balanced between arms, with none involving randomization.

6.1.2.2 Patient and Treatment Characteristics

Disposition

In the randomized phase 2 portion, 80 patients with rel/ref DLBCL were randomized (40/arm) and comprise the ITT efficacy population; 39/arm were treated. These 80 patients constitute the primary efficacy population. The allocation of patients to the other GO29365 cohorts is summarized in Appendix Figure 6. Accrual to Arm G, a single-arm evaluation of LYO pola + BR in DLBCL, was ongoing at the time of BLA submission, with efficacy data available from 32 patients.

Demographic and Other Baseline Characteristics

Table 4 and Table 5 summarize demographic and disease characteristics of the DLBCL efficacy populations. In the primary efficacy population (N = 80), the median age was 69 (range 30–86), 46% were age ≥70, and 80% had an ECOG PS of 0-1. The primary reasons patients were not candidates for HSCT included age (40%), insufficient response to salvage therapy (26%), and prior transplant (20%).

Table 4: Baseline Patient Characteristics of DLBCL Efficacy Populations

Parameter		Arm G:	Primary Efficacy Popn	
		LYO Pola + BR (N = 32)	Pola + BR (N = 40)	BR (N = 40)
Age, y	Median (range)	65 (27-83)	67 (33-86)	71 (30-84)
	≥ 65	17 (53%)	23 (58%)	26 (65%)
	≥ 70	8 (25%)	15 (38%)	22 (55%)
Sex	Male	17 (53%)	28 (70%)	25 (63%)
Race	White	26 (81%)	26 (65%)	31 (78%)
	Asian	1 (3%)	6 (15%)	4 (10%)
	Black	0	3 (8%)	0 (0%)
	Other or unknown	5 (16%)	5 (13%)	5 (13%)
Region	North America	8 (25%)	17 (43%)	11 (28%)
	US site	5 (16%)	16 (40%)	8 (20%)

Table 4: Baseline Patient Characteristics of DLBCL Efficacy Populations

Parameter		Arm G:	Primary Efficacy Popn	
		LYO Pola + BR (N = 32)	Pola + BR (N = 40)	BR (N = 40)
	Europe	17(53%)	16 (40%)	23 (58%)
	Asia/Pacific	7 (22%)	7 (18%)	6 (15%)
ECOG PS	0-1	30 (94%)	33 (83%)	31 (78%)
Primary reason for HSCT ineligibility ^a	Age	11 (34%)	13 (33%)	19 (48%)
	Comorbidities	0	1 (3%)	1 (3%)
	Inadequate response	15 (47%)	12 (30%)	9 (23%)
	Failed prior HSCT	5 (16%)	10 (25%)	6 (15%)
	Patient refused HSCT	0	2 (5%)	2 (5%)
	Other	1 (< 1%)	2 (%)	1 (3%)

Source: CSR Tables 11 and 12, Arm G interim CSR, and FDA analysis

^a In the primary efficacy population, 2 patients received HSCT (allogeneic) after study treatment.

As summarized in Table 5, the primary efficacy population had a median of 2 prior therapies, with 29% receiving one prior therapy, 25% receiving 2 prior therapies, and 46% receiving 3 or more prior therapies. Most patients (98%) had DLBCL not otherwise specified. Eighty percent had refractory disease to last therapy, 20% had prior HSCT, 88% had stage III-IV disease at study baseline, and 31% had bulky disease. The characteristics of Arm G and the pola + BR arm were similar overall, with Arm G having slightly higher proportions of patients > 1 prior line and refractory disease to last therapy (Table 5).

The pola + BR arm, when compared to the BR arm, had fewer patients aged ≥ 70 (38% vs. 55%, respectively), less high risk disease by IPI (23% vs. 43%), less bulky disease (25% vs. 38%), and more patients treated as US sites (40% vs. 20%).

Table 5: Baseline Disease Characteristics of DLBCL Efficacy Populations

Characteristic		Arm G:	Primary Efficacy Popn	
		LYO Pola + BR (N = 32)	Pola + BR (n = 40)	BR (n = 40)
Diagnosis by central review	DLBCL, NOS	30 (94%)	38 (95%)	40 (100%)
	ABC	17	19	19
	GCB	12	15	17
	COO unspecified	1	4	4
	FL	0	1 (3%)	0
	Burkitt lymphoma	0	1 (3%)	0
	Other ^b	2 ^c	0	0
Prior lines of therapy	Median (range)	2 (1-7)	2 (1-7)	2 (1-5)
	1	5 (16%)	11 (28%)	12 (30%)
	2	12 (38%)	11 (28%)	9 (23%)
	≥ 3	15 (47%)	18 (45%)	19 (48%)
Outcome of prior therapy	Refractory to last therapy	29 (91%)	30 (75%)	34 (85%)
	DOR to last therapy ≤ 12 mo.	30 (94%)	34 (85%)	33 (83%)
	HSCT failure	6 (19%)	10 (25%)	6 (15%)
Disease features at study baseline	Bulky disease (≥ 7.5 cm)	9 (28%)	10 (25%)	15 (38%)
	Stage III-IV disease	24 (75%)	34 (85%)	36 (90%)
	Extranodal disease	20 (63%)	27 (68%)	29 (73%)
CD79b detectable by IHC ^a	Evaluated	–	31 (78%)	31 (78%)
	Detectable		31	30
	Undetectable		0	1
CD79b H-score, among cases evaluated ^a	> 0	–	31/31 (100%)	30/31 (97%)
	1+ (> 0 but < 200)		6 (19%)	12 (39%)
	2+ (200 – 299)		9 (29%)	9 (29%)
	3+ (300+)		16 (52%)	9 (29%)
IPI risk at study baseline	Low (0-1)	5 (16%)	9 (23%)	3 (8%)
	Low-intermediate (2)	9 (28%)	9 (23%)	8 (20%)
	High-intermediate (3)	11 (34%)	13 (33%)	12 (30%)
	High (4-5)	7 (22%)	9 (23%)	17 (43%)

IPI, International Prognostic Index; NOS, not otherwise specified

Source: CSR Tables 11-12 and Arm G interim CSR, unless otherwise noted.

^a Source: FDA analysis

^b 1 EBV+ DLBCL, 1 high-grade lymphoma with Myc and Bcl2 and/or Bcl6 rearrangements

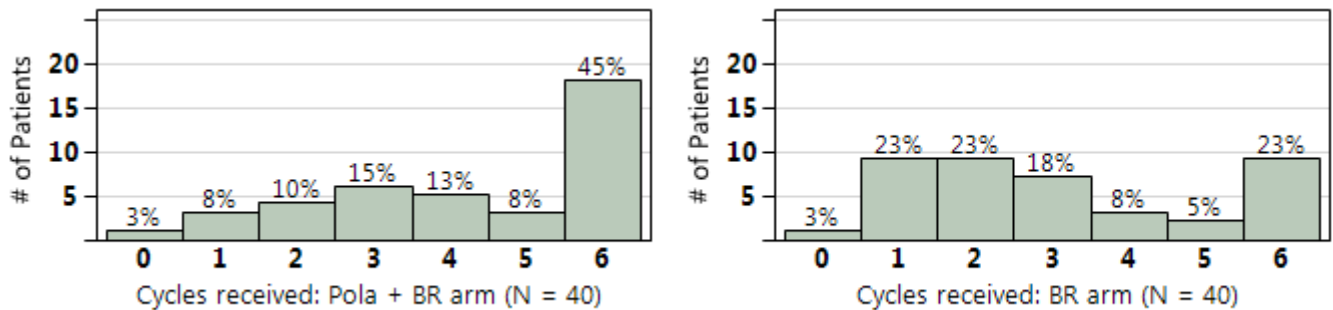
Reviewer comment:

- **The clinical reviewer disagrees with the Applicant’s assessment that the arms were well-balanced. The utility of the IPI in this relapsed or refractory setting is questionable. In addition to imbalances in IPI risk category, there were several other imbalances in patient and disease characteristics that could bias the outcomes in favor of the pola + BR arm. These imbalances are important to consider when interpreting efficacy outcomes, particularly given the small sample size.**

Patient Treatment

Table 6 summarizes treatment exposure and selected supportive care measures in the DLBCL efficacy populations. Twice as many patients in the pola + BR arm completed 6 cycles (45% vs. 23% in the BR arm). The median number of cycles was 5 and 3, respectively, with 45% of the BR arm receiving < 3 cycles (Figure 2 and Table 6). This difference in exposure was largely due to the BR arm having a higher rate of early treatment discontinuation from inefficacy.

Figure 2: Bendamustine Exposure in Primary Efficacy Population



Source: FDA analysis

Table 6: Treatment of DLBCL Efficacy Populations (ITT)

		Arm G: LYO Pola + BR (N = 32)	Primary Efficacy Popn	
			Pola + BR (N= 40)	BR (N = 40)
Exposure ^a				
Number treated			39 (98%)	39 (98%)
Bendamustine cycles received	0	0	1 (3%)	1 (3%)
	1 - 2	10 (31%)	7 (18%)	18 (45%)
	3 - 4	8 (25%)	11 (28%)	10 (25%)
	5	2 (6%)	3 (13%)	2 (5%)
	6	12 (38%)	18 (45%)	9 (23%)
	Median (Q1, Q3)	4 (2, 6)	5 (3, 6)	3 (1, 5)
Pola cycles received	6	12 (38%)	19 (48%)	N/A
	Median (Q1, Q3)	4 (2, 6)	5 (3, 6)	
Supportive care ^b				
Systemic corticosteroids before PRA ^c	For any reason	–	26 (65%)	13 (33%)
	Excluding premed, prophylaxis, and chemo support	–	8 (20%)	7 (18%)
	Lymphoma symptom control	–	3 (8%)	2 (5%)
GCSF	Primary prophylaxis	–	18 (46%)	12 (31%)

^a Source: FDA analysis

^b Source: CSR and response to 2/27/19 IR

^c Steroid dose was not collected.

Reviewer comments:

- The longer exposure overall in the pola + BR arm is driven by a lower rate of treatment discontinuation from PD compared to the BR arm. This suggests better short-term disease control in the pola arm.
- The protocol did not require that the corticosteroid dose used for lymphoma symptom control be stable, and the dose was neither capped nor captured in the CRF. Imbalances in steroid use are unlikely to have a significant impact on efficacy. The higher use of steroids in the pola + BR arm appears to be driven by reasons other than lymphoma symptom control, and is likely due in part to longer exposure to study treatment.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

For data on concomitant GCSF and corticosteroids, refer to **Table 6** and **Table 12**. The other categories are not applicable.

6.1.2.3 Efficacy Results – Primary Endpoint

FDA adjudication resulted in multiple revisions to the reported efficacy outcomes per IRC (see Section 5.2, Table 3). The primary efficacy endpoint, based on CR rates, was unchanged. The following outcomes were affected:

- BOR (including two additional PRs in the pola + BR arm)
- Designation of SD vs. PD, with more PD cases on FDA analysis
- Number of NE cases, which was substantially lower on FDA analysis
- DOR and PFS

The efficacy results presented are based on the FDA adjudication, unless otherwise specified. The PI is based on these adjudicated results. Efficacy per IRC, as reported by the Applicant prior to FDA adjudication, is summarized in Appendix Table 26. All outcomes are based on intention-to-treat (ITT) analysis.

Table 7 summarizes IRC-assessed response rates at PRA and BOR, including in the primary efficacy population. At EOT, the ORR and CR rate were numerically more than 2-fold higher in the pola + BR arm than in the BR arm. The PET CR rate per IRC was 40% with pola + BR vs. 18% with BR, with overlapping 95% CIs. This represented a 22% higher observed CR rate (95% CI: 3, 41) in the pola arm.

Similarly, per INV assessment, the PET CR rate at EOT was 43% (95% CI: 27, 59) in the pola + BR arm and 15% (95% CI: 6, 30) in the BR arm (source: CSR). For this time point, the concordance in CR rates per INV and IRC was 94% for both arms combined (source: CSR).

Table 7: FDA-Adjudicated Response per IRC in Patients with Relapsed or Refractory DLBCL

Outcome	Primary Efficacy Popn (ITT)		Arm G
	Pola + BR (N = 40)	BR (N = 40)	LYO Pola + BR (N = 32)
PET-CT Based Response at End of Therapy ^{a,e}			
Objective response (95% CI) ^b Nominal p-value	18 (45%) (29, 62)	7 (18%) (7, 33)	11 (34%) (19, 53) –
	.007		
CR (95% CI) Nominal p-value CR Rate Difference, % (95% CI) ^b	16 (40%) (25, 57)	7 (18%)^c (7, 33)	11 (34%) (19, 53) – –
	.026 22 (3, 41)		
PR	2 (5%)	0 (0%)	0 (0%)
SD	2 (5%)	1 (3%)	1 (3%)
PD	13 (32%)	24 (60%)	15 (47%)
NE	7 (18%)	8 (20%)	5 (16%)
Not treated	1	1	0
Stopped early or not assessed due to AE	4	3	2
Stopped early for other reasons ^d	1	4	1
Not radiographically evaluable at baseline	0	0	1
Not IRC reviewed	1	0	0
No PET; SD by CT	0	0	1
Best Overall Response ^e			
Objective response (95% CI) Nominal p-value	25 (63%) (46, 77)	10 (25%) (13, 41)	15 (47%) (29, 65) –
	.002		
CR (95% CI)	20 (50%) (34, 66)	9 (23%) (11, 38)	14 (44%) (26, 62)
PR	5 (13%)	1 (3%)	1 (3%)
SD	3 (8%)	8 (20%)	3 (9%)
PD	8 (20%)	19 (48%)	11 (34%)
NE	4 (10%)	3 (8%)	3 (9%)

Source: FDA analysis

^a Per modified Lugano 2014 criteria. Bone marrow confirmation of PET-CT CR was required

^b Clopper-Pearson method for rates by arm, Miettinen-Nurminen for rate difference.

