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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

POLATUZUMAB VEDOTIN (POLIVY)

(Hoffmann-La Roche Limited)

Indication: In combination with bendamustine and rituximab for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, who are not eligible for autologous stem cell transplant and have received at least one prior therapy.

Service Line:	CADTH pCODR Clinical Guidance Report
Version:	Final
Publication Date:	April 21, 2021
Report Length:	102 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Table of Contents

Tables

Figures

Abbreviations

ABC: Activated B Cell

AE: Adverse Event

AESI: Adverse Events of Special Interest

ANC: Absolute Neutrophil Count

ASCT: Autologous Stem Cell Transplant/Transplantation

BG: Bendamustine and Obinutuzumab

BOR: Best Overall Response

BR: Bendamustine and Rituximab Combination

CAR T-cell: Chimeric Antigen Receptor T-cell

CCO: Cancer Care Ontario

CDOP: Cyclophosphamide, Doxil, Vincristine, Prednisone

CEOP : Cyclophosphamide, Etoposide, Vincristine

CEPP: Cyclophosphamide, Etoposide, Procarbazine

CGP: Clinical Guidance Panel

CI: Confidence Interval

CNS: Central Nervous System

COO: Cell of Origin

CR: Complete Response

CT: Computed Tomography

CTCEA: Common Terminology Criteria for Adverse Events

DA-EPOCH: Cyclophosphamide, Doxorubicin, Etoposide, Vincristine

DCR: Disease Control Rate

DHAP: Dexamethasone–Cisplatin–Cytarabine

DLBCL: Diffuse Large B-Cell Lymphoma

DOR: Duration of Response

DSU: Decision Support Unit

ECOG PS: Eastern Cooperative Oncology Group Performance Status

EFS: Event-free Survival

EOT: End of Treatment

ESHAP:	Etoposide, Methylprednisolone, Cytarabine, Cisplatin
ESS:	Effective Sample size
FL:	Follicular Lymphoma
GCB:	Germinal Centre B Cell Type
G-CSF:	Granulocyte Colony Stimulating Factor
GDP:	Gemcitabine, Dexamethasone, Cisplatin
GemOx:	Gemcitabine and Oxaliplatin
HDT:	High-Dose Therapy
HR:	Hazard Ratio
HRQoL:	Health-Related Quality of Life
HSCT:	Hematopoietic Stem Cell Transplant
ICE:	Ifosfamide, Etoposide, Carboplatin
IME:	Ifosfamide, Mitoxantrone, Etoposide
INV:	Investigator
IPD:	Individual Patient Data
IPI:	International Prognostic Index
IPTW:	Inverse Probability Treatment Weighting
IRC:	Independent Review Committee
ITC:	Indirect Treatment Comparison
ITT:	Intention-to-Treat
IV:	Intravenous
LC:	Lymphoma Canada
LDH:	Lactate dehydrogenase
LYO:	Lyophilized
MAIC:	Matching-adjusted indirect comparison
MEP :	Mitomycin C–Etoposide–Cisplatin
MINE :	Mesna, Ifosfamide, Mitoxantrone, Etoposide
MMAE :	Monomethyl Auristatin E
NHL:	Non-Hodgkin Lymphoma
NICE:	The National Institute for Health and Care Excellence

NOC/c:	Notice of Compliance with Conditions
NOS:	Not Otherwise Specified
NR:	Not reported
ORR:	Overall Response Rate
OS:	Overall Survival
PAG:	Provincial Advisory Group
PD:	Progressive Disease
PEP-C:	Prednisone, Etoposide, Procarbazine And Cyclophosphamide
pERC:	pCODR Expert Review Committee
PET-CT:	Positron Emission Tomography – Computed Tomography
PFS:	Progression-Free Survival
pola-BR:	Polatuzumab Vedotin Plus Bendamustine And Rituximab
PR:	Partial Response
PS:	Performance Status
PSWA:	Propensity Score Weighted Analysis
QoL:	Quality of Life
R/R:	Relapsed or Refractory
R-CEOP:	Rituximab, Cyclophosphamide, Etoposide, Vincristine, And Prednisone
R-CHOP:	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
RCT:	Randomized Controlled Trial
R-DHAP:	Rituximab, Dexamethasone, Cytarabine And Cisplatin
R-DICEP:	Rituximab, Dose-Intensive Cyclophosphamide, Etoposide, Cisplatin
R-GDP:	Rituximab, Gemcitabine, Cisplatin, and Dexamethasone
R-GemOx:	Rituximab, Gemcitabine, And Oxaliplatin
RWD:	Real-World Database
RWE:	Real-World Evidence
SAE:	Serious Adverse Events
SAS:	Statistical Analysis System
SCT:	Stem Cell Transplant
SD:	Stable Disease

SLR:	Systematic Literature Review
SOC:	Standard of care
TEAEs:	Treatment emergent adverse events
TINAS:	Therapy-Induced Neuropathy Assessment Scale
TTP:	Time to Progression

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding polatuzumab vedotin (POLIVY®). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted PAG Input, and a summary of submitted Registered Clinician Input are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR) for the treatment of adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), who are not eligible for autologous stem cell transplant (ASCT) and have received at least one prior therapy.

On July 9th, 2020, Health Canada issued a Notice of Compliance with conditions (NOC/c), pending the results of trials to verify clinical benefit, for pola-BR for the treatment of adult patients with R/R DLBCL, NOS, who are not eligible for ASCT and have received at least one prior therapy.[1] The CADTH reimbursement request is aligned with the Health Canada NOC/c.

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that delivers an anti-mitotic agent, monomethyl auristatin E (MMAE), to B-cells, which results in the killing of malignant B-cells. The polatuzumab vedotin molecule consists of MMAE that is attached to a humanized immunoglobulin G1 monoclonal antibody. The monoclonal antibody binds to CD79b, which is a cell surface component of B-cell receptor that is expressed in over 95% of DLBCLs. Binding to CD79b enables delivery of MMAE, which binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.[2]

Polatuzumab vedotin is administered by intravenous (IV) infusion. The Health Canada recommended dose is 1.8 mg/kg polatuzumab vedotin every 21 days in combination with BR for 6 cycles.[1] The three drugs can be administered in any order on the first day of each cycle. The recommended dose of bendamustine is 90 mg/m^2/day on the first and second day when administered with polatuzumab vedotin and rituximab. The recommended dose of rituximab is 375 mg/m^2.[3]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The systematic review included one phase Ib/II, open label, randomized controlled trial (RCT), the GO29365 trial. GO29365 enrolled patients with R/R DLBCL after at least one prior regimen. This study had several different arms, including patients with follicular lymphoma (FL), or combining polatuzumab with obinutuzumab plus bendamustine, not of relevance to this review. This review will focus on the phase II arm that compared, in a randomized fashion, patients who received pola-BR with those who received BR alone, for six 21-day cycles. The study is ongoing and is scheduled to end once all patients enrolled have had at least two years of follow up from the time of treatment completion or have discontinued the study.[4] Randomization was performed using an interactive voice/web response system and was stratified by duration of response (DOR) to prior therapy (≤ 12 months versus > 12 months).[5]

The primary outcome was achievement of a complete response (CR), measured at the primary response assessment (6 weeks after cycle 6 Day 1 or last dose of study medication) as measured by Positron Emission Tomography – Computed Tomography (PET-CT) scan and as determined by an Independent Review Committee (IRC).[3] Objective responses were assessed using the modified Lugano 2014 response criteria and the analysis was conducted on the intention-to-treat (ITT) population. Secondary outcomes

included progression-free survival (PFS), DOR, best overall response (BOR) and IRC-assessed CR rate at EOT (end of treatment) based on CT (computed tomography) only. Overall survival (OS) was assessed as an exploratory endpoint. Patients who did not have documented disease progression or death, had observations censored on the date of the last tumour assessment, or if no tumour assessments were performed after the baseline visit, at the time of randomization and enrollment plus one day. For OS, patients for whom death had not been documented had observations censored on the last date at which they were known to be alive. Health-related quality of life (HRQoL) was not assessed in this study.[4]

