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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

Polatuzumab vedotin is a CD79b-directed antibody–drug conjugate and is a new molecular entity (NME). In this application, the Applicant seeks the approval of polatuzumab vedotin (b) (4)

(b) (4)

(b) (4). The BLA application was based on the pivotal Study GO29365, which is an open-label, randomized, multicenter study of Polatuzumab vedotin in combination with bendamustine and a rituximab product (BR) versus BR alone for six 21-day cycles. The primary objective of the study GO29365 was to determine whether the addition of Polatuzumab vedotin to BR improves complete response (CR) rate compared with BR alone in adult patients with DLBCL, not otherwise specified, who have received at least one prior therapy.

The key efficacy results in study GO29365 are summarized below:

- **Major outcome** in Study GO29365 is complete response (CR) rate at primary response assessment. CR rate is 40% (95% CI: 25, 57) in P+BR group and 18% (95% CI: 7, 33) in BR group. The estimated difference in CR rates between P+BR and BR groups is 22% (95% CI: 3, 41). Subgroup analyses and additional sensitivity analyses have not revealed major issues in interpretation of the major outcome analysis.
- **Duration of response** exceeds 12 months in 48% (12/25; P+BR) and 20% (2/10; BR) of patients who achieved a partial response (PR) or CR.
- **Best overall response** (BOR) rate is 62% (95% CI: 46, 77) in P+BR group and 25% (95% CI: 13, 41) in BR group.
- In **lyophilized formulation** of polatuzumab vedotin in combination with BR single-group cohort, CR rate at primary response assessment is 34% (95% CI: 19, 53) and BOR rate is 47% (95% CI: 29, 65).
- A benefit observed on a CR outcome may not necessarily translate to a **benefit in survival**. No definitive conclusions can be drawn from progression-free survival (PFS) and overall survival (OS) results in Study GO29365 due to limited number of events.

Study GO29365 has demonstrated the benefit of polatuzumab vedotin in combination with BR over BR alone for the treatment of patients with R/R DLBCL in CR rate and provided supportive evidence in duration of response.

2 INTRODUCTION

This section summarizes information on the drug development for this submission and submitted studies selected for the review.

2.1 Overview

Polatuzumab vedotin is a CD79b-directed antibody-drug conjugate consisting of three components: 1) the humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for human CD79b; 2) an anti-mitotic agent; and 3) a protease-cleavable linker.

Regulatory Interactions

Applicant was notified that IND is on partial clinical hold on September 4, 2014. Partial hold was issued per 21 CFR 312.42(b)(1)(i) and 21 CFR 312.42(b)(2)(i): Unreasonable and significant risk of illness or injury to human subjects. Specifically, excessive toxicities were noted for patients treated at the 2.4 mg/kg dose level, including deaths, serious adverse events, and discontinuations due to adverse events. No new patients may be enrolled at the 2.4 mg/kg dose level. Patients currently on treatment at 2.4 mg/kg should decrease the dose to less than or equal to 1.8 mg/kg or discontinue treatment.

In January 2015, the Agency recommended collection of additional safety data at the lower 1.8 mg/kg dose level. The Applicant discontinued the 2.4 mg/kg dose permanently and limited treatment with polatuzumab vedotin to 6-8 cycles to further mitigate the undesirable effects of polatuzumab vedotin, specifically peripheral neuropathy.

The Agency has determined that polatuzumab vedotin in combination with rituximab and bendamustine for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (b) (4) meets the criteria for Breakthrough Therapy designation on September 12, 2017.

Clinical Studies

Submitted studies in support of efficacy evaluation are listed in Figure 1. This BLA includes one pivotal Study GO29356. The supporting studies will not be discussed in this review because their target patient populations or treatment regimens are different from those intended for the proposed indication. Details on the pivotal study are provided in the statistical evaluation section of this review.

2.2 Data Sources

Reviewed data were provided electronically in standard data formats. Study GO29365 datasets are available in the following location:

Original submission:

<\\CDSESUB1\evsprod\BLA761121\0001\m5\datasets\go29365>

Efficacy datasets re-adjudicated by Applicant per FDA criteria:

<\\CDSESUB1\evsprod\BLA761121\0043\m5\datasets>

Figure 1. Clinical Studies

Study No.	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
GO29365	Open-label, multicenter, Phase Ib safety run-in; randomized Phase II (Pola+BR vs. BR), Phase II single arm expansion (Pola+BG), single arm (Arm G) cohort (140 mg Lyo DP Pola+BR)	R/R DLBCL (excluded transformed, CNS, FL Grade 3b) Ineligible for autologous SCT	Total treated in study (including control)=110* A) Pola+BR=45** B) Pola+BG=26 C) BR=39	Pola 1.8 mg/kg+BR q 21 days × 6 cycles Pola 1.8 mg/kg+BG q 21 days × 6 cycles BR q 21 days × 6 cycles
		R/R FL (Grade 1–3a) Ineligible for autologous SCT	Total treated in study (including control)=111 A) Pola+BR=44 B) Pola+BG=26 C) BR=41	Pola 1.8 mg/kg+BR q 28 days × 6 cycles Pola 1.8 mg/kg+BG q 28 days × 6 cycles BR q 28 days × 6 cycles
GO27834	Open-label, multicenter, single arm, Phase II (Pola+R or G)	R/R DLBCL Ineligible for autologous SCT	Total treated in study=84 A) Pola (2.4 mg/kg)+R=39 B) Pola (1.8 mg/kg)+G=45	Pola 2.4 mg/kg+R q 21 days for up to 1 year or until PD or unacceptable toxicity Pola 1.8 mg/kg+G q 21 days × 8 cycles
		R/R FL (Grade 1–3a)	Total treated in study=83 A) Pola (2.4 and 1.8 mg/kg)+R=40 B) Pola (1.8 mg/kg)+G=43	Pola 2.4 mg/kg+R q 21 days for up to 1 year or until PD or unacceptable toxicity Pola 1.8 mg/kg+R q 21 days for up to 1 year or until PD or unacceptable toxicity Pola 1.8 mg/kg+G q 21 days × 8 cycles
DCS4968g	Open-label, multicenter, single arm Phla/Ib dose escalation/ expansion (pola mono, pola+R)	B-NHL: indolent NHL (Grade 1–3a FL, MZL, SLL), Grade 3b FL, DLBCL, MCL, CLL with a clinical indication for treatment	Total DLBCL=40 A) Pola mono=39 B) Pola+R=1 Total Other (R/R iNHL, MCL, CLL)=55 A) Pola mono=47 B) Pola+R=8	Pola 0.1–2.4 mg/kg (monotherapy) until PD or unacceptable toxicity Pola 2.4 mg/kg+R until PD or unacceptable toxicity
GO29044	Open-label, multicenter, single arm Phlb/II (Pola+R/G-CHP)	Dose escalation: newly diagnosed or R/R B-NHL (≤1 prior line of systemic therapy)	Total Other NHL=7 A) Pola+R+CHP=3 B) Pola+G+CHP=4	Pola 1.0–1.8 mg/kg+R-CHP q 21 days × 6–8 cycles Pola 1.4–1.8 mg/kg+G-CHP q 21 days × 6–8 cycles
		Expansion: previously untreated DLBCL with IPI 2–5	Total 1L DLBCL=75 A) Pola+R+CHP=50 (n=45 at 1.8 mg/kg) B) Pola+G+CHP=25 (n=21 at 1.8 mg/kg)	Pola 1.8 mg/kg+R-CHP q 21 days × 6–8 cycles Pola 1.8 mg/kg+G-CHP q 21 days × 6–8 cycles

2L=second-line; B-NHL=B-cell non-Hodgkin's lymphoma; BG=bendamustine + obinutuzumab; BR=bendamustine + rituximab; CHP=cyclophosphamide, doxorubicin, and prednisone/prednisolone; CLL=chronic lymphocytic leukemia; CNS=central nervous system; DLBCL=diffuse large B-cell lymphoma; DP=drug product; FL=follicular lymphoma; G=obinutuzumab; HSCT=hematopoietic stem cell transplantation; iNHL=indolent non-Hodgkin's lymphoma; IPI=International Prognostic Index; Lyo=lyophilized; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; PD=progressive disease; Pola=polatuzumab vedotin; R=rituximab; R/R=relapsed or refractory; SCT=stem cell transplant; SLL=small lymphocytic lymphoma.