^c Includes 1 patient with midtreatment CR who proceeded to HSCT after 3 cycles.

^d Due to inefficacy or patient decision

^e Results of PET-CT were prioritized over CT.

Reviewer comments:

- **Prior to FDA adjudication, 65% of the BR arm was reported as NE for the primary efficacy endpoint, and 40% of the BR arm was NE for BOR per IRC (Table 26).**
- **In the randomized phase 2 comparison, the 95% CIs for CR rate at EOT overlap. The CIs also overlap for BOR and for best response of CR. Given the small numbers of patients, there is high uncertainty as to the magnitude of the treatment effect with the addition of pola. Nevertheless, the observed differences between arms in terms of overall response and depth of response are clinically meaningful.**
- **All p-values are nominal; there was no prespecified hypothesis testing.**

In Arm G (LYO pola + BR), the observed CR rates per IRC at EOT (34%) and at any point (44%) were numerically lower than in the pola + BR arm (40% and 50%, respectively; Table 7). The numbers of patients are small, however, and CIs overlap.

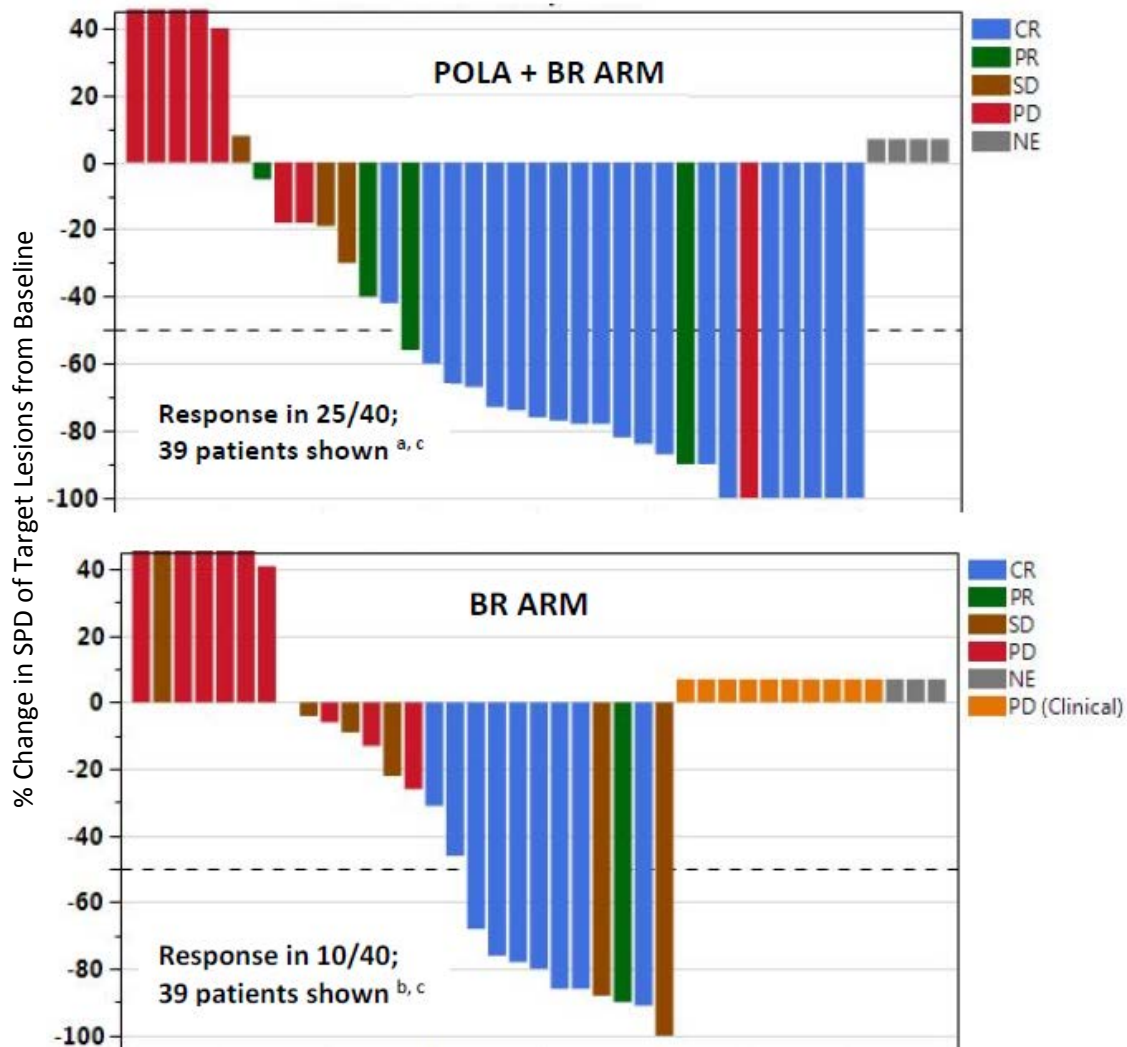
6.1.2.4 Efficacy Results – Secondary and Other Relevant Endpoints

A. Best Overall Response

BOR per IRC is summarized in Table 7, with corresponding waterfall plots shown in Figure 3. For the BOR assessment, PET-CT results were prioritized over CT results. As with the EOT assessment, the rates of objective response and CR at any point, per IRC, were numerically more than 2-fold higher in the pola + BR arm, with overlapping 95% CIs. A best response of CR or PR per IRC was achieved by 63% of the pola + BR arm and 25% of the BR arm, whereas a best response of CR was achieved by 50% and 23%, respectively.

Similarly, per INV assessment, the pola + BR arm had a best ORR of 70% (CR 58%), whereas the BR arm had a best ORR of 33% (CR 20%)(source: CSR).

Figure 3: Waterfall Plots of BOR per IRC



Source: FDA analysis.

SPD = sum of products of greatest diameter.

Note: In some cases, the x-axis may represent maximal change from baseline, rather than maximal reduction from baseline.

^a One additional patient had BOR of PR.

^b One additional patient had BOR of SD. The patient shown with 0% change had SD.

^c NE cases and cases of clinical PD were arbitrarily assigned a +7% change to permit graphical representation, and are shown on the graph's rightmost portion.

Reviewer comments:

- In both arms, it is unusual that almost all objective responses are CRs. The Applicant could not explain this finding, noting however that the PET CR rates per IRC and per INV were

concordant (source: response to IR).

- **In the control arm, the ORR of 25% is approximately half that described in the literature on BR in rel/ref DLBCL (Table 1). Cross-study comparisons are limited, in part due to differences in bendamustine dosing, patient characteristics, and study design. Nevertheless, the outcomes in this randomized phase 2 study raise the question of underperformance of the control arm.**

B. Duration of Response

In patients who achieved a best response of PR or CR, responses tended to be more durable in the pola + BR arm than the BR arm. DOR per IRC is summarized in Table 8 and Figure 4. The estimates of median DOR are not reliable because of the small number of patients. Of the 25 patients in the pola + BR arm, 16 (64%) had a DOR per IRC of at least 6 months, and 12 (48%) had a DOR of at least 12 months. Of the 10 responding patients in the BR arm, 3 had a DOR per IRC lasting at least 6 months, and 2 had a DOR lasting at least 12 months.

Table 8: Time-to-Event Efficacy Endpoints (Randomized Phase 2)

Outcome	Pola + BR (N = 40)	BR (N = 40)
DOR per IRC		
Number of responders	23	10
Number censored	12 (52%)	3 (30%)
Median (95% CI), mo. ^{a, b}	12.6 (4.6, NE)	7.7 (1.8, NE)
Range, mo.	0.6, 22.5+	0, 18.9
PFS per IRC		
Number of events	24 (60%)	32 (80%)
Median (95% CI), mo.	7.6 (4.7, 14.6)	2.4 (1.5, 4.1)
HR (95% CI) ^c	0.29 (0.16, 0.52)	
Overall Survival		
Number of deaths	23 (58%)	28 (70%)
Median (95% CI), mo.	12.4 (8.9, NE)	4.7 (3.7, 8.3)
HR (95% CI) ^c	0.42 (0.24, 0.75)	

Source: FDA statistical reviewer

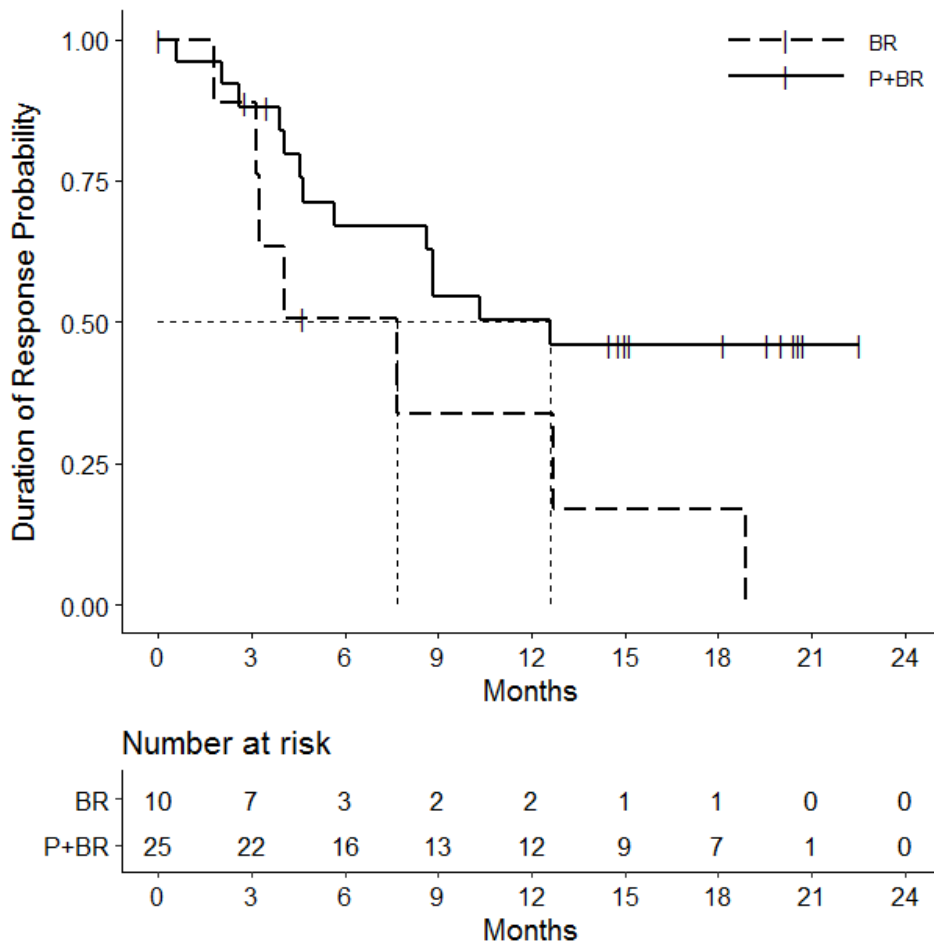
Note: + sign denotes a censored value.

^a All medians are Kaplan-Meier estimates.

^b CIs with complementary log-log transformation

^c Cox proportional hazards model

Figure 4: FDA-Adjudicated DOR per IRC (Randomized Phase 2)



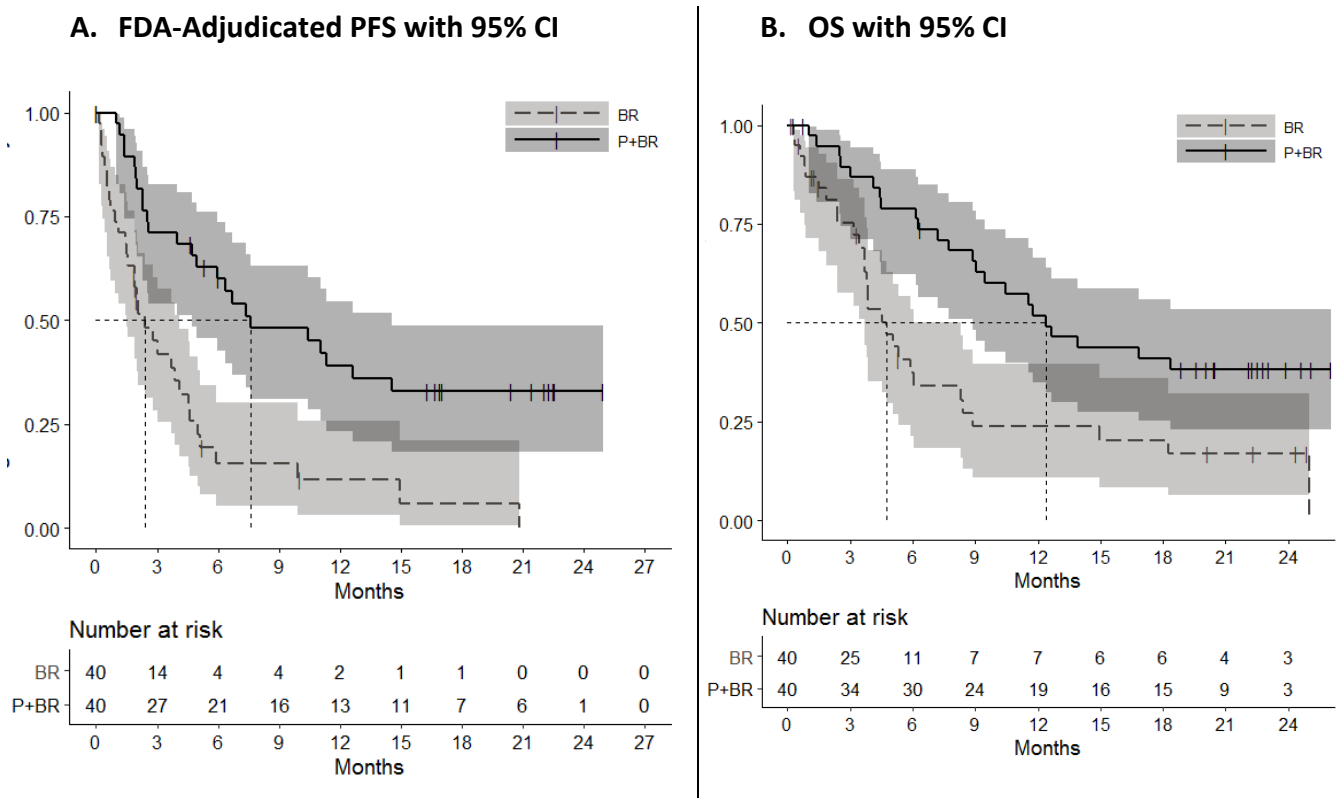
Source: FDA statistical reviewer.
 Note: DOR is censored for NALT in remission.