Peripheral neuropathy is a recognized adverse effect of polatuzumab therapy, and thus patients were assessed for signs of neuropathy by the investigator, using the Total Neuropathy Score, and by the patient reported Therapy-Induced Neuropathy Assessment Scale (TINAS).[4]

With respect to safety, treatment emergent adverse events (TEAEs) were defined as those that are new or worsened from baseline grade or are unknown to have worsened from baseline. The AE reporting window was 90 days after the last study drug or initiation of non-protocol specified anti-cancer treatment, whichever came first, after which serious adverse events (SAE) or adverse events of special interest (AESI) were reported.[6]

Study population

Study GO29365 randomized 80 patients, in a 1:1 ratio, to either pola-BR or BR. The population enrolled were predominantly male (66%), White (71%), and had a median age of 69 years. Most patients (80%) had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Although patients were to have DLBCL, there was 1 patient (3%) with FL and 1 patient (3%) with Burkitt's lymphoma enrolled. With respect to prior therapy, 80% were considered refractory, 84% had a DOR of 12 months or less, and 20% were considered to have failed hematopoietic stem cell transplant (HSCT). Differences in baseline characteristics between pola-BR and BR of greater than 10% were observed for race (White: 65% versus 78%, respectively), primary reason for HSCT ineligibility (age: 33% versus 48% and failed prior HSCT: 25% versus 15%, respectively), outcome of last therapy (refractory: 75% versus 85% respectively), disease features at baseline (bulky disease: 25% versus 38%, respectively), and International Prognostic Index (IPI) risk at baseline (high: 23% versus 43%).[6]

Efficacy

The key efficacy outcomes from GO29365 are presented in Table 1. The primary analysis cut-off date was April 30, 2018, which occurred after all treated patients had one year of follow-up after the preliminary response assessment. The median duration of follow-up in the primary analysis for GO29365 was 22.3 months.[2] The sponsor also provided longer term efficacy with a data cut-off for the clinical study report of January 2, 2020 and the median duration of follow-up was 42.2 months.

Primary outcome: IRC-Assessed CR rate by PET-CT at EOT

The percentage of patients with CR at EOT, by IRC assessment using PET-CT, was the primary outcome. CRs occurred in 16 (40%) patients in the pola-BR group and in 7 (18%) patients in the BR group, for a difference between groups of 22% (95% CI: 3%, 41%; p=0.026).[6]

Partial responses (PRs) were observed in 2 (5%) patients in the pola-BR group and no patients in the BR group. Investigator-assessed CRs were similar to those by IRC, 17 (43%) in the pola-BR group and 6 (15%) in the BR group. [2]

Secondary outcomes:

IRC-Assessed CR rate at EOT based on CT only

The CR rate at the EOT by IRC assessment using CT only was much lower than reported when using PET-CT for both treatment groups. At the time of the primary analysis the CR rate in the pola-BR group was 22.5% compared to 2.5% in the BR group. However, the difference in CR rate between the treatment groups as assessed by CT alone was 20.0% (95% CI: 5.5 to 35.1) which was consistent with the difference based on PET-CT assessment. [3]

IRC-Assessed ORR at EOT

The IRC-assessed ORR at EOT was 45% (n=18) in the pola-BR group and 17.5% (n=7) in the BR group. PRs were observed in 2 patients (5%) in the pola-BR group and no patients in the BR group at EOT. [2]

IRC-Assessed BOR

BOR was also reported, and there were more patients with a best response of CR in the pola-BR group (50%) compared to the BR group (23%). PRs occurred in 5 patients (12.5%) in the pola-BR group and 1 patient (2.5%) in the BR group. The ORR based on best response was 62.5% with pola-BR and 25% with BR.[2] Results for BOR were unchanged at the time of the longer term follow up.[4]

IRC-Assessed DOR

At the time of the primary analysis, the median DOR by IRC was 12.6 months (95% CI: 7.2 to not estimable [NE]) with pola-BR and 7.7 months (95% CI: 4.0 to 18.9) with BR for a HR of 0.47 (95% CI: 0.19 to 1.14).[2] The confidence interval (CI) of the HR suggests that the difference in DOR may not be significant between pola-BR and BR, although there was no formal prespecified statistical testing of the difference between treatment groups and there was only a small number of patients included in the analysis; thus, there is uncertainty in the reported results of DOR. Of the 25 patients in the pola-BR group who had an IRC-assessed BOR of CR or PR, 16 (64%) had a DOR of at least 6 months compared to 3 patients (30%) in the BR group. There were 12 patients (48%) in the pola-BR group and 2 patients (20%) in the BR group who had a DOR of at least 12 months.[7] The median DOR at the time of the updated analysis was 10.9 months (95% CI: 5.7 to 40.7) with pola-BR and 10.2 months (95% CI: 4.0 to 19.6) with BR, for a HR of 0.60 (95% CI: 0.25, 1.43).[4]

IRC-Assessed PFS

Median PFS by IRC was 9.5 months (95% CI: 6.2 to 13.9) with pola-BR and 3.7 months (95% CI: 2.1 to 4.5) with BR, representing a HR of 0.36 (95% CI: 0.21 to 0.63), or a 64% reduction in risk of either progression or death.[2] Similar to DOR, given the limitations of the analyses (small sample size, lack of prespecified statistical testing and control for multiple comparison), these results are uncertain.

At the time of the updated analysis, PFS by IRC was 9.2 months (95% CI: 6.0 to 13.9) with pola-BR and 3.7 months with BR (95% CI: 2.1 to 4.5) for a HR of 0.38 (95% CI: 0.22 to 0.65), indicating little change from the primary analysis.[4]

Exploratory Outcomes

OS

Median OS was 12.4 months (95% CI: 9.0 to NE) with pola-BR and 4.7 months (95% CI: 3.7 to 8.3) with BR. This corresponds to a HR of 0.42 (95% CI: 0.24, 0.74), or a 58% reduction in risk of death.[2] Similar to the reasons noted above for DOR and PFS, these results are uncertain and are considered exploratory. Results for BOR were unchanged at the time of the longer term follow up.[4]

Subgroup analyses were conducted post hoc, and all subgroup analyses were limited by small sample sizes. There did not appear to be any differences in response based on subgroups identified to be of interest to this review including IPI score (≥3 versus <3), ECOG PS (≥ 2 versus 0 or 1), prior lines of anti-lymphoma therapy (≥2 versus 1) and DOR to prior anti-lymphoma therapy (>12 months versus ≤12 months).[2]

Harms

In this section, harms are presented for the safety evaluable population (N=78), and for the expanded safety evaluable population (N=84).