[Source: Applicant, Summary of Clinical Efficacy]

3 STATISTICAL EVALUATION

This section presents statistical review of the pivotal Study GO29365.

3.1 Data and Analysis Quality

Data from the Study GO29365 were provided electronically with standard formats. The data and analysis quality of the submission was acceptable to perform the review. See Section 3.2.1 on outcome assessment issues.

3.2 Evaluation of Efficacy

This section presents efficacy review of the pivotal Study GO29365. All tables and figures are per Reviewer's analysis, unless otherwise noted.

3.2.1 Study Design and Outcomes

Study GO29365 Design

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

Patient Population

This review focuses on efficacy in patients randomized to polatuzumab vedotin in combination with rituximab and bendamustine (P+BR; N=40) or rituximab and bendamustine (BR; N=40) in relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

Study Period

First patient entered the Study GO20365 on October 15, 2014. Aside from Arm G, the last patient entered study on September 13, 2016, and data cutoff was April 30, 2018, one year after all patients completed their primary response assessment (April 11, 2017).

A new formulation single-group cohort (Arm G, n=20-30) was added in November 2017 for R/R DLBCL to evaluate the lyophilized formulation of polatuzumab vedotin in combination with BR with the main objective of providing pharmacokinetic (PK)/safety data. In May 2018, Arm G was subsequently expanded by adding an additional 10 patients (total planned enrolled of approximately 40 patients) to provide additional data on secondary efficacy outcomes. Aside from patients enrolled in Arm G, all patients treated with polatuzumab vedotin in Study GO29365 were treated with the liquid formulation. This submission includes efficacy data from the first 32 patients to enroll in Arm G of Study GO29365, with a clinical cutoff date of 15 November 2018, based on their projected primary response assessment (PRA).

Primary Objective

To evaluate the efficacy of the combination of polatuzumab vedotin plus BR compared with BR alone in patients with R/R DLBCL as measured by positron emission tomography (PET)-defined complete response (CR) rate using Modified Lugano 2014 Response Criteria (positron emission tomography–computed tomography [PET-CT] criteria) at the time of primary response assessment (6-8 weeks after Cycle 6 Day 1 or last dose of study medication) per Independent Review Committee (IRC).

Major Outcome

Percentage of patients with complete response (CR) at primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) by PET/CT scan per IRC is the major efficacy outcome.

Additional Outcomes

Key additional efficacy outcomes for Study GO29365:

- **Overall response rate (ORR)**, defined as percentage of patients with CR or PR at primary response assessment by PET/CT per IRC
- **Best overall response (BOR)**, defined as percentage of patients with CR or PR while on study by PET/CT per IRC
- **Duration of response (DOR)**, defined as time from the first response of PR or CR to death, progression, or last adequate assessment per IRC. Duration of response was censored at the date of the last adequate assessment prior to initiation of a new anti-cancer therapy.
- **Progression-Free Survival (PFS)**, defined as time from randomization to death, progression, or last adequate assessment per IRC. PFS was censored at the date of the last adequate assessment prior to initiation of a new anti-cancer therapy.
- **Overall Survival (OS)**, defined as time from randomization to death or last adequate assessment per IRC.

Response Assessment

Radiographic Assessment

Tumor response was assessed by the IRC and the investigator on the basis of physical examinations, CT scans, PET scans, and bone marrow examinations using the modified Lugano 2014 response criteria.

PET-CT scans were required at three timepoints, i.e., at screening, at an interim response assessment after Cycle 3 of study treatment (i.e., between Cycle 3 Day 15 and Cycle 4 Day 1), and at the primary response assessment visit. CT scans without PET scans were scheduled to be obtained every 6 months until approximately 2 years after the primary response assessment visit.

The modified Lugano 2014 response criteria were used to assess overall response to study treatment.

A full tumor assessment including radiographic assessment had to also be performed any time disease progression or relapse was suspected. The same radiographic method of assessment and the same technique was to be used for all response evaluations to ensure consistency across different timepoints. As part of tumor assessment, physical examinations were to include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly (clinical response assessment).

Central review of radiological scans (FDG-PET and CT) was conducted by an Independent Review Facility that provided:

- An independent assessment of radiographic response using modified Lugano PET staging and separately, CT-staging criteria
- An overall tumor response and progression assessment (integrating both the radiographic responses and clinical data findings to provide separate PET- and CT staging assessments) for each enrolled subject.

The IRC, composed of board-certified radiologists and an oncologist with experience in malignant lymphoma, assessed all patients for response on the basis of imaging results and bone marrow biopsy results for all patients during the Phase II portion of the study. Response assessments performed by the IRC were blinded.

FDA-adjudication of the IRC-assessment

Clinical and statistical review teams have identified issues in IRC response assessment (see Table 1 and clinical review). The differences between the FDA's and Applicant's response assessments are primarily due to differences in PET-CT vs CT scans integration. Additional issues included the following: high percentage of non-evaluable responses in BR (26/40, 65%) and P+BR (9/40, 22%) groups, discrepancies in response category (e.g. SD or PD), discrepancies in first response dates, discrepancies in censoring or event dates, discrepancies in event vs censoring status.

Table 1. 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 a 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 clinical (nonradiographic) progression events as PD. The Applicant instead classified patients with non-radiographic disease progression as NE for efficacy per IRC, missing multiple progression events.
NALT (including	FDA censors DOR and PFS at	For consolidative radiation, patients need not be

Setting	Difference in approach	Comment
HSCT) in absence of PD	date of last radiographic disease assessment prior to NALT, rather than not censoring.	censored if, at study baseline, they also had radiographically evaluable disease outside of the radiation field.
Response	FDA views SD (no molecular response) by PET, with PD by CT, as PD, rather than SD.	CT response with no PET performed was called NE per Applicant's algorithm. 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 International Working Group criteria. PET-CT remained required for first CR resignation. 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.
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 investigator for overall response (including BOR), DOR, and PFS. In contrast to response per investigator, for response per IRC, only the PET result was considered for follow-up assessments; the CT result was discounted, even if PET was not performed and the CT showed PD. Thus, for time-to-event analyses per IRC, cases where CT showed PD, but no PET was performed, were not considered PD in the Applicant's analysis. Rather such patients were inappropriately reported as failure-free for DOR or PFS per IRC.
DOR, PFS	After PET CR, if follow-up PET has SD, FDA views as PD and thus a 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.