C. Progression-Free and Overall Survival

PFS per IRC and OS are summarized in Table 8, with Kaplan-Meier estimates shown in Figure 5. The estimated median PFS was > 5 months longer in the pola + BR arm (7.6 months) than in the BR arm (2.4 months), corresponding to a HR of 0.29 (95% CI: 0.16, 0.52).

On exploratory analysis, the estimated median OS was > 7 months longer in the pola + BR arm (12.4 vs. 4.7 months), corresponding to a HR of 0.42 (95% CI: 0.24, 0.75).

Figure 5: PFS per IRC and Overall Survival (Randomized Phase 2)



Source: FDA statistical reviewer

For PFS, estimated median follow up was 20 months in the pola + BR arm, 10 months in the BR arm.

Reviewer comments:

- **The survival data support the efficacy of pola when added to BR, in that the direction of the observed treatment effect is consistent with the response rate and DOR data. However, there are multiple limitations in the survival analyses which lead to high uncertainty, including**
 - the small number of patients
 - lack of prespecified hypothesis testing and type I error control
 - multiple imbalances in baseline characteristics that may favor the experimental arm, and that cannot be adequately addressed through multivariable analyses.
- **The PFS and OS data are not sufficient to support the regular approval sought by the Applicant, (b) (4). The regulatory recommendation is therefore based on CR rate at EOT, BOR, and DOR.**

D. Patient-Reported Outcomes

The TINAS is an 11-item questionnaire that assesses the severity of neuropathy-related symptoms in the last 24 hours. The questionnaire was administered to patients in both the phase 1 and phase 2 portions of Study GO29365. In the reviewer’s opinion, the results in patients with rel/ref DLBCL are not interpretable due to the high degree of missingness.

Because of programming errors in the electronic PRO device, the baseline assessment was inaccessible to patients for 9 months, resulting in significant loss of baseline data (source: CSR Section 6). Compliance in the BR arm declined more rapidly than in the pola + BR/BG arms; scores after Week 11 and Week 29 were based on < 25% of patients in the BR and pola + BR/BG arms (source: CSR Section 6.1).

6.1.2.5 Additional Analyses Conducted on the Individual Trial

A. Efficacy in Relapsed or Refractory FL

In patients with rel/ref FL, results of the randomized phase 2 portion revealed no difference in efficacy between pola + BR and BR alone (Table 9).

Table 9: Overview of Efficacy in Relapsed or Refractory FL (GO20365)

Outcome	FL Population, Randomized Phase 2 (ITT)	
	Pola + BR (N = 39)	BR (N = 41)
ORR by PET-CT at PRA – IRC (95% CI)	77% (61, 89)	73% (57, 86)
CR by PET-CT at PRA – IRC ^a (95% CI)	69% (52, 83)	63% (47, 78)
BOR (PET-CT or CT) – INV (95% CI)	90% (76, 97)	88% (74, 96)
DOR, median (95% CI), mo. – INV ^b	16.1 (14.1, NE)	15.4 (10.2, NE)
PFS – INV		
Patients with event, n	18 (46%)	21 (51%)
Median (95% CI), mo.	18.5 (16.0, NE)	17.3 (12.4, NE)

Source: CSR Tables 10 and 35. Cycle length in FL was 28 days.

^a Primary endpoint

^b Estimated median follow-up for DOR, 22 mo.

Reviewer comment:

- In rel/ref FL, the lack of efficacy of pola when added to BR contrasts with the findings in DLBCL. The inefficacy in FL is not explained differences in CD79b expression between these types of lymphoma.

B. Efficacy of Pola + BG in Relapsed or Refractory DLBCL

In the DLBCL cohorts who received pola + BG, the CR rate at PRA per IRC was 29% (Table 10). This is similar to the 34% CR rate at PRA in Arm G (LYO pola + BR).

Table 10: Response to Pola + BG in DLBCL

PET-based response (ITT) per IRC at EOT	Pola + BG
	Phase 1 + 2 (N = 27)
ORR	11 (41%)
CR	8 (29%)
PR	3 (11%)
SD	2 (7%)
PD	5 (19%)
NE	9 (33%)

Source: CSR

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Single-agent efficacy data: In contrast to pola 2.4 mg/kg dosing, which remains on partial hold due to excess toxicity including neurotoxicity (IND 109409), virtually no single-agent efficacy data are available in DLBCL at the 1.8 mg/kg dose. Table 11 summarizes response rates to pola monotherapy in the supportive study DCS4968g.

Table 11: Response to Polatuzumab Vedotin in DLBCL (Study DCS4968g)

BOR per INV, n	Dose of Single-Agent Pola		
	< 1.8 mg/kg (n = 8)	1.8 mg/kg (n = 4)	2.4 mg/kg (n = 27)
CR	0 (0%)	0 (0%)	4 (15%)
PR	1 (13%)	2 (50%)	10 (37%)
No response	7 (88%)	2 (59%)	8 (30%)
Missing	–	–	1 (4%)

Source: Study DCS4968g CSR, Table 95

Reviewer comments:

- Although pola 2.4 mg/kg has clear single-agent activity in DLBCL (in 27 patients, ORR 52%), this dose was not moved forward in combination regimens due to toxicity concerns. There are virtually no data on the single-agent activity of pola 1.8 mg/kg in DLBCL.
- There are no efficacy data with pola 1.8 mg/kg + R in DLBCL (Study GO27834).

7.2. Integrated Assessment of Effectiveness

Efficacy is based on IRC-assessed CR rate at EOT, DOR, and BOR in Study GO29365, which included a randomized, open-label, study of 80 patients with rel/ref DLBCL after at least one prior regimen. Patients were randomized 1:1 to receive either pola + BR or BR alone for six 21-day cycles. Eligible patients were not candidates for autologous HSCT at study entry, with the primary reasons being age (40%), insufficient response to salvage therapy (26%), and prior transplant failure (20%). The primary endpoint was IRC-assessed CR rate by PET-based criteria at EOT.

The median age was 69 years (range: 30–86 years), and most patients (98%) had DLBCL not otherwise specified. The median number of prior therapies was 2, with 29% receiving one prior therapy, 25% receiving 2 prior therapies, and 46% receiving 3 or more prior therapies. Eighty percent of patients had refractory disease to last therapy. The pola + BR arm, when compared to the BR arm, had fewer patients aged ≥ 70 (38% vs. 55%, respectively), less high risk disease by IPI (23% vs. 43%), and less bulky disease (25% vs. 38%).

In the pola plus BR arm, patients received a median of 5 cycles, with 48% receiving 6 cycles. In the BR arm, patients received a median of 3 cycles, with 23% receiving 6 cycles. The difference in exposure is driven by the higher rate of early treatment discontinuation due to inefficacy in the BR arm.

At EOT, the observed ORR and CR rate per IRC were more than 2-fold higher in the pola + BR arm. The PET CR rate per IRC was 40% with pola + BR vs. 18% with BR, with overlapping 95% CIs. This represented a 22% higher observed CR rate (95% CI: 3, 41) in the pola arm. The observed rates of objective response and CR at any point were also more than 2-fold higher in the pola + BR arm, with overlapping 95% CIs. A best response of CR or PR per IRC was achieved by 63% of the pola + BR arm and 25% of the BR arm, whereas a best response of CR was achieved by 50% and 23%, respectively.

In patients who achieved a best response of PR or CR, responses tended to be more durable in the pola + BR arm. Of the 25 responding patients in the pola + BR arm, 16 (64%) had a DOR per IRC of at least 6 months, and 12 (48%) had a DOR of at least 12 months. Of the 10 responding patients in the BR arm, 3 had a DOR per IRC lasting at least 6 months, and 2 had a DOR lasting at least 12 months.

The estimated median PFS was > 5 months longer in the pola + BR arm (7.6 months) than in the BR arm (2.4 months), with a corresponding HR of 0.29 (95% CI: 0.16, 0.52). On exploratory analysis, the estimated median OS was > 7 months longer in the pola + BR arm (12.4 vs. 4.7 months), with a corresponding HR of 0.42 (95% CI: 0.24, 0.75).

In a parallel, open-label randomized phase 2 comparison of pola + BR vs. BR in rel/ref FL, there was no added efficacy with pola.

In rel/ref DLBCL, there is high uncertainty as to the magnitude of the treatment effect with the addition of pola, especially given the small number of patients. However, there is sufficient evidence of a positive treatment effect in this population based on depth of response at EOT, BOR, and DOR per IRC. Refer to Section 1 and Section 10 for regulatory recommendations.

8. Review of Safety

8.1. Safety Review Approach

The primary safety population consists of patients with DLBCL in Study GO29365 who received BR with (N = 45) or without (N = 39) pola (original liquid formulation), including 6 recipients of pola + BR in the phase 1b portion. For increased sensitivity, the analysis is supplemented by review of a larger safety population from Study GO29365, comprised of all recipients of pola or LYO pola + BR or BG in Study GO29365 (N = 173). This population is referred to as the expanded pola safety population. With the exception of deaths, the safety analysis is based on the primary data cutoff dates.

The safety analysis considers all-causality treatment-emergent AEs (TEAEs) in recipients of any study drug. TEAEs were defined as AEs that are new or worsened from baseline grade or are unknown to have worsened from baseline. AEs related to the underlying disease, defined in the Appendix, were discounted from the safety analysis. The primary safety analysis, based largely on a randomized comparison, informed which AEs the reviewer regards as adverse reactions (ARs) for labeling purposes.

With the exception of AEs of special interest (AESIs), the Applicant used single MedDRA preferred terms (PTs) for AE reporting. For increased sensitivity, FDA used a combination of individual MedDRA PTs and custom groupings of PTs as defined in the Appendix (Table 28). All presented analyses use the FDA grouping.

For Studies GO29365, the AE reporting window was 90 days after the last study drug or initiation of non-protocol specified anti-cancer treatment, whichever occurred first, after which SAEs or AESIs were reported. For Studies GO27834 and DCS4968g, the AE reporting window was 30 days, after which related SAEs and second malignancies were reported.

The clinical reviewer used JMP 13 to conduct safety analyses using the data analysis datasets, supplemented by safety narratives. With the exception of deaths, the safety analysis is based on the primary data cutoff dates.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Refer to Section 8.4.1 for the number of patients treated across arms in Study GO29365. Table

12 summarizes exposure in the primary safety population. As noted in the primary efficacy population, the groups had a large difference in exposure to bendamustine, with a median of 5 cycles in the pola + BR group and a median of 3 cycles in the BR group.

Table 12: Treatment Characteristics of Primary Safety Population

Parameter		Primary Safety Population (DLBCL)	
		Pola + BR (n = 45)	BR alone (n = 39)
Exposure			
Total bendamustine cycles	1 - 2	8 (18%) ^b	18 (46%) ^b
	3 - 4	13 (29%)	10 (26%)
	5	3 (7%)	2 (5%)
	6	21 (49%)	9 (23%)
	Median	5	3
	Mean RDI (SE) ^c	91 (2) %	92 (10) %
Bendamustine duration, mo.	Median (range)	3.2 (0, 5.1)	1.4 (0, 4.4)
	Q1, Q3	1.4, 3.7	0.7, 3.0
Total pola cycles	6 ^d	22 (49%)	N/A
	Median (range)	5 (1 - 6)	
	Mean RDI (SE) ^c	94 (1.8) %	
Supportive care^e			
GCSF	Primary prophylaxis	19 (42%)	12 (31%)
	GCSF use across cycles	36% - 57%	33% - 55%
Sulfonamides	Any use	20 (44%)	16 (41%)
Antivirals	Any use	30 (67%)	23 (59%)

Source: FDA analysis (exposure), Applicant (supportive care)

^a Age ≥ 75: 8 (18%) in pola + BR group, 12 (31%) in BR group

^b 1 cycle of bendamustine: 3 (7%) in pola + BR group, 8 (23%) in BR group

^c RDI calculations were based on the number of cycles actually received, thus do not account for early discontinuation.

^d Number having 1-2 and 3-4 cycles same as for bendamustine; 2 pts had 5 doses.

^e Source: primary prophylaxis per response to 2/27/19; otherwise from CSR (section 9.1.9.2 and supplementary tables)

Reviewer comment:

- Whereas GCSF use for any reason was captured electronically, the Applicant determined use of GCSF PP through retrospective chart review in response to an IR.

8.2.2. Relevant Characteristics of the Safety Populations

In the primary safety population overall (N = 84), 32 patients (62%) were aged ≥ 65, with a higher proportion of patients in the BR arm being aged ≥ 70. Most patients (83%) had an ECOG PS of < 2, 52 (62%) had renal impairment (38% of population with mild impairment, 21% moderate, 2% severe), 15 (18%) had hepatic impairment, and 27 (32%) had a history of peripheral neuropathy at study baseline (Table 13).