Adverse Events (AEs)

In the safety evaluable population, overall, 100% of patients in the pola-BR group and 97% of patients in the BR group experienced an AE. Grade 3 or 4 AEs occurred in 84% of patients in the pola-BR group and 72% of patients in the BR group, a clear numerical difference between groups.[8] Anemia was the most common AE that occurred in the pola-BR group (54% versus 26% in BR [grade 3

or 4: 28% versus 18%]) followed by neutropenia (54% versus 39% [grade 3 or 4: 46% versus 33%]) and thrombocytopenia (49% versus 28% [grade 3 or 4: 41% versus 23%]) and peripheral neuropathy (44% versus 8% [no grade 3 or 4]). Diarrhea was also a common AE with pola-BR (39% versus 28% [grade 3 or 4: 3% in each group]). [2] All of these AEs occurred numerically more frequently in the pola-BR group than in the BR group. These data were consistent with that of the expanded safety evaluable population and the updated analysis. [4]

Serious Adverse Events (SAEs)

In the safety evaluable population, SAEs occurred in 64% of patients on pola-BR and 62% on patients on BR, thus there was no clear difference in groups for the risk of SAEs. The most common SAEs with pola-BR were pneumonia (8% versus 8% in BR), febrile neutropenia (10% versus 10%) and pyrexia (10% versus zero), thus pyrexia was numerically more common in the pola-BR group than in the BR group.[3] These findings were consistent with that of the expanded safety evaluable population (see Table 16) and the updated analysis.[4]

Mortality

There were 4 deaths (9% of patients) with pola-BR that were described as AEs and 6 deaths (15%) with BR alone. With pola-BR, the fatal AEs all appeared to be related to infection and/or pneumonia. With BR alone, three deaths occurred due to infection, and 1 each for cardiac, unspecified cerebrovascular accident, and sudden death.[6]

Discontinuations Due to AEs

In the safety evaluable population, there were numerically more treatment discontinuations due to AEs with pola-BR than with BR, occurring in 33% of pola-BR and 13% of patients in the BR group; 31% of patients in the pola-BR group discontinued polatuzumab vedotin. Dose modifications/interruptions occurred with 72% of patients in the pola-BR group and 49% of BR alone. [8] These findings were consistent with that of the expanded safety evaluable population (see Table 16) and the updated analysis.[4]

Table 1: Highlights of Key Outcomes

	POLA + BR N = 40	BR N = 40
Primary outcome: CR Rate at EOT based on PET-CT, n (%)		
Complete response, IRC, n (%)	16 (40)	7 (18)
Difference between groups, % (95% CI)	22 (3 to 41)	
Secondary outcomes:		
IRC-Assessed CR rate at EOT based on CT		
Complete response, IRC, n (%)	9*(23)	1*(3)
Difference between groups, % (95% CI)	20.0 (5.5 to 35.1)	
IRC-Assessed ORR at EOT		
Objective response, EOT, n (%)	18 (45)	7 (18)
Partial response, n (%)	2 (5)	0
Stable disease, n (%)	6 (15)	1 (3)
Progressive disease, n (%)	8 (20)	10 (25)
Missing or Not evaluable, n (%)	8 (20)	22 (55)
-no EOT scan performed due to AE	3 (8)*	0
-no EOT scan for IRC	1(3)*	0
-no scans in study, withdrew from study	2 (5)*	2 (5)*
-EOT scan unavailable by IRC	1(3)*	0
-EOT CT performed without PET	1(3)*	0
-clinical progression, no scan performed	0	14(35)*

	POLA + BR N = 40	BR N = 40
-no EOT scan performed, interim scan PD by INV and SD by IRC	0	4
-no EOT scan performed; death from AE	0	2 (5)*
IRC-Assessed BOR		
Objective response, BOR, n (%)	25 (63)	10 (25)
Complete response, n (%)	20 (50)	9 (23)
Partial response, n (%)	5 (13)	1 (3)
Stable disease, n (%)	5 (13)	9 (23)
Progressive disease, n (%)	6 (15)	8 (20)
Missing or Not evaluable, n (%)	4 (10)	13 (33)
IRC-Assessed DOR		
Patients with an event, IRC, n (%)	13/25 (52)	8/10 (80)
Median (95% CI), months	12.6 (7.2 to NE)	7.7 (4.0 to 18.9)
HR (95% CI)	0.47 (0.19, 1.14)	
IRC-Assessed PFS		
Events by IRC assessment, n (%)	25 (63)	32 (80)
Median (95% CI), months	9.5 (6.2 to 13.9)	3.7 (2.1 to 4.5)
HR (95% CI)	0.36 (0.21, 0.63)	
OS		
Deaths, n (%)	23 (58)	28 (70)
Median (95% CI), months	12.4 (9.0 to NE)	4.7 (3.7 to 8.3)
HR (95% CI)	0.42 (0.24, 0.75)	
Harms		
AE, n/N (%)	45/45 (100)	38/39 (97)
SAEs, n/N (%)	29/45 (64)	24/39 (62)
Fatal AEs, n/N (%)	4/45 (9)	6/39 (15)
AE resulting in treatment discontinuation, n/N (%)	14/45 (31)	6/39 (15)

AE = adverse event; BOR = best overall response; CI = confidence interval; CR = complete response; CT = computed tomography; DOR = duration of response; EOT = end of treatment; HR = hazard ratio; IRC = independent review committee; NE = not evaluable; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; PR: Partial Response SD = stable disease

*HR assessed using a Cox proportional hazards model

* %/n value estimated

Sources: Sehn et al., 2020 [2], EPAR, 2019 [3], FDA CR [6]

Limitations

There was no blinding in the GO29365 trial. This is less likely to have biased findings for clinical outcomes such as mortality, IRC-assessed PFS and ORR, and more likely to have biased patient-reported outcomes and assessment of harms. The only patient-reported outcome was TINAS, which was used to assess the impact of peripheral neuropathy. The results of this assessment may have been biased by lack of blinding, considering the fact that neuropathy is a known AE of polatuzumab vedotin. AEs may have been more likely to be assigned a different severity by investigators based on whether they were experienced by patients in the pola-BR or BR groups, and patients may have been more or less likely to report AEs if they knew whether they were receiving pola-BR or BR.

There was no pre-specified statistical hypothesis for the primary outcome, the CR rate difference between groups. Additionally, there were no adjustments made for multiple statistical comparisons; therefore, the analysis of any of these outcomes is at risk of Type 1 error.

There were only 40 patients in each group in the included study, and this small sample size limits confidence in the analysis. There was no power calculation performed based on a pre-specified hypothesis. There were imbalances in baseline characteristics for numerous parameters, and the size of these imbalances is difficult to place into perspective given the small sample size in the study. Notably, the majority of imbalances in baseline characteristics had the potential to bias results in favour of pola-BR. The sponsor assessed these outcomes in multiple Cox regression models and found that these baseline imbalances did not appear to impact the efficacy results.

The sponsor analysis of a number of different outcomes did not follow FDA recommendations. The differences between the sponsor analysis and FDA recommendations are summarized in Table 11. In many cases, the sponsor analysis resulted in a reduced number of progression events, as they counted these as 'not evaluable'. This approach by the sponsor mainly impacted outcomes that rely upon progression events, such as PFS.

The combination of BR is not a relevant comparator for the Canadian setting (refer to Section 7 for a comparison and critical appraisal of pola-BR to relevant comparators in Canadian practice). The lyophilized formulation of pola-BR, which is the formulation that is being used in Canada, was not studied in the open label RCT component of GO29365. Instead, it was added as a single arm to GO29365 as a protocol amendment. After conducting a comparative analysis of pharmacokinetics, the FDA concluded that there were no meaningful differences between the lyophilized formulation and the solution of pola-BR. [6]

HRQoL was not assessed in the included study. The only patient-reported outcome was TINAS, which was used to assess the impact of peripheral neuropathy, a known adverse effect of polatuzumab vedotin. This analysis had some limitations, including the fact that baseline data were only available for half of trial patients, and there was a large amount of attrition that occurred during the study, and eventually only 29% of patients were continuing to be adherent to the questionnaire.