NALT = new anti-lymphoma therapy; NE = Non-evaluable

[Source: FDA Efficacy Assessment]

The FDA and the Applicant have come to a consensus on most of the response assessment issues by following criteria outlined in Table 1. The Applicant has re-submitted key efficacy datasets and re-analyzed the data (see Section 2.2: Data Sources). The only remaining difference between FDA-adjudicated response assessment and the Applicant's re-adjudicated response assessment is PD date for patient (b) (6): FDA PD date is (b) (6) (scan date), Applicant's PD date is (b) (6) (recorded date).

Unless otherwise noted, all efficacy results presented herein are per FDA-adjudicated IRC response assessment. Response assessment per investigator has not been adjudicated by the FDA and is not presented. Applicant-reported efficacy results for the major outcome based on originally submitted data per investigator are shown in the Appendix.

Clinical Outcome Assessment

Peripheral neuropathy symptom severity and symptom interference, as measured by the Therapy-Induced Neuropathy Assessment Scale v1.0 (TINAS) were assessed. The TINAS is an 11-item questionnaire that assesses the severity of neuropathy-related symptoms in the last 24 hours. Each item is scored on a 0-10 scale, with 0 being the symptom is not present, and 10 being the symptom is as bad as the patient can imagine. Completion of the TINAS was scheduled weekly and at the same time of day over the course of study treatment. On study visit days, the TINAS questionnaire was to be completed prior to the completion of other study assessments and the administration of study treatment. Following the study treatment period, the TINAS was to be completed once per week for the first 2 months, then once per month for the next 10 months. Responses were entered electronically by the patient either while on-site or at home, using the patient's own electronic device or a device provided to them for this study to allow for secure access and transmission of data to a centralized database maintained by the electronic patient-reported outcome vendor.

3.2.2 Statistical Methodologies

Analysis Population

Intent-to-Treat Population (ITT) included all patients randomized to treatment. All patients in the ITT population were analyzed according to the treatment arm to which they were randomized. Safety population for the purposes of this review included 45 P+BR-treated patients (40 from the randomized group and 6 from the single-arm safety group) and 39 BR-treated patients with R/R DLBCL from Study GO29365.

Sample Size Determination

Eighty patients were planned to be enrolled and randomized 1:1 to BR and P+BR groups. The sample size was not calculated based on a pre-specified hypothesis. With 40 patients per group, 95% exact Clopper-Pearson confidence intervals (CI) for estimation of the true CR rate were calculated, given various assumptions on response rates (see Table 2).

Table 2. Confidence Intervals for Potential Response Rates

Polatuzumab vedotin + BR CR rate	No. of Patients with CR (95% CI for rate)
80%	32 (64%, 91%)
75%	30 (59%, 87%)
70%	28 (53%, 83%)
65%	26 (48%, 79%)
60%	24 (43%, 75%)

BR = bendamustine + rituximab; CR = complete response.

[Source: Applicant, CSR, Table 11]

For the single-group cohort treated with lyophilized polatuzumab vedotin and assuming the CR is 40%, a total of 40 patients were estimated to be needed to achieve statistical power of 92% at a one-sided alpha level of 2.5%. Null and alternative hypotheses for the exact binomial one-sample test: H_0 : PET CR rate $\leq 15\%$, H_1 : PET CR rate $>15\%$.

Reviewer's Comment: *The protocol specifies PET CR. PET-CT criteria per FDA-adjudicated-IRC response assessment were used for both single and randomized cohorts.*

Analysis of Major Outcome

The response rates were estimated with the percentage of patients with response per study group, along with the corresponding Clopper-Pearson exact 95% confidence intervals. The 95% confidence interval for the CR rate difference between P+BR and BR groups was estimated based on a normal approximation. A specific method for estimating rate difference was not specified in the protocol – Miettinen-Nurminen method is used in this review (Miettinen and Nurminen, 1985). No statistical hypothesis was pre-specified for testing CR rate difference between study groups. Bayesian analyses with uniform priors were conducted by the Reviewer to further characterize the treatment effect.

Analysis of Additional Outcomes

Response Rates

Analysis of ORR and BOR rates per study group was the same as the major outcome analysis.

Time-to-Event Outcomes

Median duration of response, progression-free survival, and overall survival were estimated with Kaplan-Meier method. Hazard ratio was estimated with cox proportional hazards model that included randomization stratification factor: duration of response to prior anti-lymphoma

therapy. Figures and tables show 95% confidence intervals based on complementary log-log transformation.

Clinical Outcome Assessment

The PRO analyses included patients in the intent-to-treat population and were analyzed according to assigned treatment. The mean TINAS score at each visit was calculated and plotted. In the event of patients not completing individual TINAS items, missing data were handled per developer scoring instructions, such that a prorated total score was calculated if $\geq 50\%$ of items were answered using the following equation: Prorated total score = [Sum of item scores] x [Total no. of items] / [No. of items answered]

Multiplicity

No adjustment for multiplicity was pre-specified for additional outcomes.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 3 and Table 4 show disposition of patients and demographics, respectively. Most frequent reason for study discontinuation was death in both BR (70%) and P+BR (57%) groups. Most frequent reasons for polatuzumab vedotin discontinuation were an adverse event (30%) and progressive disease (15%). Generally, patients did not differ substantially on demographic and baseline factors between BR and P+BR groups.

Table 3. Study GO29365 Disposition of Patients with R/R DLBCL

	BR	P+BR	Overall	LYO P+BR
n	40	40	80	32
Discontinued Study (%)				
No	4 (10)	11 (28)	15 (19)	16 (50)
Yes	36 (90)	29 (72)	65 (81)	16 (50)
Death	28 (70)	23 (57)	51 (64)	15 (47)
Other	0 (0)	1 (2)	1 (1)	1 (3)
Physician Decision	1 (2)	0 (0)	1 (1)	0
Progressive Disease	2 (5)	0 (0)	2 (2)	0
Withdrawal by Patient	5 (12)	5 (12)	10 (12)	0
Received at least one dose (%)				
No	1 (2)	1 (2)	2 (2)	0
Yes	39 (98)	39 (98)	78 (98)	32 (100)
Completed all treatments (%)				
No	31 (78)	22 (55)	53 (66)	20 (62)

	BR	P+BR	Overall	LYO P+BR
Yes	9 (22)	18 (45)	27 (34)	12 (38)
Discontinued polatuzumab vedotin (%)				
No	40 (100)	19 (48)	59 (74)	12 (38)
Yes	0 (0)	21 (52)	21 (26)	20 (62)
Adverse Event	0 (0)	12 (30)	12 (15)	7 (22)
Lack of Efficacy	0 (0)	1 (2)	1 (1)	0
Other	0 (0)	1 (2)	1 (1)	1 (3)
Progressive Disease	0 (0)	6 (15)	6 (8)	9 (28)
Withdrawal by Patient	0 (0)	1 (2)	1 (1)	1 (3)
Death	0	0	0	2 (6)
Discontinued bendamustine (%)				
No	10 (25)	19 (48)	29 (36)	12 (38)
Yes	30 (75)	21 (52)	51 (64)	20 (62)
Adverse Event	4 (10)	13 (32)	17 (21)	7 (22)
Death	1 (2)	0 (0)	1 (1)	2 (6)
Lack of Efficacy	1 (2)	1 (2)	2 (2)	0
Other	1 (2)	0 (0)	1 (1)	1 (3)
Physician Decision	1 (2)	0 (0)	1 (1)	0
Progressive Disease	21 (52)	6 (15)	27 (34)	9 (28)
Withdrawal by Patient	1 (2)	1 (2)	2 (2)	1 (3)
Discontinued rituximab (%)				
No	9 (22)	19 (48)	28 (35)	12 (38)
Yes	31 (78)	21 (52)	52 (65)	20 (62)
Adverse Event	4 (13)	12 (57)	16 (31)	7 (35)
Death	1 (3)	0 (0)	1 (2)	2 (10)
Lack of Efficacy	1 (3)	1 (5)	2 (4)	0
Other	2 (6)	1 (5)	3 (6)	1 (5)
Physician Decision	1 (3)	0 (0)	1 (2)	0
Progressive Disease	21 (68)	6 (29)	27 (52)	9 (45)
Withdrawal by Patient	1 (3)	1 (5)	2 (4)	1 (5)