Table 13: Baseline Characteristics of Primary and Expanded Safety Populations

Characteristic		Primary Safety Population (DLBCL)		Expanded Safety Population
		Pola + BR ^a (N = 45)	BR (N = 39)	Pola or LYO Pola + BR/BG for DLBCL or FL (N = 173)
Arm	Safety run-in, DLBCL	6	0	–
	Rand phase 2, DLBCL	39	39	–
	DLBCL, pola + BR/BG	–	–	71 (41%) ^b
	DLBCL, Arm G (LYO pola + BR)	–	–	32 (18%)
	FL, pola + BR/BG	–	–	70 (40%)
Age, y	Median (range)	67 (33-86)	71 (30-84)	66 (27-86)
	≥ 65	26 (58%)	26 (67%)	95 (55%)
	≥ 70	17 (38%)	22 (56%)	58 (34%)
Sex	Male	31 (69%)	25 (64%)	99 (57%)
Race	White	31 (69%)	30 (77%)	137 (79%)
ECOG PS	0-1	39 (87%)	31 (89%)	158 (91%)
	2	6 (13%)	8 (21%)	15 (9%)
Hepatic impairment	None	38 (84%)	31 (79%)	151 (87%)
	Mild	5 (11%)	8 (21%)	15 (9%)
	Moderate	2 (4%)	0 (0%)	6 (3%)
	Missing	0 (0%)	0 (0%)	1 (<1%)
Renal impairment	None	19 (23%)	13 (15%)	77 (45%)
	Mild	16 (19%)	16 (19%)	60 (35%)
	Moderate	10 (12%)	8 (10%)	35 (20%)
	Severe	0 (0%)	2 (2%)	1 (< 1%)
H/o peripheral neuropathy	Yes	18 (21%)	9 (11%)	55 (32%)

Table 13: Baseline Characteristics of Primary and Expanded Safety Populations

Characteristic	Primary Safety Population (DLBCL)		Expanded Safety Population
	Pola + BR ^a (N = 45)	BR (N = 39)	Pola or LYO Pola + BR/BG for DLBCL or FL (N = 173)

Source: FDA analysis

Note: Pola dose was 1.8 mg/kg throughout. Cycle length was 21 days for DLBCL, 28 days for FL.

^a Excluding patients treated with LYO pola.

^b Includes 45 patients from the primary safety population.

Reviewer comment:

- **In the primary safety population, although the intended population was transplant-ineligible, most patients had an ECOG PS of < 2. The minority of patients (18%) had hepatic impairment (2 cases moderate and none severe, reflecting the eligibility criteria). Safety and dosing of pola in patients with more than mild hepatic impairment will be issues in the real-world setting.**

8.2.3. Adequacy of the Safety Database

The safety database was acceptable for review. Inadequacies, such as the lack of ISS analysis datasets, were addressed through IRs. Most of the safety data is with the liquid formulation of pola.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity or quality arose.

8.3.2. Categorization of Adverse Events

AEs were graded using NCI CTCAE version 4 and were classified using MedDRA terminology. Mapping of verbatim terms to PTs in Study G029365 was generally appropriate.

8.3.3. Routine Clinical Tests

The schedule of routine clinical testing was sufficient for safety review.

8.4. Safety Results

8.4.1. Deaths

Table 14 and Table 15 summarize all reported deaths in Study G029365 according to treatment group and cause, per FDA adjudication. Data are based on the safety update report (SUR) with a cutoff of 10/2018. In this analysis, fatal AEs represent all-cause events that occurred in the

absence of NALT or PD. The reviewer classified deaths occurring in the setting of untreated PD (not directly attributable to PD but occurring in its context) as PD deaths. Deaths that occurred after NALT, but were not directly due to PD, were grouped with PD deaths.

The rates of fatal AEs were similar in patients with DLBCL and FL, with DLBCL patients having a higher incidence of deaths from PD. On FDA analysis, in patients with DLBCL, fatal AEs (in the absence of NALT or PD) were reported in 9% (4/45) of the pola + BR arm (3 within 90 days of last dose) and 15% (6/39) of the BR arm.

With all histologies combined, fatal AEs were reported in 6% (11/173) of recipients of pola or LYO pola + BR/BG (8 within 90 days of last dose), and 9% (7/80) of recipients of BR. Infection was the leading cause of death across treatment groups.

Table 14: Causes of Death as of Safety Update in All Patients Treated on Study GO29365

Treatment Group	# Treated (from N of 253)	# Deaths	Fatal AEs ≤ 30 Days After Last Dose
DLBCL, BR/BG + pola 1.8 mg/kg After NALT or PD AE Infection Bleeding	71	44 39 5 (7%) 4 ^a 1 ^b	2
DLBCL, Arm G (BR + LYO pola 1.8 mg/kg) After NALT or PD AE (infection)	32	12 10 2 (6%)	1
DLBCL, BR alone After NALT or PD AE Infection Cardiac CVA, unspecified Sudden death	39	28 22 6 (15%) 3 1 1 1	3
FL, BR/BG + pola 1.8 mg/kg After NALT or PD AE Infection Pulmonary edema Sudden death	70	14 10 ^d 4 (6%) 2 1 ^e 1 ^e	1
FL, BR alone After NALT or PD AE (CVA, ischemic)	41	5 4 1 (2%)	0

Table 14: Causes of Death as of Safety Update in All Patients Treated on Study GO29365

Treatment Group	# Treated (from N of 253)	# Deaths	Fatal AEs ≤ 30 Days After Last Dose

Source: FDA analysis. Data cutoff: 11 Oct 2018.

Note: Cycle length was 21 days for DLBCL, 28 days for FL.

^a Three pulmonary, 1 CNS (herpes meningoencephalitis).

^b Fatal hemoptysis in setting of pneumonia, anticoagulation, and thrombocytopenia

^c Includes 1 case of PML. Presented after 1 cycle in patient with 2 prior lines of therapy.

^d Includes a death attributed to PD, which was untreated, in a patient (b) (6) (b) (6) who presented shortly beforehand with fulminant hepatic failure, with suspected cirrhosis. No liver biopsy was done, and the hepatic failure was ongoing at the time of death.

^e Possibly cardiac related (pulmonary edema in setting of severe aortic stenosis; sudden death in setting of decompensated CHF and lung infection).

Table 15: Fatal AEs in Recipients of Pola or LYO Pola + BR/BG

ID	Age at entry	Primary cause of death per FDA analysis	Study day	Cycles received	Days since last treatment
DLBCL: BR + pola (from N of 45)					
(b) (6)	56	Respiratory failure (pulmonary edema) in setting of bacterial pneumonia and arrhythmia. Suspected complication of infection.	31	1	28
(b) (6)	81	Massive hemoptysis in setting of neutropenic pneumonia, anticoagulation, thrombocytopenia	42	1	39
(b) (6)	82	Pneumonia, consistent with atypical pathogen; nonneutropenic	75	3	31
(b) (6)	72	Herpetic meningoencephalitis	317	6	197
DLBCL: BR + LYO pola (from N of 32)					
(b) (6)	65	Neutropenic sepsis complicated by ARDS and cardiac arrest	48	2	26
(b) (6)	61	Neutropenic sepsis	134	3	68
DLBCL: BG + pola (from N of 26)					
(b) (6)	30	Fungal and bacterial pneumonia (wbc	41	2	17

Table 15: Fatal AEs in Recipients of Pola or LYO Pola + BR/BG

ID	Age at entry	Primary cause of death per FDA analysis	Study day	Cycles received	Days since last treatment
		count unknown) complicated by respiratory failure and cardiopulmonary arrest			
FL: BR/BG + pola (from N of 70)					
(b) (6)	86	Acute pulmonary edema, h/o severe AS	42	2	11
	70	Sudden death, in setting of G3 decompensated CHF (had history of CHF) and lung infection	154	5	40
	83	PML	176	1	161
	40	Pneumonia	639	--	490

Source: FDA analysis. Data cutoff: 11 Oct 2018.

8.4.2. Serious Adverse Events

In patients with DLBCL, the overall incidence of grade ≥ 3 AEs was 10% higher in recipients of BR + pola (84%) than BR alone (74%)(Table 16). However, the arms had similar reported incidences of grade ≥ 4 AEs (58% and 54%, respectively) and SAEs (62% with BR + pola, 62% with BR). Table 16 provides a breakdown of SAEs according to SOC and PT. In both arms, the more common SAEs were mainly infection-driven. The pola arm had a 2-fold higher incidence of pneumonia SAEs.

Similarly, on FDA analysis,

- In Arm G (N = 32), 81% had grade ≥ 3 AEs, 53% grade ≥ 4 , 69% SAEs
- In the expanded pola safety population (N = 173), 83% had grade ≥ 3 AEs, 49% grade ≥ 4 , 60% SAEs

Table 16: SAEs in Primary Safety Population

Event	Pola + BR (N = 45)		BR (N = 39)	
	n	%	n	%
Age grade ≥ 3 AE	38	84	29	74
Age grade ≥ 4 AE	26	58	21	54
Any SAE	29	64	24	62
SAEs in ≥ 5% by System Organ Class				
Infections and infestations	13	29%	12	31%
Blood and lymphatic system disorders	7	16%	5	13%
Gastrointestinal disorders	6	13%	5	13%
General disorders, admin. site conditions	4	9%	4	10%
Respiratory, thoracic, mediastinal disorders	4	9%	2	5%
Nervous system disorders	2	4%	3	8%
Cardiac disorders	1	2%	2	5%
SAEs in > 2% by Preferred Term or Grouped Preferred Term				
Pneumonia	7	16%	3	8%
Febrile neutropenia	5	11%	5	13%
Pyrexia	4	9%	0	0%
Sepsis	3	7%	4	10%
Anemia	2	4%	1	3%
Gastrointestinal hemorrhage	2	4%	0	0%
Thrombocytopenia	2	4%	1	3%

Source: FDA analysis

Bolded categories are involved ≥ 5% more in the BR + pola arm.

Reviewer comments:

- **No major safety differences are evident between the lyophilized and liquid formulations of polatuzumab vedotin.**

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In DLBCL patients on pola + BR (N = 45), AEs led to pola dose reduction in 4%, pola interruption in 51%, and permanent discontinuation of all treatment in 31% (Table 17). In both arms, cytopenias were the leading causes of any treatment discontinuation, accounting for 57% of cases in the pola + BR arm (Table 17). In the BR arm (N = 39), 15% discontinued treatment due to AEs.

Table 17: AEs Resulting in Treatment Modification or Discontinuation

Action Due to AE	Pola + BR (N = 45)	BR (N = 39)
Any study drug		
Discontinuation	14 (31%)	6 (15%)
Of all treatment	12	6
Of bendamustine alone	2	0
Dose reduction	8 (18%)	4 (10%)
Dose interruption (delay/withholding)	23 (51%)	15 (38%)
Polatuzumab vedotin		
Discontinuation	12 (27%)	N/A
Dose reduction	2 (4%) ^b	
Dose interruption	22 (49%)	
Cause of any treatment discontinuation		
Neutropenia and/or thrombocytopenia	8/14 ^c	2
Fatal AE	3 ^d	2 ^d
Pneumonitis	1	0
Muscle atrophy	1	0
Infection	1	1
Hypoxia	0	1

Source: FDA analysis

^a All treatment was discontinued.

^b Both due to peripheral neuropathy

^c Includes one case of pancytopenia

^d For pola + BR, PTs were hemoptysis, pulmonary edema, and pneumonia; for BR, PTs were pneumonia and sepsis.

8.4.4. Significant Adverse Events

Refer to Sections 8.4.1 and 8.4.2.

8.4.5. Treatment-Emergent Adverse Events and Adverse Reactions

A. Primary Safety Population

Table 18 summarizes all-cause AEs reported commonly (> 10%) in the primary safety population. Peripheral neuropathy and hepatotoxicity are discussed further in Section 8.6..

In recipients of pola + BR (N = 45), the most common (incidence ≥ 30%) AEs were neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, nausea, and pyrexia. Other AEs reported in ≥ 20% of patients were decreased appetite, abdominal pain, cough, and pneumonia.

Of the common AEs, those having a $\geq 5\%$ higher incidence in recipients of pola + BR compared to BR included cytopenias, peripheral neuropathy, diarrhea, pyrexia, appetite decrease, pneumonia, infusion-related reaction (IRR), vomiting, weight decrease, dizziness, upper respiratory tract infection (URTI), and several chemistry-related AEs. The clinical reviewer considers these to be ARs for labeling purposes. Thus, the most common ARs ($\geq 20\%$) included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

Table 18: TEAEs (> 10% Any Grade) in Primary Safety Population

SOC or Main SOC / PT or Grouped PT	Pola + BR (N = 45)		BR (N = 39)	
	Any Grade, %	Grade 3-5, %	Any Grade, %	Grade 3-5, %
BLOOD, LYMPHATIC				
Neutropenia	49	42	44	36
Thrombocytopenia	49	40	33	26
Anemia	47	24	28	18
Leukopenia	13	7	23	18
Lymphopenia	13	13	8	8
Febrile neutropenia	11	11	18	18
INFECTIONS, INFESTATIONS				
Pneumonia	22	16 ^b	15	2.6 ^c
URTI	13	0	8	0
Herpesvirus infection	11	0	10	2.6
Sepsis	7	7	10	2.6
GASTROINTESTINAL				
Diarrhea	38	4.4	28	5
Nausea	33	0	41	0
Abdominal pain	22	7	18	2.6
Vomiting	18	2.2	13	0
Constipation	18	0	21	2.6
Mucositis	11	0	21	0
GENERAL CONDITIONS				
Fatigue	40	4.4	36	2.6
Pyrexia	33	2.2	23	0
Decreased appetite	27	2.2	21	0
Infusion-related reaction	18	2.2	8	0
Asthenia	11	0	15	0
Chills	11	0	8	0
Edema	11	0	21	2.6
NERVOUS SYSTEM				
Peripheral neuropathy (SMQ broad)	40	0	8	0

Table 18: TEAEs (> 10% Any Grade) in Primary Safety Population

SOC or Main SOC / PT or Grouped PT	Pola + BR (N = 45)		BR (N = 39)	
	Any Grade, %	Grade 3-5, %	Any Grade, %	Grade 3-5, %
Neuropathy peripheral ^a	20	0	3	0
Peripheral sensory neuropathy ^a	13	0	0	0
Dizziness	13	0	8	0
RESPIRATORY, THORACIC, MEDIASTINAL Cough	22	0	26	0
SKIN, SUBCUTANEOUS Rash	18	2.2	18	8
Pruritus	13	0	10	2.6
INVESTIGATIONS Weight decreased	16	2.2	8	2.6
Renal insufficiency	13	0	13	2.6
METABOLISM, NUTRITION Hypokalemia	16	9	10	2.6
Hypoalbuminemia	13	2.2	8	0
Hypocalcemia	11	2.2	5	0

Source: FDA analysis. **Bolded** terms have ≥ 5% higher incidence of all-grade AEs in the pola + BR group.