Subgroup analyses appear to have been conducted post hoc, rather than being pre-planned; thus, these analyses should not be used to draw any conclusions about the efficacy of pola-BR in these subgroups. Subgroups identified in the systematic review protocol to be of interest included transplant ineligible patients who relapsed/were refractory to first line treatment, patients non-responsive to salvage chemotherapy and who therefore did not undergo ASCT, and patients who relapsed post-transplant. Therefore, no data are available from the trial for these subgroups of interest.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, PAG Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Lymphoma Canada (LC) provided input from two online surveys of DLBCL patients: those without experience with pola-BR, and one in patients with pola-BR experience. A total of 114 patients responded to both surveys (107 without, and 7 with pola-BR experience). The majority of patients lived in Canada (82%), were female (53%) and were greater than 60 years of age (48%).

From the patient perspective the most debilitating physical symptoms associated with DLBCL and treatment included fatigue, enlarged lymph nodes, drenching night sweats, weight loss, loss of appetite, flu-like symptoms, and persistent cough. Aside from the physical effects of the disease and treatment, DLBCL patients also experienced mental and emotional stress including fear of disease recurrence, memory loss, anxiety, problems concentrating, difficulty sleeping, loss of sexual desire, stress of diagnosis, and depression. The top-rated factors that patients valued in a new drug or therapy for DLBCL were longer survival and longer remission than current therapies, followed by better QoL. Close to half of the survey respondents indicated that they would be willing to tolerate the side effects of a new treatment if they were short term events. Half of the respondents indicated that they would choose a doctor-recommended treatment with known side effects, even the side effects were potentially serious.

All of the seven patients who had experience with pola-BR had received this treatment in 2020, with the majority receiving treatment through a clinical trial, and the rest accessing pola-BR through a private program. All patients except one were currently in remission at the time of the survey. Two of the seven patients did not experience any side effects with pola-BR. Nausea and fatigue were the most commonly reported side effects of pola-BR therapy. Other side effects included neutropenia, thrombocytopenia, low blood pressure, loss of taste, rash and peripheral neuropathy. Only one patient required hospitalization due to side effects and two patients experienced nausea that lasted longer than two months. Patients noted that they would be willing to accept treatments with undesirable side effects if recommended by their physician. Overall, patients considered pola-BR to be an acceptable treatment option, offering improved overall physical and mental well-being.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Numerous clinical eligibility criteria
- Criteria for discontinuation of therapy
- Sequencing with other therapies including CAR-T

Economic factors:

- BR is not funded across all jurisdictions

Registered Clinician Input

A total of three joint clinician inputs were provided: two clinicians provided input on behalf of Ontario Health (Cancer Care Ontario [CCO]) Hematology Cancer Drug Advisory Committee (DAC), 20 individual clinicians provided input on behalf of the BC Cancer Agency and University of British Columbia (UBC), and three on behalf of LC.

Inputs received from registered clinicians indicate that there is currently no standard of care (SOC) regimen for transplant ineligible R/R DLBCL patients, as there have been no randomized trials that establish the superiority of one regimen over another for this patient population. Treatment options for these patients include sequential single agent chemotherapy drugs, or chemotherapy combinations, which are mostly palliative. Steroids and/or radiation may be offered in the palliative setting, mainly for symptom control. The clinicians noted that the most frequently used treatment in the R/R setting is platinum-based combination chemotherapy, and that this option is generally unsuitable for older patients or those with comorbidities as it is often too intensive and toxic. The registered clinician input suggested that many patients in the R/R setting have already received and failed platinum-based regimens, and therefore require novel options. The addition of novel agents to chemotherapy may be difficult due to overlapping toxicities, and access is often restricted to clinical trials. Clinicians providing input anticipated that pola-BR would represent a new SOC. The clinician group inputs also noted other places in the treatment algorithm where pola-BR is anticipated to be used beyond the funding request. In the absence of universally established SOC, and based on its efficacy, tolerability, and potential for long term durable disease control, pola-BR is believed to provide clinicians with a therapeutic option for patients with R/R DLBCL who are not eligible for (ASCT) and have failed on at least one prior therapy. The clinicians also remarked on the possibility of serving as a bridge to ASCT or Chimeric Antigen Receptor (CAR) T-Cell Therapy as opposed to standard platinum-based chemotherapy (i.e., Rituximab, Gemcitabine, Cisplatin, and Dexamethasone [R-GDP]). They also noted that pola-BR could possibly replace conventional palliative chemotherapy following ASCT relapse.

All three clinician groups indicated that they had prior experience with pola-BR. The LC and BC Cancer Agency/UBC clinicians noted that pola-BR has a similar side-effect profile to BR, except for a higher incidence of neutropenia. Clinicians from LC also noted that severe neuropathy (grade 2 or higher) would be a contraindication for polatuzumab. Overall, it was believed that pola-BR is a more favourable option in R/R DLBCL over platinum-based regimens. Regarding retreatment with pola-BR, all three clinician groups were unaware or uncertain of the availability of evidence at this time.

Summary of Supplemental Issues

Issue 1: Review of Efficacy and Safety from Non-randomized Groups in the GO29365 Trial

There were several treatment arms in GO29365, and some of these studied the lyophilized form of polatuzumab vedotin. The lyophilized version was developed after GO29365 had begun, therefore the RCT portion of the study used the solution and the lyophilized version was added as a protocol amendment. Two arms with lyophilized versions of polatuzumab vedotin were added to the study, Arm G (N=42) and Arm H (N=64), both in patients with R/R DLBCL. Arm G was planned to include 10 patients who had one prior line of therapy, and Arm H had at least 30% with one prior line of therapy. The primary objective of Arm G was to assess the pharmacokinetics and safety of the lyophilized formulation of polatuzumab vedotin, while the primary objective of Arm H was to assess efficacy. [4] See Section 6 for further description of the design of GO29365.

The median age of 70 years was similar in the lyophilized cohorts compared to the RCT arms of the study (69 years). There was an even split of males (49%) and females (51%) in the lyophilized cohorts, which was different than the RCT component of the study, which had 66% males. The majority of patients were white in the lyophilized cohorts (78%) and in the RCT component of the study (71%). Most patients in the lyophilized cohort had an ECOG performance status of 0 or 1 (87%), as was the case in the RCT component (80%). With respect to prior therapy, 76% were refractory to their last prior lymphoma therapy (versus 80% in the RCT phase), and 70% were refractory to the last prior anti-CD20 drug. [2,4]

Deaths occurred in 48% of patients across both arms, for a median survival of 11.0 months (95% CI: 8.3, 14.2). Median PFS was 6.1 months (95% CI: 5.1, 8.0) across both arms. CRs were observed in 40% of patients, using independent review by PET, and the median DOR was 6.2 months (95% CI: 5.4, 11.6).[4] The median DOR and PFS were numerically lower in these lyophilized cohorts than in the pola-BR group in the RCT phase. Arms G and H of study GO29365 are still ongoing, while the RCT phase is complete.

Across Arms G and H, 99% of patients experienced at least one AE, and 77% of the AEs were grade 3 or 4. Common AEs included neutropenia (31% in Arms G and Arm H [27% were grade 3 or 4]), and this was consistent with the RCT phase. Other common AEs were thrombocytopenia (18% [14% grade 3 or 4]) and anemia (26% [8% grade 3 or 4]).[4] SAEs were reported in 51% of patients. Febrile neutropenia was the most common SAE (9% of patients), followed by sepsis (8% of patients) and pyrexia (7%). Febrile neutropenia (11%) was the most common SAE in the RCT phase. There were seven patients who had an AE resulting in death, and sepsis was the most common reason for death, occurring in four patients. Pneumonia was the most common reason for death in the RCT phase. There were 15% of patients who discontinued polatuzumab vedotin due to an AE (compared to 33% in the RCT phase). Dose interruptions of polatuzumab vedotin occurred in 42% of patients. Notable harms such as infection, anemia, thrombocytopenia and neutropenia are described above.[4]

See section 7.1 for more information.