Table 4. Study GO29365 Demographic and Baseline Disease Characteristics of Patients with R/R DLBCL

	BR	P+BR	Overall	LYO P+BR
n	40	40	80	32
Age				
Median (range)	71 (30, 84)	67 (33, 86)	68 (30, 86)	65 (27, 83)
< 65	14 (35)	17 (42)	31 (39)	15 (47)
≥ 65	26 (65)	23 (57)	49 (61)	17 (53)
Race (%)				
American Indian or Alaska Native	1 (2)	0 (0)	1 (1)	0
Asian	4 (10)	6 (15)	10 (12)	1 (3)
Black or African American	0 (0)	3 (8)	3 (4)	0
Unknown	4 (10)	5 (12)	9 (11)	5 (16)
White	31 (78)	26 (65)	57 (71)	26 (81)
Sex (%)				
Female	15 (38)	12 (30)	27 (34)	15 (47)
Male	25 (62)	28 (70)	53 (66)	17 (53)
Region (%)				
Asia/Pacific	6 (15)	7 (18)	13 (16)	7 (22)
Eastern Europe	11 (28)	9 (22)	20 (25)	5 (16)
North America	11 (28)	17 (42)	28 (35)	8 (25)
Western Europe	12 (30)	7 (18)	19 (24)	12 (38)
Type (%)¹				
Burkitt Lymphoma	0 (0)	1 (2)	1 (1)	0
DLBCL, Nos	4 (10)	4 (10)	8 (10)	1 (3)
DLBCL, Activated B-Cell	19 (48)	19 (48)	38 (48)	17 (53)
DLBCL Germinal Center B-Cell	17 (42)	15 (38)	32 (40)	12 (38)
Follicular Lymphoma	0 (0)	1 (2)	1 (1)	0
Other	0	0	0	2 (6) ²
Ann Arbor Stage (%)				
Stage I	0 (0)	2 (5)	2 (2)	3 (9)
Stage II	4 (10)	4 (10)	8 (10)	5 (16)
Stage III	8 (20)	10 (25)	18 (22)	5 (16)

	BR	P+BR	Overall	LYO P+BR
Stage IV	28 (70)	24 (60)	52 (65)	19 (59)
Bulky Disease (%)	15 (38)	10 (25)	25 (31)	9 (28)
ECOG (%)				
Missing	1 (2)	1 (2)	2 (2)	0
≥ 2	8 (20)	6 (15)	14 (18)	2 (6)
0	17 (42)	12 (30)	29 (36)	7 (22)
1	14 (35)	21 (52)	35 (44)	23 (72)
International Prognostic Index (%)				
0-1 (low risk)	3 (8)	9 (22)	12 (15)	NA
2	8 (20)	9 (22)	17 (21)	NA
3	12 (30)	13 (32)	25 (31)	NA
4	12 (30)	8 (20)	20 (25)	NA
5	5 (12)	1 (2)	6 (8)	NA
Lines of prior anti-lymphoma therapy (%)				
1	12 (30)	11 (28)	23 (29)	5 (16)
2	9 (22)	11 (28)	20 (25)	12 (38)
3	10 (25)	12 (30)	22 (28)	9 (28)
4	8 (20)	2 (5)	10 (12)	3 (9)
5	1 (2)	3 (8)	4 (5)	1 (3)
7	0 (0)	1 (2)	1 (1)	1 (3)
Primary Stem Cell Transplant Ineligibility Reason (%)				
Age	19 (48)	13 (32)	32 (40)	11 (34)
Co-Morbidities	1 (2)	1 (2)	2 (2)	0
Failed Prior Transplant	6 (15)	10 (25)	16 (20)	5 (16)
Insufficient Response to Salvage Therapy	9 (22)	12 (30)	21 (26)	15 (47)
Other	1 (2)	2 (5)	3 (4)	1 (3)
Patient Refused Transplant	2 (5)	2 (5)	4 (5)	0
Performance Status	2 (5)	0 (0)	2 (2)	0
Response to the last prior anti-lymphoma therapy (%)				
No CR and No PR	34 (85)	30 (75)	64 (80)	29 (91)

	BR	P+BR	Overall	LYO P+BR
DOR to prior anti-lymphoma therapy (%)³				
≤ 12 Months	33 (82)	32 (80)	65 (81)	NA
> 12 Months	7 (18)	8 (20)	15 (19)	NA

BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group performance status; ITT = intent-to-treat; NOS = not otherwise specified; R/R = relapsed/refractory; DOR = duration of response.

¹ World Health Organization 2016 DLBCL status confirmed by central lab review of pathology reports and tissue samples.

² Ebv+ Dlbcl, Nos; High-Grade b-Cell Lymphoma, with Myc and Bcl2 and/or Bcl6 Rearrangements

³ Stratification factor. Duration of response to prior therapy was based on interactive voice or Web-based response system (IxRS).

3.2.4 Efficacy Results

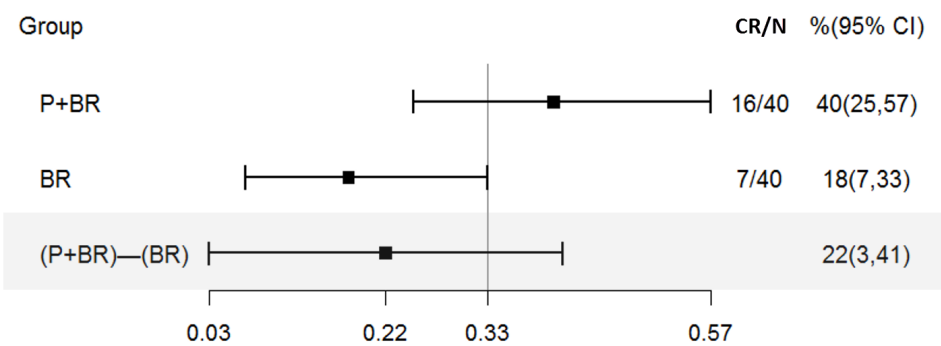
This section describes key efficacy results.

3.2.4.1 Major Efficacy Outcome: Complete Response at Primary Response Assessment

Complete response rate at Primary Response Assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication), measured by PET/CT per IRC are shown in Figure 2. The complete response (CR) rate is 40% (95% CI: 25, 57) in P+BR group and 18% (95% CI: 7, 33) in BR group. The estimated difference in complete response rates between P+BR and BR groups is 22% (95% CI: 3, 41).

Bayesian analyses have been conducted to characterize the magnitude and uncertainty of the treatment effect. The estimated magnitude of the treatment effect, as measured by the difference in complete response rates between patients treated with P+BR and BR, is 21% (95% Credible Interval: 2, 40). This means that complete response rates in P+BR group are likely higher than in BR group by 21%, on average. The probability that the treatment effect (measured as difference in effect) exceeds 0 is 99%. The probability that the treatment effect exceeds 10% is 88%. The probability that the treatment effect exceeds 20% is 56%.