^a Ungrouped PT

^b Includes 2 events with fatal outcome

^c Includes 1 event with fatal outcome

Other clinically relevant AEs (<10% or with a <5% difference) in recipients of pola + BR, which the reviewer recommends be considered ARs, include:

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

B. Expanded Safety Population

Because of the small number of patients in the primary safety population, the clinical reviewer evaluated safety in all pola recipients in Study GO29365 for increased sensitivity, in an effort to detect rarer, but clinically relevant safety signals.

Of the 173 recipients of pola, 60% had SAEs and 6% had fatal AEs in the absence of NALT or PD (Sections 8.4.1, 8.4.2). The AE dataset reported grade 5 AEs in 21 patients (12%); however, some occurred after NALT or PD.

In the Appendix, Table 27 summarizes common all-cause AEs in the expanded safety population. AEs with a $\geq 30\%$ incidence were nausea, diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, and pyrexia. Other AEs in $\geq 20\%$ were decreased appetite, anemia, constipation, vomiting, and abdominal pain. Infections reported in $\geq 10\%$ included URTI, febrile neutropenia, pneumonia, and herpesvirus infection. Of the 103 patients with DLBCL, tumor lysis syndrome (ungrouped PT) was reported as an AE in 3%.

Table 19 summarizes the most common AEs that the clinical reviewer considers ARs for labeling purposes. These include diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting.

Table 19: Most Common ARs ($\geq 20\%$ Any Grade or $\geq 5\%$ Grade 3 or Higher) in Expanded Pola Safety Population

SOC or Main SOC / PT or Grouped PT	Pola or LYO Pola + BR/BG (N = 173)	
	Any Grade, %	Grade 3-5, %
Blood and Lymphatic System Disorders		
Neutropenia	44	39
Thrombocytopenia	31	23
Anemia	28	14
Febrile neutropenia ^a	13	13
Leukopenia	13	8
Lymphopenia	12	12
Nervous System Disorders		
Peripheral neuropathy	40	2.3
Gastrointestinal Disorders		
Diarrhea	45	8
Vomiting	27	2.9
General Disorders		
Fatigue	40	5
Pyrexia	30	2.9
Decreased appetite	29	1.7
Infections		
Pneumonia	13	10 ^b
Sepsis	6	6 ^c
Metabolism and Nutrition Disorders		
Hypokalemia	18	6

Source: FDA analysis.

^a GCSF PP was given to 46% of all patients.

^b Includes 5 events with fatal outcome; ^c Includes 4 events with fatal outcome.

Other ARs or possible ARs in the expanded safety population include:

- General disorders: IRR (15%)
- Infection: URTI (16%), lower respiratory tract infection (10%), herpesvirus infection (12%), CMV infection (1.2%)
- Respiratory: dyspnea (19%), pneumonitis (1.7%)
- Nervous system disorders: dizziness (10%)
- Investigations: weight decrease (10%), transaminase elevation (9%), lipase increase (3.5%)
- Musculoskeletal disorders: arthralgia (7%)
- Eye disorders: blurred or decreased vision (1.2%)

Reviewer comments:

- **The safety profile in recipients of pola is similar in the primary safety population and expanded safety population, despite the heterogeneity in histology and cycle length in the latter. This supports the use of the expanded safety population to inform the safety sections of the PI. The clinical reviewer recommends adding these data to Sections 5 and 6, because of the small number of patients in the primary safety population and because pola is a new molecular entity. Evaluating a larger safety population might detect rarer, but clinically relevant safety signals that could otherwise be missed, such as PML and drug-induced liver injury.**
- **In the absence of a large randomized trial, some AEs that are listed as ARs do not have a higher incidence in the pola + BR group compared to the BR group, including several infectious complications. However, the clinical reviewer recommends reporting these as ARs given their clinical significance, the myelosuppressive potential of pola, imbalances in infection prophylaxis in the primary safety population, and the paucity of randomized data.**

8.4.6. Laboratory Findings

For the primary safety population, Table 20 summarizes treatment-emergent laboratory abnormalities with $\geq 5\%$ higher incidence in the pola + BR arm, as determined by FDA analysis of shifts in grade from baseline. The incidences of grade 3-4 cytopenias were similar, with the exception of numerically higher incidences of grade 3-4 leukopenia and neutropenia in the pola + BR arm. However, comparisons are limited by differences in exposure and in use of GCSF prophylaxis.

Table 20: Treatment-Emergent Lab Abnormalities with $\geq 5\%$ Higher Incidence in Pola Arm

	Pola + BR (N = 45)			BR (N = 39)		
	% Any Grade	% G3-4	% G4	% Any Grade	% G3-4	% G4
HEMATOLOGY^a						
Leukopenia	84	36	4	72	28	23
Neutropenia	80	47	13	51	31	18
Anemia	73	9	0	62	10	0
Thrombocytopenia	73	24	11	64	23	15
CHEMISTRY						
Creatinine increase	84	4	0	77	5	3
Hypoalbuminemia	42	2	0	38	3	0
Hypocalcemia	40	4	2	26	0	0
ALT increase	38	0	0	8	3	0
Lipase increase	36	9	2	13	5	3
AST increase	33	0	0	26	3	0
Hypokalemia	33	7	0	26	5	0
Hypomagnesemia	31	4	2	26	0	0
Amylase increase	24	0	0	18	3	3

Source: FDA analysis

^aOf 31 patients with post-baseline CD4 counts, 21 (68%) developed any-grade and grade 3-4 CD4 lymphocytopenia. Too few patients in the BR arm (12) had post-baseline CD4 counts to permit comparison.

Minor differences with the Applicant's analyses are not unexpected, in part due to slight methodologic differences.

8.4.7. Vital Signs

Not systematically evaluated in G029365.

8.4.8. Electrocardiograms / QT

Not systematically evaluated in G029365.

8.4.9. Immunogenicity

Refer to clinical pharmacology review. Of 144 recipients of pola in Study G029365 (excluding Arm G), 134 were evaluable for anti-pola ADAs. The baseline incidence of ADAs was 3.7% (5/134), and the reported incidence of treatment-emergent ADAs was 6% (8/134)(Source: CSR Section 8). There are too few patients to evaluate the relationship between ADA positivity and safety.

8.5. Safety Analyses by Demographic Subgroups

In the primary safety population, there are insufficient data to evaluate safety according to demographic subgroups. In the expanded pola safety population,

- 95/173 patients (55%) were aged ≥ 65. Patients aged ≥ 65 had a numerically higher incidence of SAEs (61/95 or 64%) than patients aged < 65 (41/78 or 53%)(source: FDA analysis).
- There are insufficient data to evaluate safety according to race.

8.6. Analysis of Submission-Specific Safety Issues

8.6.1. Peripheral Neuropathy

Peripheral neuropathy (PN) events were conservatively assessed by using the broad SMQ “peripheral neuropathy” category, which groups PTs of PN (sensory and/or motor) and related medical conditions. Although patients with DLBCL and FL have different cycle lengths and potentially different exposures, the incidences of any-grade PN in recipients of pola were comparable (Table 21). In the expanded pola safety population (N = 173), the combined incidence of PN was 40%, with a median time to onset of 2 months. The PN was mostly grade 1-2, with a 2% overall incidence of grade 3 PN and no reported grade 4 or SAE cases. Of the 69 affected patients, 42 (61%) had reported improvement or resolution after a median of 1 month, and 33 (48%) had resolution of all PN AEs (source: response to 5/23/19 FDA labeling revisions). Of the patients with PN, 7% had pola dose reduction and 7% discontinued pola due to PN.

Table 21: Incidence of Peripheral Neuropathy (SMQ Broad) in Study GO29365

	DLBCL ^a	FL ^a	Any Histology	Any Histology
	Pola + BR/ BG (N = 71)	Pola + BR/ BG (N = 70)	Pola or LYO Pola + BR/BG (N = 173)	BR (N = 80)
Any PN (SMQ broad)	28 (39%)	34 (49%)	69 (40%)	14 (18%) ^b
Grade 1	18 (25%)	24 (34%)	45 (26%)	10 (13%)
Grade 2	8 (11%)	8 (11%)	20 (12%)	4 (5%)
Grade 3	2 (3%)	2 (3%)	4 (2%)	0
Grade 4 or 5	0	0	0	0
PN leading to:				
Pola discontinuation	3 (4%)	0	5 (3%) ^c	–
Pola dose reduction	2 (3%)	3 (4%)	5 (3%)	–
Pola dose interruption	1 (1%)	1 (1%)	2 (1%)	–
Months to onset				
Median (range)	–	–	2.1 (0 - 11.4)	–
Q1, Q3	–	–	1.0, 3.5	–
Months to improvement or resolution ^d	–	–		–
Median (range)	–	–	1.0 (0 - 26.7)	–

Table 21: Incidence of Peripheral Neuropathy (SMQ Broad) in Study GO29365

	DLBCL ^a	FL ^a	Any Histology	Any Histology
	Pola + BR/ BG (N = 71)	Pola + BR/ BG (N = 70)	Pola or LYO Pola + BR/BG (N = 173)	BR (N = 80)
Q1, Q3	–	–	0.4, 6.0	–

Source: FDA analysis and response to 5/15/2019 IR.

^a Cycle length was 21 days for DLBCL, 28 days for FL.

^b Any PN with BR: 3/39 (8%) in DLBCL, 11/41 (27%) in FL

^c Denominator is the number of patients in the safety population.

^d Clarification was pending as to whether this instead represents time to complete resolution.

Similarly, in the primary safety population, of the 45 recipients of pola + BR, 18 (40%) had treatment-emergent PN events, of whom 8 (44%) had ongoing PN at baseline (source: SCS Section 2.1.6.2). The median time to onset was 1.8 months; 61% had reported resolution by the primary data cutoff, with a median time to resolution of 0.6 months (source: SCS Section 2.1.6.2).

The PN associated with pola was predominantly sensory and most commonly reported as either unspecified PN or peripheral sensory neuropathy (Table 22).

Table 22: Preferred Terms For PN (SMQ Broad) in Recipients of Pola

PT or Grouped PT	# of Patients (N = 62) ^a
Peripheral sensory neuropathy ^b	51 (82%)
Peripheral neuropathy	23 (37%)
Muscular weakness	10 (16%)
Gait disturbance	4 (6%)
Peripheral motor neuropathy	3 (5%)
Polyneuropathy	2 (3%)
Other	3 (5%) ^c

Source: FDA analysis

^a From 141 recipients of pola + BR/BG for DLBCL or FL in Arms A-F

^b Also includes paresthesia, hypoesthesia, and neuralgia

^c Hypotonia, muscle atrophy, peroneal nerve palsy

Reviewer comment:

- Use of SMQ broad criteria for PN overestimates the incidence of PN, as demonstrated by the 18% incidence in recipients of BR, which is not associated with PN.

8.6.2. Neutropenia and Infections

In the primary safety population, < 50% of recipients of pola + BR received GCSF PP (Section 8.2.2). Use of GCSF PP, as well as PJP and herpesvirus prophylaxis, was optional prior to Arm G. In the pola + BR group (N = 45), 29% had grade ≥ 3 or serious infections, 12% had febrile neutropenia, 43% had neutropenia reported as an AE, and 47% had treatment-emergent grade ≥ 3 neutropenia (grade 4, 13%) by laboratory analysis (Section 8.4.6).

Similarly, in the expanded pola safety population (N = 173), 46% reportedly had GCSF PP, 32% had grade ≥ 3 or serious infections (sepsis 6%), 13% had febrile neutropenia, and 44% had neutropenia reported as an AE. Patients who received GCSF PP had a numerically lower incidence of having at least one G ≥ 3 or serious infection (absolute difference 9%), but a similar (albeit numerically higher) incidence of febrile neutropenia (Table 23). Atypical or opportunistic infections included:

- 5 patients (3%) with CMV infection or reactivation
- 1 case each of PML, cerebral toxoplasmosis, herpes meningoencephalitis, PJP pneumonia, fungal pneumonia unspecified, respiratory syncytial virus infection, and clostridial sepsis.
- 21 patients (12%) with herpesvirus infection.