Issue 2: Summary and Critical Appraisal of Sponsor-submitted Indirect Treatment Comparisons (ITC)

In the absence of direct evidence comparing pola-BR to all relevant comparators, the sponsor submitted a matching-adjusted indirect comparison (MAIC) comparing the efficacy of pola-BR to other treatments in R/R DLBCL. Specifically, the MAIC compared the efficacy of pola-BR to rituximab in combination with gemcitabine and oxaliplatin (R-GemOx), pixantrone, tisagenlecleucel (CAR T-cell therapy, and axicabtagene ciloleucel (CAR T-cell therapy). The justification for using the MAIC approach was based on the network feasibility assessment which showed a lack of a common comparator between studies of pola-BR and other therapies. The MAIC used individual patient characteristics from patients in the GO29365 study to generate weights for patients in order to mimic the baseline summary statistics reported in the other trials. The weighted results showed statistically significant differences in CR between pola-BR and R-GemOx (CR= 37.2%; 95% CI: 15.9% to 76.1%), and tisagenlecleucel (CR= 23.2%; 95% CI: 9.8% to 36.0%). Inversely, the results showed no statistical difference between pola-BR and axicabtagene ciloleucel for both CR (-6.5; 95% CI: -25.5 to 13.5) and OS (1.38; 95% CI: 0.57 to 3.31).[9] No MAIC was conducted for safety or HRQoL outcomes. Overall, the applicability of sponsor's analysis is impacted by the limited scope and potential limitations of the submitted analysis. This is largely due to a weak and sparse evidence base. Limitations to the evidence base due to population heterogeneity, limited adjustment for all prognostic factors and effect modifiers, reduced precision due to small samples sizes, and inclusion of open-label non-comparator studies limited the robustness of any possible analysis. Additionally, although the MAIC was extensive, it was not able to convincingly

overcome the limitations inherent in the evidence base. Overall, the results of this analysis must be interpreted with caution. Little can be elucidated on the comparative efficacy to other products based solely on this submitted ITC analyses.

See section 7.2 for more information.

Issue 3: Summary and Critical Appraisal of the Sponsor-submitted Propensity Score Weighted Analysis (PSWA)

The sponsor also submitted a PSWA to compare OS and PFS between pola-BR in the GO29365 trial and a "basket" of chemotherapy regimens used in the Alberta Oncology Outcomes (O2) real-world database (RWD). This analysis was performed using the inverse probability treatment weighting (IPTW) methodology and numerous sensitivity analyses. However, the submitted PSWA has major limitations that hinder the potential applicability of the comparative results. The applicability of sponsor's submitted analysis is impacted by limitations related to the size of the cohort used, the ability to efficiently weight between RWD and trial data, and important clinical differences between study arms. Hence, the results should be interpreted with caution. No firm conclusions can be drawn on the comparative effectiveness of pola-BR based on the submitted RWE analyses alone.

See section 7.3 for more information.

Comparison with Other Literature

The CADTH CGP and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of Generalizability of Evidence for pola-BR for R/R DLBCL

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Age	The median age reported in the randomized phase II portion of GO29365 was 69 years. A total of 65% of patients in the BR arm and 58% of patients in the pola-BR are were 65 years of age or older.	Is the age of included patients in the GO29365 representative of the patient population seen in clinical practice?	Yes, the age distribution is representative of the patient population seen in clinical practice.
	Race	The breakdown of race as reported in the randomized phase II portion of GO29365 was: White: 71% Asian: 12% Black: 4% Other: 13%	Are the trial results generalizable to patients of all races?	Yes, the trial results are generalizable to patients of all races.
	ECOG PS	A total of 80% of patients in the randomized phase II portion of GO29365 had an ECOG PS of 0 to 1.	Are the trial results generalizable to patients with an ECOG PS of 2 or greater?	Patients with an ECOG PS of 2 or higher should not be excluded from eligibility for pola-BR and should be considered on a case-by-case basis.
	Measurable disease	Per the inclusion criteria, patients were required to have at least one bi-dimensionally measurable lesion on imaging scan defined as > 1.5 cm in dimension.	In clinical practice, would patients be required to have measurable disease prior to initiating therapy with pola-BR?	Patients with non-measurable disease, such as those with pleural effusions or bone-only disease, should be eligible for treatment with pola-BR.
Intervention	Formulation (liquid vs lyophilized)	The randomized phase II portion studied the liquid formulation of polatuzumab vedotin with BR, however a lyophilized formulation was developed for commercialization. Two nonrandomized cohorts (arm G and H with a total of 106 patients) further studied the lyophilized formulation of polatuzumab vedotin in combination with BR. There were some differences in the baseline disease and demographic characteristics of the pooled lyophilized cohorts (arms G and H) and overall liquid formulation	Can the results of the liquid formulation studied in the randomized arms of the trial (C and D) be generalized to the lyophilized formulation that is the commercialized formulation for use in patients?	Yes, the efficacy and safety results of the liquid formulation would be expected to be similar and representative of patients treated with the lyophilized formulation of pola-BR.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		(Arms C and D) including a lower proportion of males (49% vs. 66%), a higher proportion of patients reporting White race (78% vs. 71%), a lower proportion of patients with ECOG PS 2 (13% vs. 20%), a higher proportion that failed prior HSCT (29% vs. 20%), and a slightly lower proportion of patients with bulky disease at baseline (26% vs. 31%), which may indicate the populations in these arms are not directly comparable. The median duration of follow-up for the pooled lyophilized arms was shorter at 9.7 months compared to 22.3 months at the time of the interim analysis for the pooled randomized arms with the liquid formulation. The results for CR rate (36.8%) of the pooled lyophilized cohorts was similar to the pola-BR arm (arm C) CR rate of 40%. ORR was also very similar, with a rate of 42.5% in the pooled lyophilized arms and 45% in the randomized pola-BR arm. DOR was lower at 6.2 months for the pooled lyophilized arms compared to 12.6 months in the randomized pola-BR arm, however the data was noted to be immature at the time of analysis. Median PFS was also shorter at 6.1 months in the pooled lyophilized arms compared to 9.2 months in the pola-BR arm, whereas median OS was similar at 11.0 months and 12.4 months, respectively.		
Comparator	Relevant comparators	The comparator selected in the randomized phase II portion was bendamustine in combination with rituximab. The sponsor submitted a MAIC comparing pola-BR to pola-BR to R-GemOx,	Can the results of the trial be generalized comparing pola-BR to BR be generalized to commonly used	While there is uncertainty in the comparative evidence of pola-BR to other relevant comparators in clinical practice, BR would not be expected to be any worse than more commonly used treatments in clinical practice.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		pixantrone, tisagenlecleucel (Tisagenlecleucel), and axicabtagene ciloleucel (Yescarta). The sponsor also submitted a RWE study comparing standard of care therapies from patient data from an Alberta, Canada database to pola-BR. Both the MAIC and RWE studies had several limitations identified, resulting in significant uncertainty in the reported results.	comparators in Canadian clinical practice (i.e., certainty in the clinical benefit)?	
Outcomes	Appropriateness of primary and secondary outcomes	The primary outcome of the randomized phase II portion of the trial was CR rate and did not include prespecified statistical hypothesis testing between treatment arms. As such, secondary outcomes were not controlled for multiplicity. Secondary outcomes included ORR, DOR, PFS, and OS.	Were the selection of endpoints appropriate and of clinical relevance to this indication and therapeutic setting? Are there any concerns regarding the interpretation of results?	The endpoints selected were appropriate and of clinical relevance, however the limitations such as lack of control for multiple testing do introduce some uncertainty in the results. Overall, pola-BR does convincingly appear to have clinical benefit over BR as demonstrated in the trial.
Setting	Countries participating in the trial	The GO29365 trial was conducted in 54 centres in 12 countries including Canada, US, France, Spain, Australia, Czech Republic, Italy, Turkey, Great Britain, Hungary, Germany, Korea, and Netherlands. There were 4 Canadian sites, which included 44 Canadian patients.	Are there any known differences in the practice patterns between Canada and other countries that the trial was conducted in? Can the results be applied to Canadian patients?	The CGP does not anticipate significant differences in practice patterns between other participating countries and Canada due to the various treatment options and lack of standard of care in this patient population. The results can be applied to Canadian patients.