Figure 2. Study GO29365 Complete Response Rate in Patients with R/R DLBCL



(P+BR) – (BR) = difference in complete response rates

3.2.4.2 Additional Efficacy Outcomes

Response Rates

Response rates are generally higher in P+BR group compared to BR group, supporting major outcome efficacy (see Table 5), especially in the best overall response rate of CR or PR: 62% (95% CI: 46, 77) in P+BR group and 25% (95% CI: 13, 41) in BR group. Response rate in a single-group cohort of lyophilized formulation of P+BR is 34% (95% CI: 19, 53) – the null hypothesis is rejected.

Table 5. Study GO29365 Response Rates in Patients with R/R DLBCL

	Primary Efficacy Population (ITT)		Arm G
Outcome per IRC	P + BR (N = 40)	BR (N = 40)	LYO P + BR (N = 32)
Response at Primary Response Assessment			
Objective response	18/40, 45 (29, 62)	7/40, 18 (7, 33)	11/32, 34 (19, 53)
CR: n/N, % (95% CI)	16/40, 40 (25, 57)	7/40, 18 (7, 33)	11/32, 34 (19, 53)
CR Rate Difference: % (95% CI)	22 (3, 41)		NA
PR: n (%)	2 (5)	0 (0)	0 (0)
PD: n (%)	13 (32)	24 (60)	15 (47)
SD: n (%)	2 (5)	1 (2)	1 (3)
NE: n (%)	7 (18)	8 (20)	5 (16)
Best Overall Response			
Objective response	25/40, 62 (46, 77)	10/40, 25 (13, 41)	15/32, 47 (29, 65)
CR: n/N, % (95% CI)	20/40, 50 (34, 66)	9/40, 22 (11, 38)	14/32, 44 (26, 62)
PR: n (%)	5 (12)	1 (2)	1 (3)
PD: n (%)	8 (20)	19 (48)	11 (34)
SD: n (%)	3 (8)	8 (20)	3 (9)
NE: n (%)	4 (10)	3 (8)	3 (9)

CR = Complete Response; PR = Partial Response; SD = Stable Disease;

NE = Non-Evaluable; PD = Progressive Disease; CI = Confidence Interval

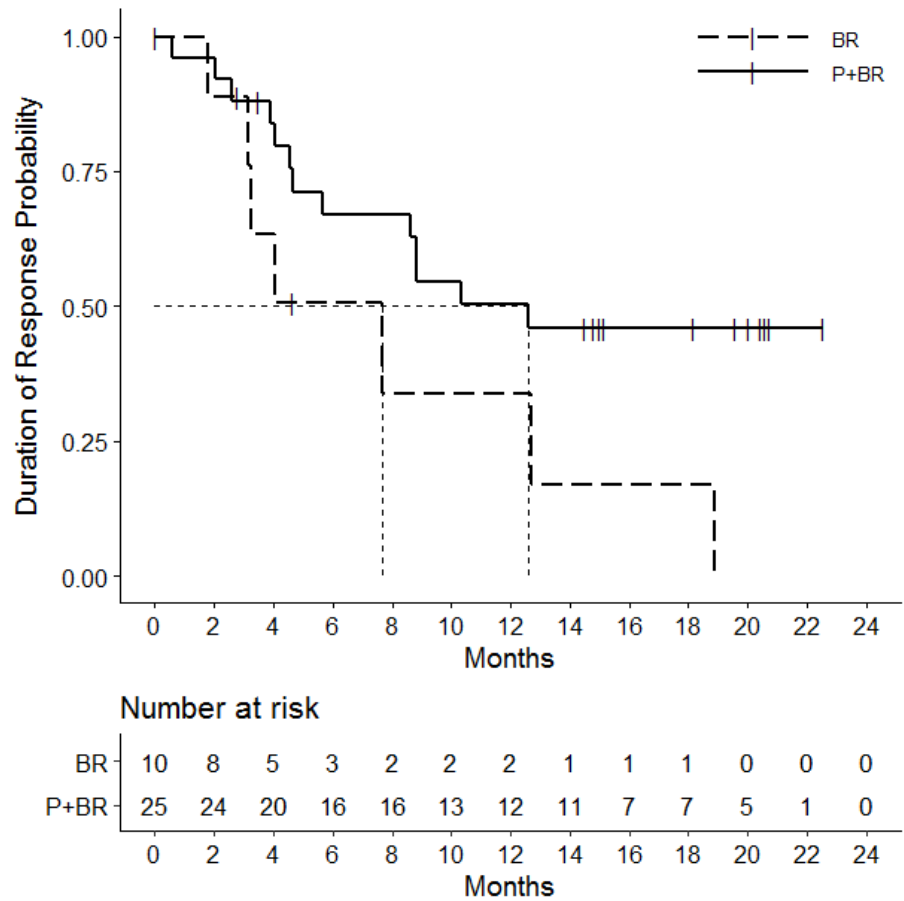
ITT = Intent-to-Treat; LYO P = lyophilized formulation of polatuzumab vedotin

Reviewer's Comment: Rounding half to even per International Organization for Standardization rule (e.g 2.5 => 2, 3.5 => 3).

Duration of Response

Responses in P+BR group are durable. Figure 3 shows Kaplan-Meier curves, Table 6 and Table 7 show duration of response per patient. Percentage of patients with duration of response exceeding 12 months is 45% (12/25) in P+BR group and 20% (2/10) in BR group. Estimated median duration of response is 12.6 months (4.6, NE) in P+BR group and 7.7 months (1.8, NE) in BR group, but these estimates may be unreliable due to small number of events. Duration of response results are supportive of the major efficacy outcome.

Figure 3. Study GO29365 Duration of Response in Patients with R/R DLBCL



Reviewer’s Comment: Duration of response is not directly comparable between P+BR (n=25) and BR (n=10) groups because results are based on a subset of patients with CR or PR.

Table 6. Study GO29365 Duration of Response in P+BR Group

Index	DOR (months)	Event	Reason
1	0.6	Event	Death
2	2	Event	Disease progression
3	2.6	Event	Disease progression
4	3.5	Censored	Last tumor assessment before NALT
5	3.9	Event	Disease progression
6	4	Event	Disease progression
7	4.5	Event	Disease progression
8	4.6	Event	Disease progression
9	5.7	Event	Disease progression
10	8.6	Event	Death
11	8.8	Event	Disease progression
12	8.8	Event	Disease progression
13	10.3	Event	Death
14	12.6	Event	Disease progression
15	14.5	Censored	Last tumor assessment
16	14.8	Censored	Last tumor assessment before NALT
17	15	Censored	Last tumor assessment
18	15.2	Censored	Last tumor assessment before NALT
19	18.2	Censored	Last tumor assessment
20	19.6	Censored	Last tumor assessment
21	20	Censored	Last tumor assessment
22	20.5	Censored	Last tumor assessment
23	20.6	Censored	Last tumor assessment
24	20.8	Censored	Last tumor assessment
25	22.5	Censored	Last tumor assessment

DOR = duration of response; NALT = new anti-lymphoma therapy

Table 7. Study GO29365 Duration of Response in BR Group

Index	DOR (months)	Event	Reason
1	0	Censored	Last tumor assessment before NALT
2	1.8	Event	Disease progression
3	2.8	Censored	Last tumor assessment before NALT
4	3.1	Event	Disease progression
5	3.3	Event	Disease progression
6	4.1	Event	Death
7	4.7	Censored	Last tumor assessment
8	7.7	Event	Disease progression
9	12.7	Event	Death
10	18.9	Event	Disease progression

DOR = duration of response; NALT = new anti-lymphoma therapy

Progression-Free Survival

Progression-free survival estimation based on the data in Study GO29365 is unreliable due to high uncertainty with 24 and 32 events in P+BR and BR groups, respectively. Table 8 and Figure 4 summarize progression-free survival results. Estimated median PFS is 7.6 months (95% CI: 4.7, 14.6) in P+BR group and 2.4 months (95% CI: 1.5, 4.1) in BR group. No definitive conclusions can be drawn based on these data.