Table 23: Infection and GCSF Prophylaxis in Expanded Pola Safety Population

	Any Histology, Pola or LYO Pola + BR/BG (N = 173)	
	GCSF PP (N =79)	No PP (N =94)
Febrile neutropenia	13 (16%)	10 (11%)
At least one G ≥ 3 or serious infection	21 (27%)	34 (36%)
Neutropenia as an AE	41 (52%)	35 (37%)
Overall:		
Febrile neutropenia	23 (13%)	
At least one G ≥ 3 or serious infection	55 (32%)	
At least one infection SAE	52 (30%)	

Source: FDA analysis

Reviewer comments:

- **There are too few patients to inform the effect of GCSF PP on infection rates, evaluation of which may be confounded by selection bias (use of GCSF PP for patients at greater risk), use of secondary GCSF prophylaxis, and inconsistent use of antimicrobial prophylaxis. Although GCSF PP is not needed for BR alone, in the primary safety population there was more myelosuppression and infection reported in recipients of pola + BR than BR. However, this could reflect the myelosuppressive effect of pola, the longer exposure in the pola arm, or both.**

- **GCSF PP should be considered in recipients of pola + BR, particularly as infectious complications are expected to be higher in the general population. However, there are insufficient data to recommend its use in all patients.**
- **The proposed PI states in Section 5 to (b) (4) and omits this from Section 2 on recommended prophylactic medications. Both section should state to administer herpesvirus and PJP prophylaxis.**

8.6.3. Other AESIs

A. Infusion-Related Reactions

Among all recipients of pola or LYO pola + BR/BG in Study GO29365 (N = 173), 15% of patients had IRRs, as defined by a tailored grouping of terms. The IRRs were grade 1 in 58%, grade 2 in 35%, and grade 3 in 8% (overall incidence of grade 3 IRRs, 1.2%). Without grouped terms, IRR was reported in 12 patients (7%), with 1 case being grade 3 and the remainder grade 1-2 (source: FDA analysis).

Reviewer comments:

- **The Applicant did not propose IRR as a Warnings and Precaution. IRR warrants a warning because the risk can be mitigated and is actionable. The 1% incidence of severe IRRs in Study GO29365 is in the context of protocol-mandated premedication and a slower infusion rate for the first dose (90 minute) than for subsequent doses (30 minutes as tolerated).**
- **The Applicant originally defined IRRs as treatment-related AEs during or within 24 hours of infusion, regardless of type. This broad definition captured multiple AEs that do not describe “IRR,” such as gastrointestinal symptoms, peripheral neuropathy, and neutropenia. The clinical reviewer therefore requested a tailored grouping of terms.**

B. Hepatotoxicity

Hepatotoxicity is a Warning and Precaution for brentuximab vedotin. In the present BLA, the Applicant reported hepatotoxicity using a broad SMQ approach (Appendix). In the expanded pola safety population (N = 173), there were 35 cases (20%) of any grade hepatotoxicity based on this SMQ approach: 8 (5%) grade 3-4, none grade 5, 2 (1%) SAEs (source: FDA analysis). Two patients (1.2%) discontinued pola due to hepatotoxicity. This includes a death, reportedly from PD, in the setting of grade 4 cholestatic liver failure of unclear etiology that presented < 30 days after the last pola dose (see Section 8.4.1).

The Applicant originally reported no cases meeting Hy’s law criteria in Study GO29365. For increased sensitivity, FDA requested a Hy’s law screen across all pola studies with accompanying narratives, allowing up to a 2 week window between the transaminase elevation and bilirubin elevation (source: 4/15/2019 IR). With this approach, 6 potential Hy’s law cases were identified among ~500 patients treated with pola at any dose in Studies GO29365, GO29044, DCS4958g, and GO207834 combined.

Of 4/173 potential cases in Study GO29365:

- 1 is a true Hy's law case, involving grade 3 LFT abnormalities during the first cycle of pola + BR; the patient completed 6 cycles without dose modification (patient (b) (6)).
- 1 is from ischemic hepatitis, with self-limited grade 4 transaminase elevations developing in the setting of vomiting, abdominal pain, hypotension, and anuria, and thus is not consistent with drug-induced liver injury (patient (b) (6)).
- 2 are possible but unlikely Hy's law cases, presenting with a primarily obstructive origin (patient (b) (6)) or cirrhosis with acute hepatitis (patient (b) (6)), in the setting of disease progression.

Of the other 2 potential cases from Study GO28734:

- 1 is a possible but unlikely case, involving grade 2 transaminitis and grade 2 bilirubin elevation in a patient with hepatomegaly and mild hepatic impairment at study baseline (patient (b) (6); pola 1.8 mg/kg + obinutuzumab).
- 1 is not a Hy's law case, being attributable to disease progression (patient (b) (6); pola 2.5 mg/kg + rituximab, preceded by pinatuzumab vedotin + rituximab)

Reviewer comments:

- **In the reviewer's opinion, inclusion of hepatotoxicity as a Warning for pola (as proposed by the Applicant) is only marginally supported by the safety data from Study GO29365 or by a Hy's law screen of all pola studies in the ISS. Across the ~500 patients treated with pola across these studies, 1 true Hy's law case was identified in a recipient of pola + BR, with 3 other cases being possible but unlikely. Transient LFT abnormalities occur with a variety of chemotherapy regimens. A warning is more justifiable if hepatotoxicity is considered a potential class effect with the MMAE payload.**
- **Use of a broad SMQ approach, as proposed by the Applicant, is helpful for screening for hepatotoxicity, but includes multiple nonspecific terms (e.g. hypoalbuminemia, alkaline phosphate increase, GGT increase) and overestimates its incidence.**

C. Pulmonary Toxicity

Pulmonary toxicity, including noninfectious pneumonitis and interstitial lung disease, is a Warning and Precaution for brentuximab vedotin. Table 24 summarizes cases of potential pulmonary toxicity identified across studies in the ISS. Narratives were requested to inform causality, but information on concomitant infection was incomplete.

In the expanded pola safety population (N = 173), FDA identified 4 cases (2.3%) of pneumonitis (n = 3) or organizing pneumonia (n = 1), of which 2 were attributable to infection. Pneumonitis led to treatment interruption in 1 patient, withdrawal of rituximab in 1 patient, and discontinuation of all treatment in 1 patient.

Table 24: Potential Pulmonary Toxicity Across Studies in Recipients of Pola

Study (# of pola recipients)	ID	Regimen	PT	Infection identified	Grade	Day	Action with study drug	Resolved / recovered (duration)
GO29365 (N = 173)	(b) (6)	Pola 1.8 + BR	Pneumonitis	Yes; CMV	2	59	Interrupt all	Yes (8 d)
		Pola 1.8 + BR	Pneumonitis	Unknown	2	94	Stop rituximab	No
		Pola 1.8 + BR	Pneumonitis	No	1	97	Stop all, then BR alone	No
		Pola 1.8 + BG	Organizing pneumonia	Yes	2	140	None	No
GO27834 (N = 104)	(b) (6)	Pola 2.4 + R	Interstitial lung disease	Unknown	1	156	None	Yes (176 d)
		Pola 2.4 + R	Pulmonary fibrosis	Unknown	2	232	None	No
GO29044 (N = 69) ^a	(b) (6)	Pola 1.8 + R-CHP	Pneumonitis	Unclear; in setting of SIRS	2	115	None	Yes (20 d)
DCS4968g (N = 65) ^b	No cases	Pola +/- R	-					

Source: FDA analysis and response to 4/19/19 IR. Refer to Table 2 for study summaries.

SIRS = systemic inflammatory response syndrome

^a for pola 1.8 + R/G-CHP

^b pola ≥ 1.8 mg/kg

Pulmonary toxicity attributable to MMAE is plausible in recipients of pola, based on the pulmonary toxicity observed with BV and preclinical data. The Applicant indicated that “In non-clinical studies, lung toxicity was observed in rats that were administered repeat doses of polatuzumab vedotin (Study 10-0898). The lung toxicity was characterized by alveolar macrophage infiltration and at highest dose in males, Type II pneumocyte hyperplasia and hypertrophy. These effects were related to MMAE activity and were generally dose-dependent, minimal in severity, and reversible except for a few instances....As there is no identified antibody-antigen binding in the lung, this is considered to be possibly MMAE-related.” (source: response to 4/15/2019 IR).

Reviewer comment:

- Though the cases were reportedly less than grade 3, pulmonary toxicity should be listed in PI Section 6 as a rare but clinically relevant AR. A Warning and Precaution for noninfectious pulmonary toxicity would also be reasonable and was considered, because the risk is actionable and may be a class effect. However, the available data with pola 1.8 mg/kg do not rise to the level of a warning.

D. Ocular Toxicity

Although the Applicant did not include ocular toxicity as an AESI, there is a recognized association between ADCs and various ocular toxicities, including keratitis and corneal deposits.^{18,19} In the expanded pola safety population, 3 cases (1.7%) of decreased vision were reported, all grade 1, with 2 cases (1.2%) being attributed to study treatment. On FDA analysis, among recipients of pola 1.8 mg/kg in Studies GO29365, DCS4968g, GO27834, and GO29044 combined (N = 357), there was 1 PT of keratitis and no PTs of ocular deposits. Other, nonspecific AEs included dry eye (5 patients) and blurred or impaired vision (16 patients).

Reviewer comment:

- **There is no clear signal of ocular toxicity associated with pola in these studies. Blurred or impaired vision is nonspecific and was also reported in 2/80 recipients (2.5%) of BR alone. Because the etiology is not discernable in most cases, mention of blurred vision is reasonable in PI Section 6.**

E. Dermatologic Toxicity

Although the Applicant did not include dermatologic toxicity as an AESI, the brentuximab vedotin PI includes a Warning and Precaution for serious dermatologic reactions, and bendamustine commonly causes rash. In the primary safety population, the incidence of rash (grouped PT) was 18% in both groups. In the expanded pola safety population, there were no reported cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme. Two patients (1.2%) had rash reported as an SAE and resulting in treatment discontinuation: one grade 2 and one grade 4.

8.7. Specific Safety Studies / Clinical Trials

None

8.8. Additional Safety Explorations

Refer to the clinical pharmacology review for explorations of safety in relation to hepatic impairment.

Reviewer comment:

- **The safety of pola in patients with hepatic impairment is not defined and is an important question, particularly given the narrow therapeutic window and the relapsed or refractory patient population.**

8.8.1. Human Carcinogenicity or Tumor Development

No clinical data with study drug

8.8.2. Human Reproduction and Pregnancy

No clinical data with study drug

8.8.3. Pediatrics and Assessment of Effects on Growth

Not assessed

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable

8.9.2. Expectations on Safety in the Postmarket Setting

Because recipients of the marketed drug might not have met eligibility criteria for the study supporting BLA approval, AEs may occur with higher incidence and severity in the postmarket setting. New safety signals might also emerge with larger numbers of patients exposed.

8.9.3. Additional Safety Issues from Other Disciplines

None

8.10. Integrated Assessment of Safety

The determination of safety is based on Study GO29365. The primary safety population consisted of patients with DLBCL who received BR with (N = 45) or without (N = 39) pola, including 6 recipients of pola + BR in the phase 1b portion. For increased sensitivity, the analysis was supplemented by review of an expanded safety population, comprised of all recipients of pola or LYO pola + BR or BG in Study GO29365 (N = 173).

In the primary safety population, fatal AEs within 90 days of last treatment occurred in 7% of recipients of pola + BR. SAEs occurred in 64% of recipients of pola + BR, most often from infection. SAEs in $\geq 5\%$ included pneumonia (16%), febrile neutropenia (11%), pyrexia (9%), and sepsis (7%). AEs led to dose reduction in 18%, dose interruption in 51%, and permanent discontinuation of all treatment in 31%. The leading AEs resulting in treatment discontinuation were thrombocytopenia (9% of all patients) and neutropenia (7%).

In recipients of pola + BR, the most common ARs ($\geq 20\%$) were neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, nausea, pyrexia, decreased appetite, and pneumonia. More than 20% of patients developed grade 3 or 4 neutropenia, leukopenia, or thrombocytopenia, and $>10\%$ developed grade 4 neutropenia (13%) or grade 4 thrombocytopenia (11%).

Safety was also evaluated in 173 adult patients with rel/ref FL or DLBCL who received pola or LYO pola, bendamustine, and either rituximab or obinutuzumab in Study GO29365, including the 45 patients with DLBCL described above. The overall safety profile in the primary and expanded safety populations was similar. In the expanded safety population, fatal AEs within 90 days of last treatment occurred in 4.6%, with infection as a leading cause. SAEs occurred in 60%, most often from infection. ARs in $\geq 30\%$ of patients were nausea, diarrhea, neutropenia,

peripheral neuropathy, fatigue, thrombocytopenia, and pyrexia. Other ARs in ≥20% of patients included decreased appetite, anemia, constipation, vomiting, and abdominal pain. Infection-related events in > 10% of patients included upper respiratory tract infection, febrile neutropenia, pneumonia, and herpesvirus infection.

9. Advisory Committee Meeting and Other External Consultations

The application was not presented to the Oncologic Drug Advisory Committee or other external consultants, as it did not raise significant efficacy or safety concerns.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The following are the clinical reviewer’s recommendations for the Polivy PI. Table 25 summarizes the main changes between the Applicant’s proposed labeling and the recommended labeling. Labeling negotiations were ongoing at the time of this review.

Table 25: Summary of Significant Labeling Changes

Section	Applicant’s Proposed Labeling	Recommended Labeling
Indication	(b) (4)	In combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified after at least two prior therapies (accelerated approval)
Dosage and Administration	(b) (4)	• Administer infection prophylaxis, including for PJP and herpesvirus • Consider TLS prophylaxis • Revise and expand toxicity management guidelines. – Before dose reducing bendamustine for neutropenia, consider GCSF prophylaxis. – Before discontinuing all treatment for neutropenia or thrombocytopenia, consider pola dose reduction. – Add guidelines for IRR
Warnings and Precautions	(b) (4)	• Add IRR as a warning. • Use all recipients of pola or LYO pola + BR/BG in Study GO29365 (N = 173) as the denominator to inform safety, with more detailed descriptions of toxicity.