BR= bendamustine and rituximab combination; CGP=Clinical Guidance Panel; CR=complete response; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HSCT=hematopoietic stem cell transplantation; MAIC=matching adjusted indirect comparison; ORR=overall response rate; OS=overall survival; PFS=progression free survival; pola-BR=polatuzumab vedotin plus bendamustine and rituximab; R-GemOx= Rituximab, Gemcitabine, And Oxaliplatin; RWE=real-world evidence

Source: Sehn et al., 2020 [2]

1.2.4 Interpretation

Burden of Illness and Need

R/R DLBCL occurs in 30-40% of patients with DLBCL after first line treatment. [2] As previously discussed, salvage chemotherapy followed by ASCT is the standard approach for eligible patients, however this largely depends on age and PS, thus for a proportion of patients this is not a feasible treatment option. For transplant-ineligible patients, there is no standard treatment approach, and a number of chemotherapy approaches can be undertaken, none with a long-term curative intent. This represents more than 50% of the R/R population, but a proportion of these patients will be too unwell or comorbid to undergo any further treatment. Transplant-eligible patients who do not respond to salvage chemotherapy or relapse post-ASCT, which is up to 70% of such patients, also have

limited treatment options. Until recently, there were no good treatment options for such patients, and they were treated with palliative oral chemotherapy options or radiotherapy, with a prognosis of less than 3 to 6 months of life. Most recently, CAR T-cell therapy has become available to such patients, however this is a therapy that requires good PS and lymphoma burden that can last the several weeks it takes to manufacture cells for this therapy. As well, this therapy will be available in only select centres, thus many Canadians will have challenges in accessing this therapy in a timely manner or will not be eligible for it due to comorbidities, disease burden or PS. As such, treatment options that offer long term disease control for R/R DLBCL patients are limited.

Effectiveness

Polatuzumab vedotin when added to BR, demonstrated improved outcomes compared to BR alone in an open label RCT of 40 patients in each arm. The primary endpoint of the GO29365 trial was CR achievement, which was 40% in the pola-BR group vs. 18% in the BR group. Response rate as an outcome has some meaning in this disease, but only so if it translates into improved PFS and OS. Progression of DLBCL in the R/R setting is generally associated with a very poor prognosis, regardless of early response to a therapy. However, PFS and OS were compared as secondary outcomes, and the addition of polatuzumab prolonged the IRC-determined PFS from 3.7 months to 9.5 months, with a median DOR of 12.6 months for pola-BR compared to 7.7 months for BR. As an exploratory outcome, median OS was 12.4 months with pola-BR vs. 4.7 months with BR, corresponding to a HR of 0.42. This trial did combine two populations of patients; patients could enter the trial after just 1 line of therapy, which usually would be patients who are transplant-ineligible, or after 2 lines of therapy, which would include those who are refractory to salvage chemotherapy/progressing post-ASCT. It's possible the prognosis of these populations of patients and potential chemo-responsiveness is different. The median age of trial participants was 69 years of age, which suggests a slightly older patient population, and one third of the patients had only received 1 previous line of therapy. However, the majority of the patients were refractory to their previous treatment, which does support a high-risk group, even if only post-one line of therapy. [2]

This was an RCT, however, due to the small sample size, there were imbalances in the baseline characteristics of the two groups. Less patients in the pola-BR group had bulky disease (25% vs. 38%), were refractory to prior therapy (75% vs. 85%) and had high IPI risk at baseline (23% vs. 43%). The primary reasons for transplant ineligibility allowing for participation in this trial were different between the arms as well (age: 33% vs. 48%; inadequate response to salvage chemotherapy: 30% vs. 22%; failure of previous ASCT: 25% vs 15%). [2] It is hard to determine if these imbalances favoured one particular arm over the other. However, this adds significant uncertainty to the data and outcomes results, and as such its generalizability to real-world patients.

The choice of BR as the standard comparator is not the SOC in most jurisdictions. However, there is no other clear SOC chemotherapy regimen and the median PFS achieved of 7.7 months is comparable to other datasets of median PFS expectations in this patient population. To try and address this, both a MAIC and real-world analysis comparison using Canadian patient data, were undertaken. Both these analyses have major limitations that hinder their potential applicability and interpretation. There are many potential comparators from mostly phase II trials, retrospective analyses, or phase III trial data that are outdated. They chose to use four comparators: R-GemOx, pixantrone, tisagenlecleucel and Yescarta, each using a single-arm study for the comparator. The R-GemOx and pixantrone are more relevant comparators for the transplant-ineligible group who may have gone on trial after 1 line of therapy, while tisagenlecleucel and Yescarta are applicable comparators for the patients who have had at least two lines of therapy, including those who have failed ASCT. The studies included identified large differences in study populations and baseline criteria even after matching, and the numbers of patients were small, and thus the results are unhelpful, with too much uncertainty attached. The CAR T-cell therapy comparator is problematic as it represents a treatment that is complex and includes bridging therapy, with eligibility limitations, which is quite a different population from the pola-BR study. Thus, this comparison cannot overcome the limitations inherent in the weak and sparse evidence base.

The clinical trial data were also compared to a real-world cohort of 50 R/R DLBCL patients from Alberta, Canada, in a PSWA. However, even after matching, differences remained between the 2 groups given the small size of the RW cohort. An OS survival difference was identified pre- and post-weighing of variables, with a weighted OS of 13.3 months in the pola-BR group vs. 5.6 months in the RWD group. These values are similar to the trial differences, however, are still difficult to interpret, as the groups may not be comparable.

Overall, it does appear pola-BR improves outcomes in this population of patients, compared to other available options, which are limited in these patients. The magnitude of this benefit beyond the direct comparison to BR is difficult to measure. However,

considering there is no one single SOC treatment regimen for these patients, and unlikely that one chemotherapy regimen is significantly better than another, the BR outcomes are reasonable as a baseline comparator.

Safety

Side effects are manageable and as expected in this pre-treated population and given the mechanism of action of the drug. Anemia and neutropenia are more common as is diarrhea, which is expected when treating with three drugs instead of two. However, transfusion rates were similar between the two groups, as were grade 3-4 febrile neutropenia episodes (10%), which is acceptable in this R/R population. Use of granulocyte colony stimulating factor (G-CSF) was permitted as per the treating physician, and the majority of patients in both arms (62-72%) received at least one dose. Peripheral neuropathy was also more common in the pola-BR group (44% vs. 8%), the assessment of its impact by the TINAS instrument was limited by the amount of missing data (less than 50% of patients completed it at baseline, with further decreased participation over time). Unfortunately, this was the only patient reported outcome measure collected. However, both two patients who had polatuzumab dose reductions, did so for neuropathy, and in both cases, it resolved. All cases in the polatuzumab arm were grade 1 or 2, and 11/17 resolved or improved when treatment was completed. Thus, this is likely a meaningful side effect, however it's encouraging that there were no severe cases, and since this is time-limited treatment, it is likely acceptable and does seem to resolve when treatment is completed. Tumour lysis syndrome was not a significant challenge in this patient population and standard management approaches appear to be adequate.