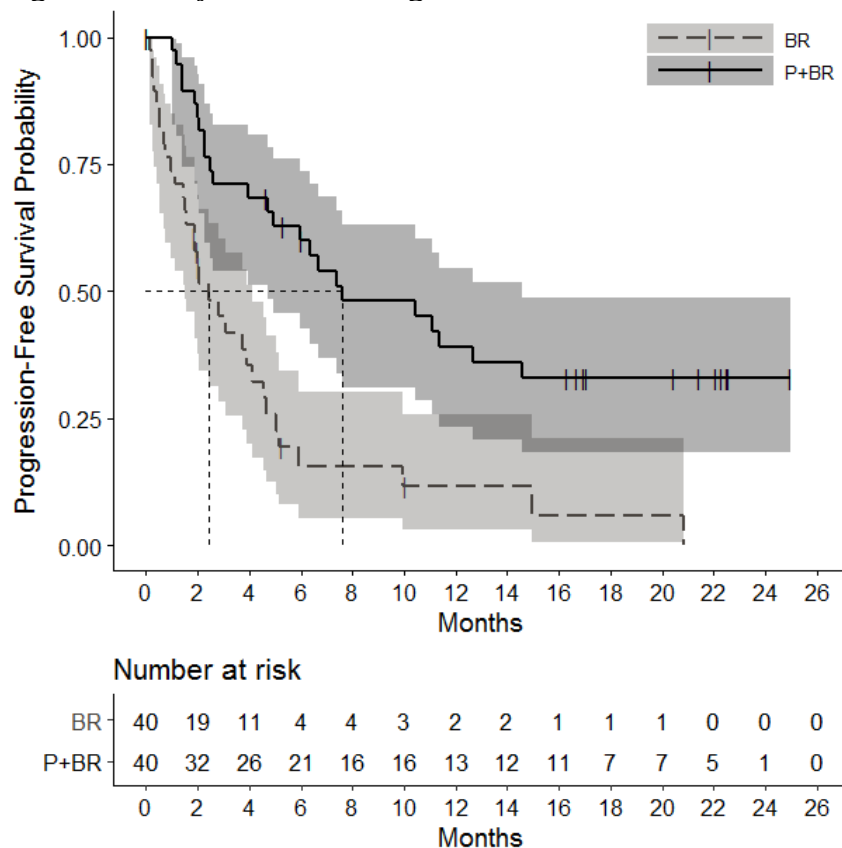
Table 8. Study GO29365 Progression-Free Survival Summary in Patients with R/R DLBCL

	BR	P+BR
	N = 40	N = 40
Number of events	32	24
Median in months (95% CI) ¹	2.4 (1.5, 4.1)	7.6 (4.7, 14.6)
Hazard Ratio (95% CI) ²	0.29 (0.16, 0.52)	

¹ Kaplan-Meier method

² Cox proportional hazards model

Figure 4. Study GO29365 Progression-Free Survival in Patients with R/R DLBCL



Overall Survival

Overall survival estimation based on the data in Study GO29365 is unreliable due to high uncertainty with 23 and 28 events in P+BR and BR groups, respectively. Table 9 and Figure 5 summarize overall survival results. Estimated median OS is 12.4 months (95% CI: 8.9, NE) in P+BR group and 4.7 months (95% CI: 3.7, 8.3) in BR group. No definitive conclusions can be drawn based on these data.

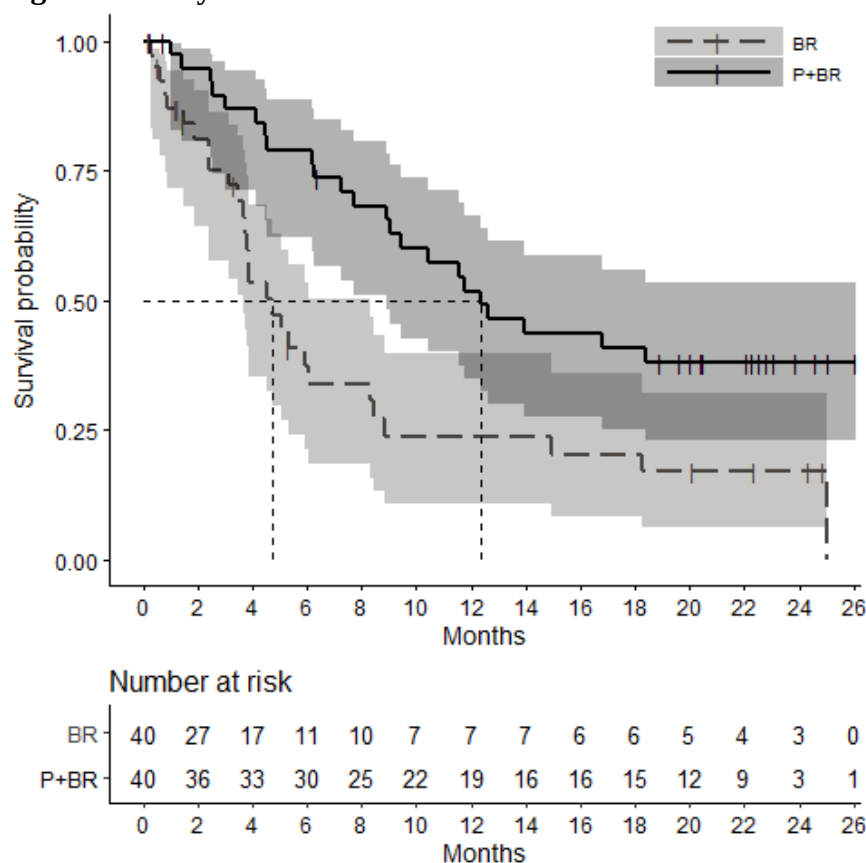
Table 9. Study GO29365 Overall Survival Summary in Patients with R/R DLBCL

	BR (N=40)	P+BR (N=40)
Deaths	28	23
Median (95% CI) ¹	4.7 (3.7, 8.3)	12.4 (8.9, NE)
Hazard Ratio (95% CI) ²	0.42 (0.24, 0.75)	