Table 25: Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	Recommended Labeling
Adverse Reactions	(b) (4)	• In addition to safety based on primary safety population, expand safety characterization to include all recipients of pola or LYO pola + BR/BG. • Use grouped PTs for more sensitive labeling. • Expand reporting of lab abnormalities. • Add pneumonitis as a clinically relevant AR.
Efficacy		• Limit efficacy reporting to response (ORR and CR rate) at EOT and BOR per IRC, with a text description of DOR. • Remove (b) (4).

Rationale for accelerated approval: Given the small numbers of patients, there is high uncertainty as to the magnitude of the treatment effect with the addition of pola to BR in patients with rel/ref DLBCL. Due to multiple limitations, the PFS and OS data from the randomized phase 2 study are not sufficiently robust to support a regular approval. However, the observed differences in depth of response, overall response, and response duration are clinically meaningful, and there is ample indication of a positive treatment effect with the addition of pola. These data are sufficient to support an accelerated approval based on CR rate at EOT, BOR, and DOR per IRC.

Rationale for recommended indication statement:

- a. Number of prior therapies: The clinical review team recommends approval of pola in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, after at least two prior therapies. This indication contrasts with the study's eligibility criteria and the Applicant's proposed indication, (b) (4).

However, a major limitation of this BLA is the small number of patients. In the primary efficacy population, only 11 patients (28%) in the pola + BR arm had one prior line of therapy. Apart from BR, the efficacy and safety of pola + BR relative to multiple standard second-line regimens have not been demonstrated. These standard salvage regimens have greater available data not only on efficacy, but on safety. In addition, there is concern that, should pola + BR be approved for second-line use, medically fit (transplant-eligible) patients could receive pola + BR in lieu of more intensive, established salvage regimens such as R-ICE, R-ESHAP, or R-DHAP.

There remains an unmet medical need for second-line regimens in patients with DLBCL who are medically inappropriate for HSCT. In patients with DLBCL who are medically inappropriate for HSCT, BR is one of several regimens that are standardly considered as

second-line. As an alternative, therefore, the clinical reviewer proposed an indication for pola in combination with BR for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, after:

- at least two prior therapies, or
- one prior therapy, in patients for whom HSCT is not planned

This qualification would address the concern that pola + BR could be prioritized over standard intensive second-line regimens in fit patients, while providing an approved second-line therapy for patients who are medically inappropriate for HSCT. Concerns about safety, however, would persist, especially in patients who are transplant-ineligible because of comorbidities or advanced age.

- b. Available therapies: Should accelerated approval be granted for relapsed or refractory DLBCL after at least 2 prior lines, the indication for pola would overlap with the indication for axicabtagene ciloleucel and tisagenlecleucel. These CAR-T therapies have regular approval in relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Although the CAR-T cell therapies can produce durable CRs, their use has limitations in the general relapsed or refractory DLBCL population because of the toxicity profile, which requires rigorous selection criteria, and because of restricted availability. In addition, the waiting period associated with CAR-T manufacture may be prohibitive in patients with symptomatic or rapidly progressing aggressive lymphomas. For these reasons, axicabtagene ciloleucel and tisagenlecleucel are not necessarily available therapies.

11. Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team does not recommend a REMS. Based on the observed safety profile of pola, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

12. Postmarketing Requirements and Commitments

The clinical team recommends the following two accelerated approval PMRs in order to verify clinical benefit. Successful outcome of either Study GO39942 (POLARIX) or Study MO40598 would suffice to fulfill the need for a confirmatory, randomized trial. However, results of both studies will be requested.

PMR: Complete Study GO39942, a randomized, double-blind, placebo-controlled trial that evaluates polatuzumab vedotin-piiq in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma. The primary endpoint would be progression-free survival. Key secondary endpoints would include complete remission rate per independent review committee and overall survival.

PMR: Complete Study MO40598, a randomized clinical trial that evaluates polatuzumab vedotin-piiq in combination with rituximab, gemcitabine, and oxaliplatin (R-GemOx) versus R-GemOx alone in patients with relapsed or refractory large B-cell lymphoma after at least 2 prior therapies. The primary endpoint would be overall survival. Secondary endpoints would include complete remission rate per independent review committee and progression-free survival.

Refer to action letter for final wording of PMRs and the milestone dates.

13. Appendices

13.1. References

1. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol* 2016;174(1):43-56.
2. Farooq U, Maurer MJ, Thompson CA, et al. Clinical heterogeneity of diffuse large B cell lymphoma following failure of front-line immunochemotherapy. *Br J Haematol* 2017;179(1):50-60.
3. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010;28(27):4184-4190.
4. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017;130(16):1800-1808.
5. Hitz F, Connors JM, Gascoyne RD, et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. *Ann Hematol* 2015;94(11):1839-1843.
6. Nagle SJ, Woo K, Schuster SJ, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *Am J Hematol* 2013;88(10):890-894.
7. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant* 2016;51(1):51-57.
8. Zelenetz AD, Gordon GI, Abramson JS, et al. NCCN Guidelines: B-Cell Lymphomas, Version 3.2019. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed 30 May 2019
9. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol* 2013;31(17):2103-2109.
10. Vacirca JL, Acs PI, Tabbara IA, Rosen PJ, Lee P, Lynam E. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. *Ann Hematol* 2014;93(3):403-409.
11. Hong JY, Yoon DH, Suh C, et al. Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma: a multicenter retrospective analysis. *Ann Hematol* 2018;97(8):1437-1443.
12. Arcari A, Chiappella A, Spina M, et al. Safety and efficacy of rituximab plus

bendamustine in relapsed or refractory diffuse large B-cell lymphoma patients: an Italian retrospective multicenter study. *Leuk Lymphoma* 2016;57(8):1823-1830.

13. Merchionne F, Quintana G, Gaudio F, et al. Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma: a retrospective analysis. *Leuk Res* 2014;38(12):1446-1450.
14. Chu PG, Arber DA. CD79: a review. *Appl Immunohistochem Mol Morphol* 2001;9(2):97-106.
15. Polson AG, Yu SF, Elkins K, et al. Antibody-drug conjugates targeted to CD79 for the treatment of non-Hodgkin lymphoma. *Blood* 2007;110(2):616-623.
16. Olejniczak SH, Stewart CC, Donohue K, Czuczman MS. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry. *Immunol Invest* 2006;35(1):93-114.
17. Dornan D, Bennett F, Chen Y, et al. Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. *Blood* 2009;114(13):2721-2729.
18. Saber H, Leighton JK. An FDA oncology analysis of antibody-drug conjugates. *Regul Toxicol Pharmacol* 2015;71(3):444-452.
19. Eaton JS, Miller PE, Mannis MJ, Murphy CJ. Ocular Adverse Events Associated with Antibody-Drug Conjugates in Human Clinical Trials. *J Ocul Pharmacol Ther* 2015;31(10):589-604.

13.2. Financial Disclosure

Covered Clinical Study: GO29365

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: 683		
Number of investigators who are Applicant employees (both full-time and part-time): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Applicant of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable interests/arrangements:	Yes ☒	No ☐
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 26		

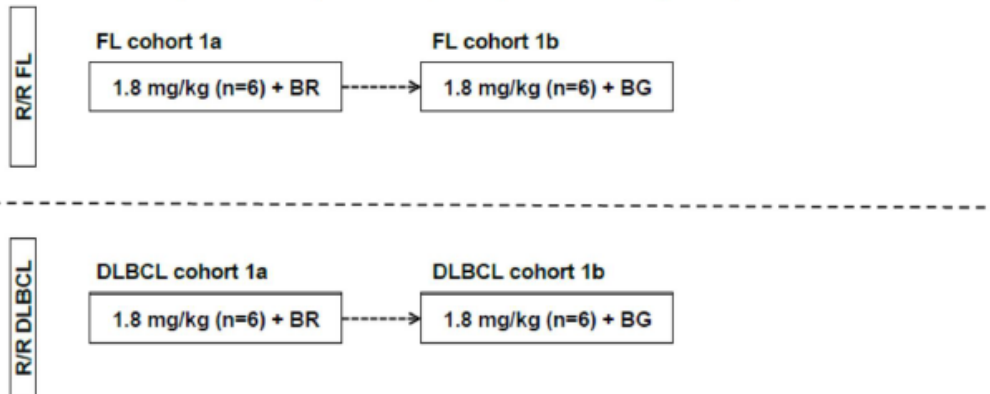
The above financial disclosures were mitigated by the following:

- For one subinvestigator with disclosed financial interests, the site enrolled a minority of the efficacy population (2 patients or 2.5%).
- For the other subinvestigator with disclosed financial interests, the site enrolled 11% of the efficacy population (9 patients), but was inspected by OSI with No Action Indicated (site 272994).
- Efficacy was assessed by an IRC.

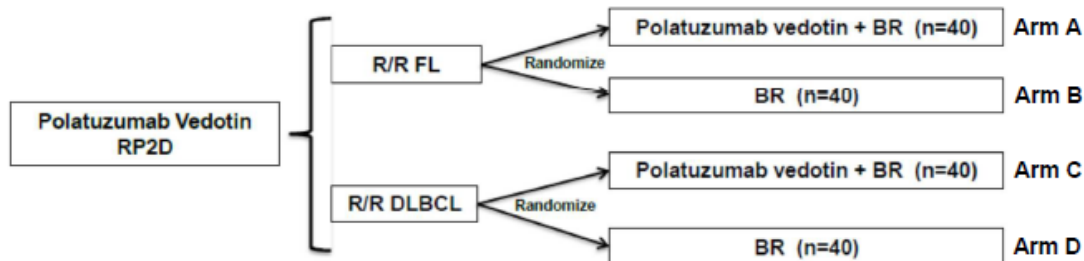
13.3. Schema and Target Accrual for Study G029365

Figure 6: Arms of Study G029365

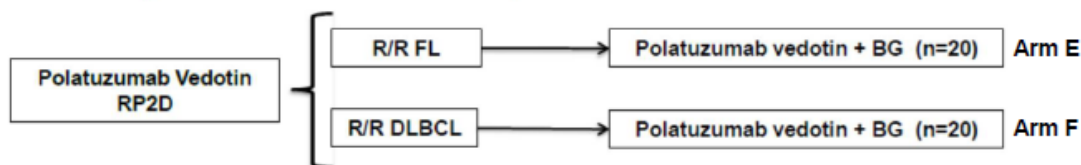
Phase Ib: Safety Run-in Separate FL (n=12) and DLBCL (n=12) cohorts



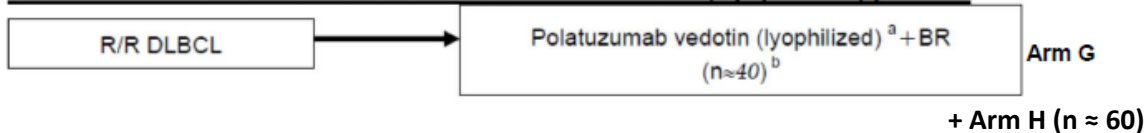
Phase II Randomization: Polatuzumab Vedotin plus BR vs BR



Phase II Expansion: Polatuzumab Vedotin plus BG



Phase II New Formulation Cohort: Polatuzumab Vedotin (Lyophilized) plus BR



Rituximab (375 mg/m²) D1 of each cycle, or **obinutuzumab** (1000 mg) D1, D8, D15 in Cycle 1, then D1 of each subsequent cycle.

Bendamustine (90 mg/m²) D2 and D3 in Cycle 1, then D1 and D2 in each subsequent cycle.

Polatuzumab vedotin (1.8 mg/kg) D2 in C1 then D1 of subsequent cycles. Lyophilized dose also 1.8 mg/kg. FL: every 28 days x 6 cycles.

DLBCL: every 21 days x 6 cycles.

Source: Summary of Clinical Efficacy, Figure 1 with modification.

13.4. Disposition of Phase 1b and 2 Cohorts A - F in Study G029365

Figure 7: Accrual and Disposition of Patients in Arms A - F

Study Phase	Phase 1b Safety Run-in			
Histology	FL		DLBCL	
Cohort	1a	1b	1a	1b
Treatment	Pola+BR	Pola+BG	Pola+BR	Pola+BG
No. patients enrolled (ITT population)	n=6	n=6	n=6	n=6
No. of patients who: Received treatment (Safety population)	n=6	n=6	n=6	n=6
Completed all treatments	4 (66.7%)	5 (83.3%)	2 (33.3%)	2 (33.3%)
Alive in follow-up	6 (100.0%)	3 (50.0%)	4 (66.7%)	1 (16.7%)
Discontinued study due to:	0	3 (50.0%)	2 (33.3%)	5 (83.3%)
Adverse event	0	0	0	1 (16.7%)
Death	0	2 (33.3%)	2 (33.3%)	4 (66.7%)
Non-safety reasons	0	1 (16.7%)*	0	0

Study Phase	Phase II Randomization				Phase II Expansion	
Histology	FL		DLBCL		FL	DLBCL
Arm	A	B	C	D	E	F
Treatment	Pola+BR	BR	Pola+BR	BR	Pola+BG	Pola+BG
No. patients enrolled (ITT population)	n=39	n=41	n=40	n=40	n=20	n=21
No. of patients who: Received treatment (Safety population)	n=38	n=41	n=39	n=39	n=20	n=20
Completed all treatments	28 (71.8%)	31 (75.6%)	18 (45.0%)	9 (22.5%)	14 (70.0%)	9 (42.9%)
Alive in follow-up	31 (79.5%)	31 (75.6%)	11 (27.5%)	4 (10.0%)	15 (75.0%)	7 (33.3%)
Discontinued study due to:	8 (20.5%) [†]	10 (24.4%)	29 (72.5%) [‡]	36 (90.0%) [§]	5 (25.0%)	14 (66.7%) [¶]
Adverse event	0	0	0	0	1 (5.0%)	0
Death	6 (15.4%)	4 (9.8%)	23 (57.5%)	28 (70.0%)	2 (10.0%)	13 (61.9%)
Non-safety reasons*	2 (5.1%) [†]	6 (14.6%)	6 (15.0%) [‡]	8 (20.0%) [§]	2 (10.0%)	1 (4.8%) [¶]

* Includes withdrawal by subject, progressive disease, physician decision, lack of efficacy, lost-to-follow-up, and other. Percentages are based on ITT population.