Treatment discontinuation was higher in the pola-BR arm (31% vs 15%), mostly due to increased AEs, which are not further defined, though some may be protocol defined cytopenias, which are not as clinically significant in real world use, as more impactful AEs such as febrile neutropenia and fatigue, were not significantly different. The difference in peripheral neuropathy rates did not seem to lead to increased discontinuation in the polatuzumab treated patients. Dose reductions occurred with 18% of patients in the pola-BR group and 10% of patients in the BR group and dose interruptions with 51% of pola-BR and 38% with BR alone, but once again, some of that was likely protocol mandated for cytopenias. Dose intensity was high in the patients that remained on treatment (>90%), and a higher proportion of Polatuzumab-BR treated patients completed 6 cycles (46.2% vs. 23.1%), due to less lymphoma progressions. The number of fatal AEs were comparable between the two groups, mostly due to infections. [2]

1.3 Conclusions

The CGP concluded that there may be a net clinical benefit to pola-BR in the treatment of R/R DLBCL, but there is insufficient evidence on which to evaluate this. The CGP based this conclusion on the fact that there is only 1 trial with a limited sample size comparing polatuzumab when added to BR, compared to BR alone, which is not necessarily considered the SOC comparator in this population. However, there are no other RCTs or other strong cohort data establishing a SOC option in this difficult to study population. Key outcomes in this patient population, such as PFS and OS, were exploratory and the study was not powered for these analyses, and as such some of the findings may be due to statistical chance. However, it is likely that pola-BR improves outcomes in these patients, but the magnitude of this improvement is uncertain.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
PAG raised the relevance of BR as a comparator as BR is not a standard treatment or publicly funded regimen for R/R DBLCL in Canada.	There is no clear SOC for R/R DLBCL in most jurisdictions, and median PFS of BR (3.7 months) was considered generally comparable to other datasets of median PFS expectations in this population. Thus, the CGP considers the choice of comparator as acceptable.
PAG seeks an additional comparison of pola-BR to other chemoimmunotherapies (e.g., rituximab-chemo) used in Canada and to CAR T-cell therapies.	The sponsor submitted two indirect treatment comparisons. The first was a MAIC comparing pola-BR to R-GemOx, pixantrone, tisagenlecleucel (Tisagenlecleucel), and axicabtagene ciloleucel (Yescarta). The second was a RWE study comparing individual patient data from the GO29365 trial to patient data from an Alberta, Canada database, which was generally representative of the mix of SOC treatments that would be seen across jurisdictions in Canada. Both the MAIC and the RWE study had a number of limitations making the results difficult to interpret, and as such, limited conclusions can be drawn for the comparison of pola-BR to other chemoimmunotherapies and to CAR T-cell therapies. Given the numerous treatment regimens used in this patient population, it is unlikely one is significantly better than another, and pola-BR appears to improve outcomes in patients in the phase Ib/II trial, which is one of the few randomized trials in this patient population. However, in the absence of strong direct or indirect comparative evidence, the magnitude of the pola-BR benefit to other therapies that may be used more frequently in this patient population remains unknown.
Eligible Patient Population	
PAG is seeking clarity on whether the following patients would be eligible for treatment with pola-BR: • Pediatric patients • Patients with prior ASCT • Patients who progressed on prior treatment with CAR T-cell therapy • Patients who failed prior ASCT vs patients who were not eligible	• Pediatric patients: Pediatric patients were not included in the trial, and thus would not be eligible for pola-BR. • Prior ASCT: Patient with prior ASCT were eligible for the GO29365 trial, and would be eligible for pola-BR. • Progression on CAR-T: Patients with prior CAR T-cell therapy were eligible for the trial, and thus would be eligible for pola-BR. Failed or ineligible for ASCT: Per the inclusion criteria, patients who were ineligible or failed ASCT were eligible for the trial, and thus would be eligible for treatment with pola-BR.
PAG identified additional exclusion criteria in the study, notably patients with transformed follicular	While patients with transformed follicular lymphoma to DLBCL and those with HIV-related aggressive histology lymphoma were excluded, the CGP

PAG Implementation Questions	CGP Response
lymphoma to DLBCL, patients with CNS lymphoma and HIV-related aggressive histology lymphoma. PAG would like to know if all these criteria need to be met for eligibility to pola-BR reimbursement.	noted it should be in the judgment of the clinician to treat these patients, as otherwise generally eligible for same treatment approaches as other aggressive B cell lymphoma patients. The CGP further noted that those with active CNS lymphoma would not be eligible for treatment.
If pola-BR was recommended for reimbursement, PAG noted that patients currently on alternate therapies for R/R DLBCL who are not progressing as well as patients who just started second line therapy would need to be addressed in a time-limited basis.	Patients on alternate therapy could be switched to pola-BR within a reasonable time frame in the judgment of the treating clinician. CGP noted that pola-BR would still be an option upon progression for R/R DLBCL patients.
PAG noted potential indication creep to using pola-BR in R/R DLBCL as a bridge to a SCT or CAR-T, R/R DLBCL who are not ineligible for transplant, previously untreated DLBCL patients in first line, and other aggressive non-Hodgkin lymphoma histologies (e.g., Burkitt, Primary Mediastinal B Cell Lymphoma, Grey Zone Lymphoma).	There is no evidence to inform indication creep to first line, however the CGP noted that pola-BR could potentially be used as bridge and for non-Hodgkin lymphoma in clinical practice although there is no evidence to inform the use of pola-BR in this way.
Implementation Factors	
PAG seeks advice on: • Treatment duration • Discontinuation criteria • Feasibility of combining polatuzumab with other chemotherapies or chemoimmunotherapies.	• Treatment duration: Patients should be treated for up to 6 cycles as per the product monograph. • Discontinuation criteria: Patients should be treated for up to 6 cycles in the absence of unacceptable toxicities. • Combining polatuzumab vedotin with other chemotherapies or chemoimmunotherapies: Polatuzumab vedotin in combination with other therapies have not been studied and/or are currently ongoing, so currently polatuzumab vedotin shouldn't be combined with other therapies.
In addition, needle and syringe are outlined in the product monograph for preparation. PAG is seeking clarity on whether this is compatible with needle-less systems or closed system transfer devices.	Following clarification with the sponsor, the use of closed system transfer devices is not described in the approved labeling or package insert; therefore, no recommendation can be made regarding the use of and type of closed system transfer device to be used with polatuzumab vedotin. Use of closed system transfer device is left to the discretion of the healthcare provider.
PAG is seeking clarity that standard management for tumor lysis syndrome applies in this setting.	Standard management for tumor lysis syndrome would apply in this setting.
PAG noted that since obinutuzumab was an option in the phase Ib/II trial, PAG is seeking clarity on whether obinutuzumab is an option for patients who experienced severe infusion-related reactions in response to rituximab.	The pivotal trial included arms in the phase Ib and phase II portion (non-randomized expansion) that studied R/R DLBCL patients treated with polatuzumab vedotin in combination with bendamustine and obinutuzumab. While the detailed methodology and reported results were not critically appraised or reviewed in detail, the CGP considered obinutuzumab to be a reasonable substitution to rituximab for patients who are intolerant to rituximab.
Sequencing and Priority of Treatments	

PAG Implementation Questions	CGP Response
PAG is seeking to confirm the place in therapy and sequencing with pola-BR including the scenarios below: • Options after failure of pola-BR including anti-CD19 CAR-T • Use of pola-BR as bridge to CAR-T. If appropriate, can bendamustine be omitted to avoid depleting T-cells? • Number and types of prior therapies that should be attempted before offering pola-BR • If BR is not tolerated, switching to polatuzumab plus other chemoimmunotherapies	• Options after failure on pola-BR: Treatment options after progression on pola-BR should be up to the treating clinician, however options such as anti-CD19 or CAR T-cell therapies could be considered. • Use of pola-BR as a bridge to CAR T-cell therapy and omitting bendamustine: pola-BR could be used as a bridge to transplant and bendamustine can be omitted if appropriate based on clinical judgement. However, there is no evidence to support its use in this way. • Number and types of prior therapies: Consistent with the trial, patients who were R/R after at least one prior line of therapy and are transplant ineligible would be eligible for pola-BR. • Switching to polatuzumab plus other chemoimmunotherapies if BR is not tolerated: There is no evidence to support the safe use of polatuzumab in combination with other chemoimmunotherapies.