¹ Kaplan-Meier method

² Cox proportional hazards model

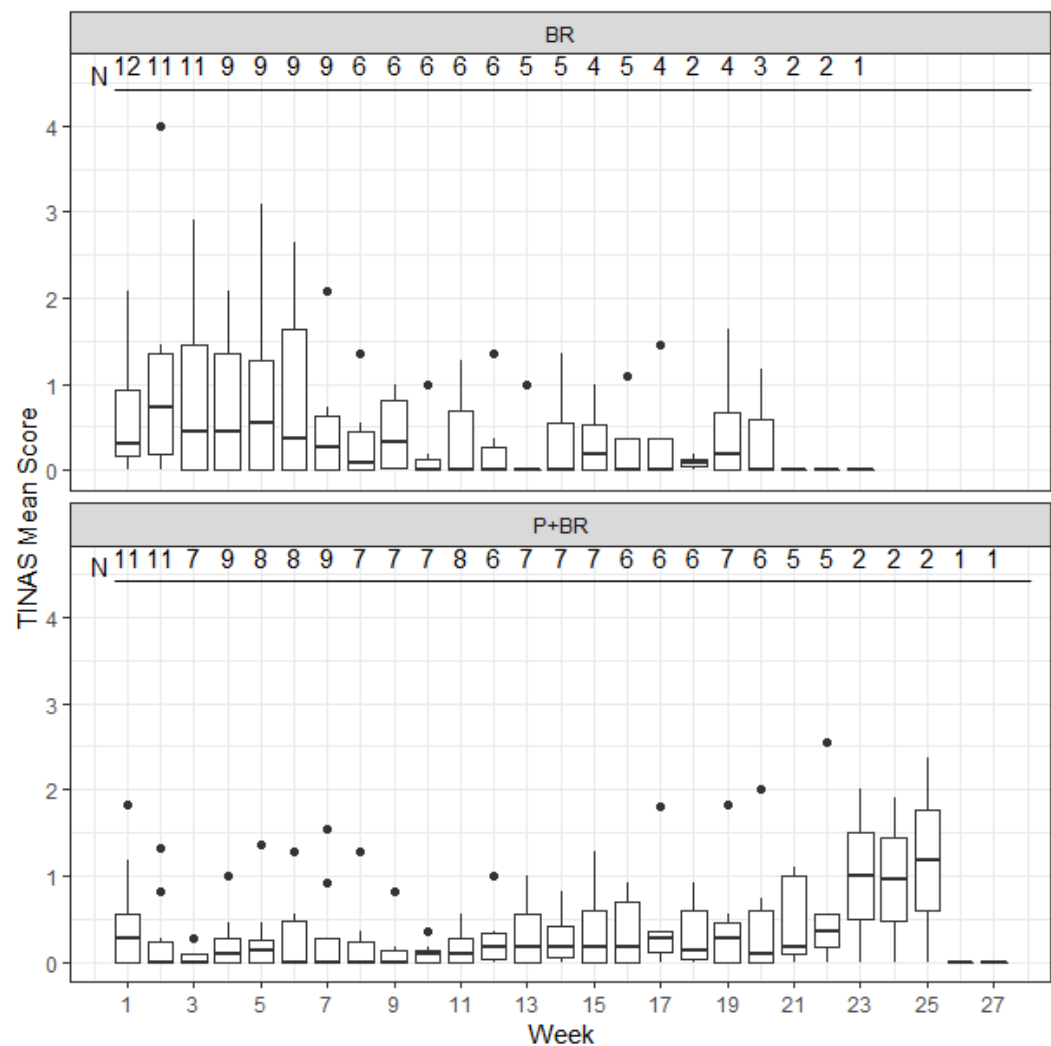
Figure 5. Study GO29365 Overall Survival in Patients with R/R DLBCL



Clinical Outcome Assessment

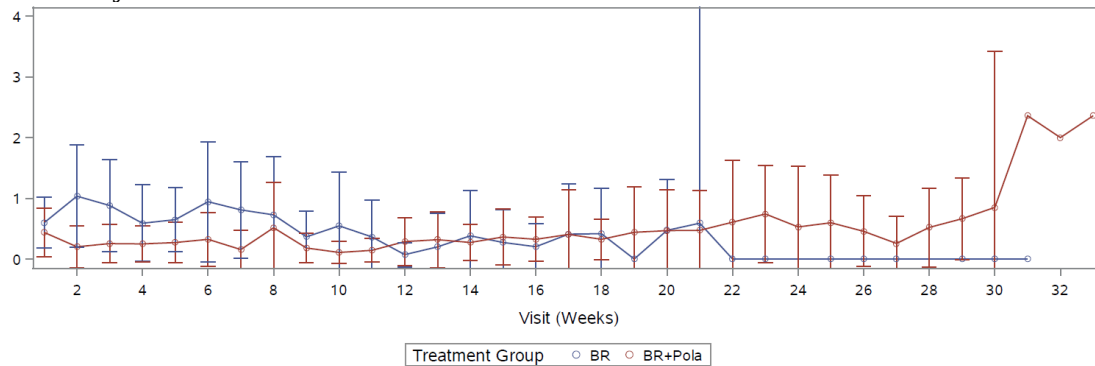
Summary of patient-reported peripheral neuropathy symptom severity and symptom interference measured by TINAS is shown by week in Figure 6 and Figure 7. Patient profiles by study day are plotted in Figure 8. No definitive conclusions can be drawn from these data due to high proportion of missing data: TINAS data on only 30% (12/40) or fewer patients per group are available.

Figure 6. Study GO29365 TINAS Mean Score by Week from Baseline to the End of Treatment in Patients with R/R DLBCL



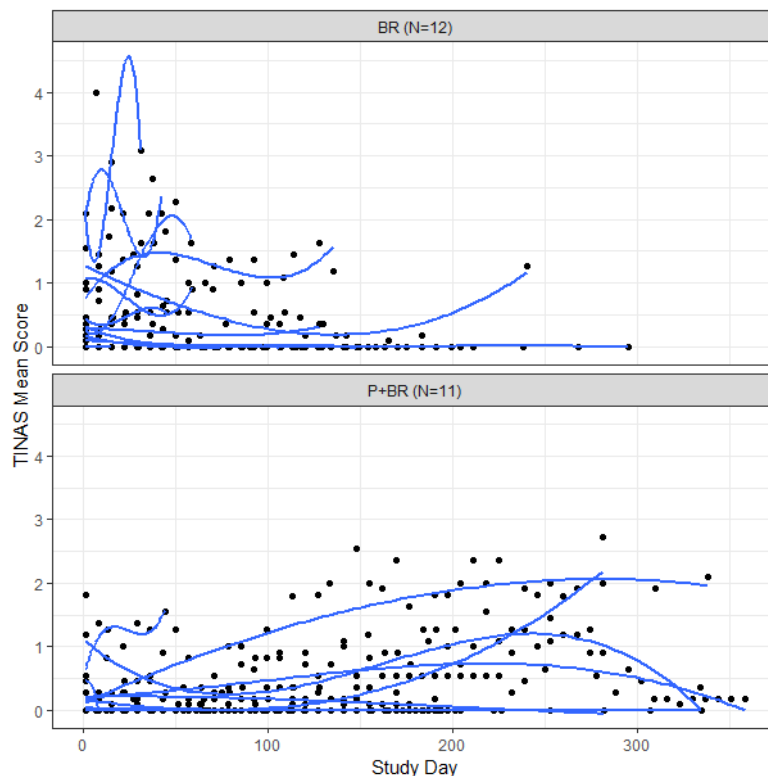
Week 1 is the baseline. N shows number of patients per week.

Figure 7. Study GO29365 TINAS Mean Score from Baseline to Last Exposure to Any Drug + 90 Days in Patients with R/R DLBCL



BR = rituximab and bendamustine; BR+Pola = polatuzumab vedotin in combination with rituximab and bendamustine; Patients who have both a baseline record and a record between 25 to 35 days after last exposure. The weekly assessment period is defined as baseline through last exposure to any drug + 90 days. Week 1 is baseline, defined as last record on or before the date of first exposure to any drug. Only TINAS records with at least 6 questions completed are considered in the plot. If more than one TINAS record is completed in a given week, only the latest is considered in this plot. 95% confidence intervals using normal approximation are shown. [Source: Applicant]

Figure 8. Study GO29365 TINAS Mean Profiles in first 365 Study Days in Patients with R/R DLBCL



3.3 Evaluation of Safety

Safety was evaluated in 45 P+BR-treated patients (40 from the randomized group and 6 from the single-arm safety group) and 39 BR-treated patients with R/R DLBCL from Study GO29365. Thirty-one percent (14/45) of patients discontinued P+BR treatment due to adverse events. Table 10 shows most frequent adverse events of Grade 3 or higher. Please refer to the clinical safety review for more detailed safety results and clinical interpretation.