Source: CSR Table 6 and 7. Data cutoff: 30 April 2018.

13.5. Reported Efficacy per IRC in Study G029365

Table 26: Response per IRC in Relapsed/Refractory DLBCL, Prior to FDA Adjudication

Outcome per IRC	Primary efficacy popn (ITT)		Arm G
	POLA + BR (N = 40)	BR (N = 40)	LYO Pola + BR (N = 32)
PET-CT Based Response at PRA			
Objective response (95% CI) ^a Nominal p-value	18 (45%) (29, 62)	7 (18%) (7, 33)	11 (34%) (19, 53)
	.007		–
CR (95% CI) Nominal p-value CR Rate Difference, % (95% CI)	16 (40%) (25, 57)	7 (18%)^b (7, 33)	11 (34%) (19, 53)
	.026		–
	22 (3, 41)		–
PR	2 (5%)	0 (0%)	0 (0%)
SD	6 (15%)	1 (3%)	3 (9%)
PD	7 (18%)	6 (15%)	5 (16%)
NE	9 (23%)	26 (65%)	13 (41%)
Best Overall Response			
Objective response (95% CI) Nominal p-value	23 (58%) (41, 73)	10 (25%) (13, 41)	15 (47%) (29, 65)
	.002		–
CR (95% CI)	20 (50%) (34, 66)	9 (23%) (11, 38)	14 (44%) (26, 62)
PR	3 (8%)	1 (3%)	1 (3%)
SD	4 (10%)	9 (23%)	5 (16%)
PD	8 (20%)	5 (13%)	3 (9%)
NE	5 (13%)	16 (40%)	9 (28%)

Source: CSR.

^a Clopper-Pearson method

^b Includes 1 pt with midtreatment CR who proceeded to HSCT after 3 cycles.

13.6. Additional Safety Analyses

Table 27: All-Cause AEs (> 10% Any Grade or ≥ 5% Grade 3 or Higher) by Decreasing Incidence in Expanded Pola Safety Population

PT or Grouped PT	Pola or LYO Pola + BR/BG for DLBCL or FL (N = 173)	
	Any Grade, %	Grade 3-5, %
Nausea	46	2
Diarrhea	44	8
Neutropenia	44	39
Peripheral neuropathy (SMQ broad)	40	2
Fatigue	40	5
Thrombocytopenia	31	23
Pyrexia	30	3
Decreased appetite	29	2
Anemia	28	14
Constipation	28	1
Vomiting	27	3
Abdominal pain	20	3
Rash	19	2
IRR (grouped term)	18	1
Cough	18	0
Dyspnea	18	1
Hypokalemia	17	7
Mucositis	17	2
Headache	16	1
URTI	16	0
Edema	14	2
Hypomagnesemia	14	1
Renal insufficiency	14	1 ^b
Asthenia	13	2
Febrile neutropenia ^a	13	13
Pneumonia	13	10 ^c
Leukopenia	13	8
Herpesvirus infection	12	1 ^b
Lymphopenia	12	12
Chills	11	0
Sepsis	6	6 ^d

Source: FDA analysis

^a GCSF PP was given to 46% of all patients.

^b Includes 1 fatal event; ^c Includes 5 fatal events; ^d Includes 4 fatal events.

13.7. FDA Grouping of Preferred Terms

Note: Neutropenic sepsis is counted under both “febrile neutropenia” and “sepsis” PTs for patient GO29365-281938-4007.

PTs excluded from AE analysis: Disease progression, Lymphoma, Lymphadenopathy, Central nervous system lymphoma.

Not excluded from analysis: Lymph node pain, tumor pain, tumor flare, mass, tumor-associated fever

Bracketed terms were considered, but did not appear as treatment-emergent AEs in the ISS or Arm G ADAE.xpt datasets.

Table 28: Grouping of Preferred Terms for FDA Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal discomfort, Gastrointestinal pain, Epigastric discomfort	Abdominal distension, Abdominal rigidity
Anemia	Anemia, Hemolytic anemia, Hemoglobin decreased, [Hematocrit decreased, RBC count decreased]	Pancytopenia
Cardiac failure	Cardiac failure, Cardiac failure congestive, Cardiomyopathy	Ejection fraction decrease, Left ventricular dysfunction
Cough	Cough, Productive cough	Hemoptysis, Upper airway cough syndrome
Diarrhea	Ungrouped preferred term	Colitis, Gastroenteritis
Dizziness	Dizziness, Dizziness postural, Vertigo	
Dyspnea	Dyspnea, Dyspnea exertional, Orthopnea	Acute respiratory failure, Respiratory failure, Respiratory distress, Tachypnea, Bronchospasm,

Table 28: Grouping of Preferred Terms for FDA Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
		Wheezing
Edema	Edema, Edema peripheral, Fluid overload, Fluid retention, Face edema, Swelling face, Peripheral swelling, Pulmonary edema, Acute pulmonary edema, Pulmonary congestion, [Generalized edema]	Localized edema, other specific sites of edema (e.g. periorbital), Swelling, [Lymphedema]
Febrile neutropenia	Febrile neutropenia, Neutropenic sepsis, Febrile bone marrow aplasia, [Neutropenic infection]	
Gastrointestinal hemorrhage	Gastrointestinal hemorrhage, Upper gastrointestinal hemorrhage, Gastric hemorrhage, Hematochezia, Hematemesis, Melena, Rectal hemorrhage, Duodenal ulcer hemorrhage, [Lower gastrointestinal hemorrhage, Intestinal hemorrhage, Large intestinal ulcer hemorrhage, Intestinal hemorrhage]	Gastric perforation, Duodenal perforation, [Mouth hemorrhage, Hemorrhoidal hemorrhage]
Headache	Headache, Migraine, Migraine with aura, Tension headache, Sinus headache, Cluster headache	Procedural headache, head discomfort
Hemorrhage intracranial	Hemorrhage intracranial, Subdural hematoma, Cerebral hemorrhage, [Subdural hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage]	
Hepatotoxicity	SMQ approach by Applicant: "Drug-related hepatic disorders - severe events only [wide]" (SMQ2000007w), SMQ "Liver related investigations, signs and symptoms [wide]" (20000008w), SMQ "Cholestasis and jaundice of hepatic origin [wide]" (20000009w) and SMQ "Liver-related coagulation and bleeding disturbances [wide]" (20000015w).	
Herpesvirus infection	Herpes simplex, Herpes virus infection, Herpes zoster, Herpes ophthalmic, Oral herpes, Ophthalmic herpes zoster, Meningoencephalitis herpetic, [Genital herpes, Varicella, Varicella zoster virus infection, Herpes dermatitis]	
Hyperglycemia	Hyperglycemia, Blood glucose increased, Diabetes mellitus, Type 2 diabetes mellitus, Diabetic metabolic decompensation, [Diabetes mellitus inadequate	

Table 28: Grouping of Preferred Terms for FDA Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
	control, Glycosylated hemoglobin increased]	
Hypersensitivity	Hypersensitivity, Drug Hypersensitivity, Infusion site hypersensitivity, Urticaria, [Angioedema]	
Hypertension	Hypertension, Blood pressure increased	
Hypogammaglobulinemia	Hypogammaglobulinemia, Blood immunoglobulin A/G/M decreased	
Hypotension	Hypotension, Orthostatic hypotension, [Blood pressure decreased]	
Infusion-related reaction	Per Applicant’s grouping	
Interstitial lung disease	SMQ broad – Interstitial lung disease, pneumonitis, [Acute respiratory distress syndrome]	
Leukopenia^a	Leukopenia, White blood cell count decrease	
Lower respiratory tract infection	Bronchitis, Lower respiratory tract infection, Lung infection, Tracheitis, and specific types; Pleural infection bacterial	
Mucositis	Stomatitis, Mucosal inflammation, Mouth ulceration, Tongue ulceration, Aphthous ulcer, Oropharyngeal pain, Oral pain, Odynophagia, [Oral mucosal erythema, Aphthous stomatitis, Oral discomfort, Oropharyngeal discomfort]	Angular cheilitis, Glossodynia, Gingival pain, Gingivitis, Noninfective gingivitis, Angina bullosa hemorrhagica, [Glossitis, Mucosal hemorrhage, Mouth hemorrhage; Esophagitis, Erosive esophagitis, Esophageal ulcer, Gastrointestinal tract irritation, Pharyngitis,

Table 28: Grouping of Preferred Terms for FDA Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
		Pharyngeal erythema, Gingival swelling, Gingival erythema, Throat irritation]
Musculoskeletal pain	Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Myalgia	Back pain, Bone pain, Pain in extremity, Arthralgia, Spinal pain, Neck pain, Flank pain, Noncardiac chest pain
Myocardial ischemia or infarction	Acute myocardial infarction, Angina pectoris, Troponin increased, Troponin I increased, [Myocardial ischemia, Angina unstable, Acute coronary syndrome, Myocardial infarction]	Cardiac arrest, Coronary artery disease, [Coronary artery stenosis or occlusion]
Nausea	Nausea, Retching	
Neutropenia	Neutropenia, Neutrophil count decreased	Pancytopenia, Aplasia
Peripheral neuropathy	SMQ broad	
Pneumonia	Pneumonia, specific types of pneumonia (e.g. Pneumocystis jirovecii), Lung infiltration, Pulmonary mycosis [Bronchopneumonia]	Bronchopneumopathy, Organizing pneumonia, Lung infection, [Bronchopulmonary aspergillosis, Pulmonary cavitation]
Pulmonary toxicity	SMQ broad for interstitial lung disease (Interstitial lung disease, pneumonitis, [Acute respiratory distress syndrome]), pulmonary fibrosis, organizing pneumonia	Lung infiltration
Rash	Dermatitis, Dermatitis acneiform/bullous/contact/exfoliative generalized, Rash, Rash generalized/ erythematous/macular/maculo-papular/papular/pruritic/pustular, Butterfly rash, [Exfoliative rash, Dermatitis allergic, Drug eruption, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic	Drug hypersensitivity, Urticaria, Eczema and its variants, Palmar-plantar erythrodysesthesia, Psoriasis, Actinic keratosis, Folliculitis, Acne,

Table 28: Grouping of Preferred Terms for FDA Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
	skin eruption, Skin toxicity]	Skin exfoliation, Skin reaction, [Dermatitis infected, Herpes dermatitis, Dermatoses, Erythema nodosum, Injection site rash]
Renal insufficiency	Acute kidney injury, Blood creatinine increased, Renal failure, Renal impairment, Anuria, Azotemia, [Glomerular filtration rate decreased, Renal failure acute/chronic, Nephropathy, Hypercreatinemia]	
Renal toxicity	SMQ wide for Renal Toxicity (Acute Renal Failure)	
Respiratory tract infection	Respiratory tract infection (unspecified) + specific types (e.g. Parainfluenzae virus infection, Respiratory syncytial virus infection, Influenza, Influenza like illness, Influenza A virus test positive), Sinobronchitis	Upper/lower respiratory tract infection, Respiratory tract congestion
Sepsis	Sepsis, Septic shock, specific types of sepsis or bacteremia (e.g. Staphylococcal, Streptococcal, Clostridial, postprocedural), Bacteremia, Bacterial sepsis, Neutropenic sepsis, Urosepsis, [Sepsis syndrome]	Distributive shock
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Pancytopenia, Immune thrombocytopenic purpura
Thrombosis or thromboembolism	Deep vein thrombosis, Venous thrombosis or its variants (e.g. Venous thrombosis limb), Pulmonary embolism, Jugular vein thrombosis, Thrombosis, [Thrombosis in device]	Thrombophlebitis, Embolism
Transaminase elevation	Hepatic enzyme abnormal, Hepatic enzyme increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminase increased, Hypertransaminasemia, Hepatotoxicity, [Hepatitis acute, hepatitis, Acute hepatic failure, Drug-induced liver injury, Hepatic failure, Hepatocellular injury]	Hepatic cirrhosis, Hepatic steatosis, Liver function test abnormal, Liver disorder, Blood alkaline phosphatase increased, [Hepatic encephalopathy]

Table 28: Grouping of Preferred Terms for FDA Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
Upper respiratory tract infection	Sinusitis, Upper respiratory tract infection, Pharyngitis, Nasopharyngitis, Laryngitis viral, specific types of URTI (e.g. Pharyngitis viral, Rhinovirus infection, Viral upper respiratory tract infection), [Tonsillitis]	Chronic sinusitis, Rhinitis not otherwise specified, Rhinitis allergic, Rhinorrhea, Laryngitis, Upper respiratory tract inflammation, Upper airway cough syndrome
Urinary tract infection	Urinary tract infection, Cystitis, [Pyelonephritis]	
Visual impairment	Visual impairment, Vision blurred, Visual acuity reduced, Corneal deposits, Diplopia, Myopia [Vision decreased, Visual field defect, Blindness]	Keratitis, Dry eye, Vitreous floaters, Vitreous detachment, Amblyopia

^a Grouping for other lab-related AEs was similar, i.e. hypokalemia + blood potassium decreased

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