Table 10. Study GO29365 Adverse Reactions of Grade 3 or Higher Occurring in > 20% of Patients with R/R DLBCL or $\geq$ 10% More in the P+BR Group

	P+BR N=45 %	BR N=39 %
Neutropenia	42	36
Thrombocytopenia	40	26
Anemia	24	18
Pneumonia	16 ^a	3 ^b

The table includes a combination of grouped and ungrouped terms.
Events were graded using NCI CTCAE version 4.

^a Includes 2 events with fatal outcome.

^b Includes 1 event with fatal outcome.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes subgroup efficacy results.

4.1 Gender, Race, Age, and Geographic Region

Table 11 shows subgroup analysis of the major outcome by key demographic subgroups. The subgroups analyses generally support the efficacy of P+BR. No outlier subgroups are observed. Study GO20365 does not contain sufficient information on patients in each treatment group to determine if subgroup response rates differ.

Table 11. Study GO29365 Subgroup Analysis of the Major Outcome in Patients with R/R DLBCL

	BR	P+BR
Age		
< 65	2/14, 14 (2, 43)	6/17, 35 (14, 62)
>= 65	5/26, 19 (7, 39)	10/23, 43 (23, 66)
Sex		
Female	3/15, 20 (4, 48)	5/12, 42 (15, 72)
Male	4/25, 16 (5, 36)	11/28, 39 (22, 59)
Race		
American Indian or Alaska Native	0/1, 0 (0, 98)	NA
Asian	1/4, 25 (1, 81)	3/6, 50 (12, 88)
Black or African American	NA	0/3, 0 (0, 71)
Unknown	0/4, 0 (0, 60)	2/5, 40 (5, 85)
White	6/31, 19 (7, 37)	11/26, 42 (23, 63)
Region		
Non-USA	5/32, 16 (5, 33)	12/24, 50 (29, 71)
USA	2/8, 25 (3, 65)	4/16, 25 (7, 52)

4.2 Other Special/Subgroup Populations

Table 12 shows subgroup analysis of the major outcome by key disease characteristic subgroups. Covariate-adjusted results are generally supportive of P+BR efficacy. High uncertainty seen in confidence intervals is due to small sample size. No outlier subgroups are observed. Study GO20365 does not contain sufficient information on patients in each treatment group to determine if subgroup response rates differ.

Table 12. Study GO29365 Covariate-Adjusted Major Outcome Efficacy Results in Patients with R/R DLBCL

Covariate	OR (95% CI)
Prior Therapy DOR (<12, ≥12)	3.34 (1.13, 10.81)
Age (<70, ≥70)	2.94 (0.95, 9.91)
Age (<65, ≥65)	3.15 (1.03, 10.61)
Bulky Disease	2.98 (0.98, 9.99)
Prior Lines (<3, ≥3)	3.08 (1, 10.38)
Stage (I,II vs III, IV)	2.98 (0.98, 9.95)
ECOG (<2)	3.02 (0.98, 10.26)
Extra-nodal Involvement	3.07 (0.98, 10.6)
Refractory	2.85 (0.87, 10.26)

5 SUMMARY AND CONCLUSIONS

This section outlines key conclusions.

5.1 Statistical Issues

The major issue affecting most key efficacy outcomes was response assessment. The issue has been resolved through FDA-adjudication of IRC response assessment and correspondence with the Applicant (see *Response Assessment* in Section 3.2.1: Study Design and Outcomes).

5.2 Collective Evidence

The efficacy of polatuzumab vedotin in combination with rituximab and bendamustine (N=40) compared to rituximab and bendamustine alone (N=40) for the treatment of patients with R/R DLBCL has been assessed based on the randomized pivotal Study GO29365. Internal consistency of P+BR favorable efficacy has been demonstrated by i) advantage over BR in the pre-specified major efficacy outcome of complete response rate at the primary response assessment ii) supporting evidence on best overall response rates and the duration of response iii) supporting efficacy evidence on lyophilized formulation of polatuzumab vedotin from a single-group cohort (N=32).

5.3 Conclusions and Recommendations

Benefit of polatuzumab vedotin in combination with rituximab and bendamustine for the treatment of patients with R/R DLBCL has been demonstrated based on the randomized pivotal Study GO29365. However, some residual uncertainty about the treatment effect exists, given the small number of patients randomized and limited number of events in the PFS and OS. Some uncertainty in treatment effect magnitude with the new lyophilized formulation of polatuzumab vedotin remains because treatment effect cannot be estimated directly in a single-group cohort. This uncertainty may be alleviated if the treatment benefit is confirmed in a large randomized trial. Treatment effect observed in the pivotal Study GO29365 should be confirmed with a progression-free or overall survival outcome in an adequately designed randomized trial.

5.4 Labeling Recommendations

Efficacy labeling should be primarily based on pre-specified major outcome (see Table 5). Aside from descriptive characterization of best overall response and duration of response, labeling should not allow for any claims on time-to-event secondary endpoints due to no multiple testing plan and limited number of events.

REFERENCES

Miettinen, O, and M Nurminen, 1985, Comparative analysis of two rates, Stat Med, 4(2):213-226.

APPENDIX

Response Rates and Duration of Response per Investigator Assessment

Figure 9. Response Rates at Primary Response Assessment by PET per Investigator

	BR (Ph II) (N=40)	Pola+BR (Ph II) (N=40)
Number of Evaluable Patients	40	40
Overall Response (CR/PR)	7 (17.5%)	19 (47.5%)
95% CI for Response Rate (Clopper-Pearson)	(7.34, 32.78)	(31.51, 63.87)
Difference in Response Rates		30.00
95% CI for Difference in Response Rates (Wilson)		(9.48, 47.37)
p-Value (Cochran-Mantel-Haenszel)		0.0036
Complete Response (CR)	6 (15.0%)	17 (42.5%)
95% CI	(5.71, 29.84)	(27.04, 59.11)
Partial Response (PR)	1 (2.5%)	2 (5.0%)
95% CI	(0.06, 13.16)	(0.61, 16.92)

Stratification factors: Duration of Response to Prior Therapy from IXRS ($\leq 12 / > 12$ months).
 95% CI for rates were constructed using Clopper-Pearson method.
 Cutoff Date: 30APR2018 Extract Date: 29JUN2018

[Source: Applicant, CSR; No FDA-adjudication]

Figure 10. Duration of Response per Investigator

	BR (Ph II)	Pola+BR (Ph II)
Patients with event (%)	11 (84.6%)	17 (60.7%)
Earliest contributing event		
Disease Progression	7	13
Death	4	4
Patients without event (%)	2 (15.4%)	11 (39.3%)
Time to event (month)		
Median	4.074	10.316
95% CI	(2.563, 12.682)	(5.585, NE)
25% and 75%-ile	2.563, 12.682	4.534, NE
Range	1.48 to 20.07*	0.59 to 22.54*

[Source: Applicant, CSR; No FDA-adjudication]

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