ASCT = autologous stem cell transplant; BR = bendamustine and rituximab; CAR T-cell therapy= Chimeric antigen receptor T cell therapy; CGP = Clinical Guidance Panel; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; HIV = human immunodeficiency virus; ITC=Indirect Treatment Comparison; MAIC = matching-adjusted indirect comparison; pola = polatuzumab; PAG = Provincial Advisory Group; PFS = progression-free survival; R/R = relapsed or refractory; R-GemOx = rituximab, gemcitabine, and oxaliplatin; RWE = real-world evidence; SCT= Stem Cell Transplant; SOC = standard of care

2 Background Clinical Information

2.1 Description of the Condition

Non-Hodgkin lymphoma (NHL) is a cancer of the immune system that encompasses more than 60 types of lymphoma.[10] The projected incidence of NHL was 8300 cases annually, with an age-standardized incidence rate of 20.8 cases per 100,000 Canadians.[11] DLBCL is an aggressive form of NHL that constitutes approximately 30% of lymphoma cases in Canada.[12,13] Molecular subtypes with prognostic implications have been identified, with an activated B cell type (ABC) being associated with inferior prognosis compared to the germinal centre B cell like (GCB). Double-hit lymphoma (concurrent translocations of MYC and either BCL2 or BCL6) is a particularly aggressive, high risk subtype with poor prognosis.[14,15] Double-expressor lymphoma (overexpression of MYC and BCL2), is not considered a separate entity, but has also been associated with worse prognosis.[16]

In Canada, after therapy with standard first-line chemotherapy with RCHOP or a similar regimen, the longer-term survival is about 60%. [14,17,18] Unfortunately, 30%–40% of patients will experience refractory disease or will relapse and require subsequent treatment.[14,19]

Eligible patients with R/R disease post-first line therapy are treated with salvage chemotherapy followed by high-dose therapy (HDT) and ASCT. [14,20,21,22] However, eligibility for this salvage approach does largely depend on performance status, age, and comorbidities, and eligibility for ASCT is also dependent on the response to salvage chemotherapy. [23, 24] Half (50%) of patients starting on salvage chemotherapy become ineligible for ASCT due to inadequate response,[25] and of those patients who proceed to ASCT, more than 50% will ultimately relapse.[23,26] Only 30% of patients treated in recent prospective trials involving salvage therapy and ASCT achieved long-term remission.[25,27] Population-based studies in Canada and Denmark have demonstrated that up to half the patients with R/R DLBCL are treated palliatively. [28,29]

Until recent evidence and approval of CAR-T therapy,[30,31,32] treatment for patients not eligible for ASCT or who have relapsed after ASCT had been largely palliative, with median survival being approximately 6 months.[33]

Patients for whom initial therapy fails have a poor prognosis and particularly patients who are ineligible for salvage therapy or transplantation, and patients who have relapsed after ASCT, do represent a critical unmet need.

2.2 Accepted Clinical Practice

Patients with R/R DLBCL have limited treatment options, ranging from supportive care to conventional salvage therapy and ASCT, with the choice of therapy depending on age and comorbidities. Patients who are not candidates for ASCT due to comorbidities, age or functional status are usually treated with palliative intent and could receive sequential single- or multi-agent therapy depending on tolerance, however none consistently offers long term survival. There is no standard palliative approach, however Alberta guideline provides a list of recommended potential chemotherapy regimens, including DHAP (dexamethasone–cisplatin–cytarabine), GDP (gemcitabine–dexamethasone–cisplatin), CEPP (cyclophosphamide–etoposide–prednisone–procarbazine), and MEP (mitomycin C–etoposide–cisplatin)12. GDP for patients who can tolerate is commonly used as it is an outpatient regimen, however as patients get older, it is too toxic. An alternative, gentler regimen is GemOx, though less popular in Canada.[34] Other options commonly used in this palliative setting are oral cyclophosphamide or etoposide and prednisone. Involved-field radiotherapy has a limited role in patients with R/R DLBCL, although it can be useful to palliatively treat symptomatic sites.

Similarly, in patients who do not respond to standard salvage therapy (most commonly GDP) or who relapse after HDT or ASCT, few treatment options are available. As above, a number of salvage chemotherapy regimens can be tried, however none provide long term remissions.

Novel therapies have been studied in phase II studies in these setting, however with modest success. Clinicians may compassionately access some of these treatments, such as lenalidomide, ibrutinib, brentuximab vedotin or pembrolizumab, on a case-by-case basis, however none have been shown to truly impact the prognosis of these patients. In such cases, clinical trials are highly recommended when feasible. Regardless of the approach, outcomes remain poor, [33] with median survival of six months.

The development of CAR T-cell therapy has opened up a novel and promising approach for R/R DLBCL. [30,31,32] It is currently approved for patients who have failed two or more lines of therapy, thus it would not be a relevant comparator for the transplant ineligible population after 1 line of therapy. As well, there are several limitations to its wide availability for the patient population who has failed 2 lines of therapy or more. Given the aggressive nature of R/R DLBCL, patients with uncontrollable disease might be unable to wait the required length of time to be seen at a specialized centre and to manufacture the cells. Such patients might need bridging therapy, the success of which can be limited in these highly refractory patients. CAR T-cell therapy has unique toxicities and may still not be appropriate for patients with comorbidities and impaired performance status. Access to CAR T-cell therapy in Canada currently remains limited, as there is infrastructure and expertise required for delivery of therapy and management of potential toxicities. As a result, travel constraints, resource limitations, and provincial funding restrictions could limit the number of patients who ultimately have access. Finally, most patients currently receiving CAR T-cell therapy will experience disease progression and will require further treatment.

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers an anti-mitotic agent (MMAE) to B-cells, which results in the killing of malignant B-cells. Polatuzumab vedotin received an initial Health Canada NOC/c on July 9th, 2020, for the treatment of adult patients with R/R DLBCL, not otherwise specified, who are not eligible for ASCT and have received at least one prior therapy, pending the results of trials to verify its clinical benefit.[1] This report focuses on the evidence from the GO29365 phase Ib/II trial, which evaluated the use of pola-BR compared to BR in adult patients with previously treated DLBCL.[2]

3 Summary of Patient Advocacy Group Input

Lymphoma Canada (LC) provided input for the review of pola-BR for the treatment of adult patients with R/R DLBCL, not otherwise specified, who are not eligible for ASCT and have received at least one prior therapy. Their input is summarized below.

LC provided input from two online surveys of DLBCL patients: those without experience with pola-BR, and one in patients with pola-BR experience. Surveys were conducted between April 18, 2018 to June 15, 2018 and from August 31, 2020 to October 5, 2020, respectively. Given the treatment stage for which pola-BR is indicated, LC noted significant difficulty in recruiting patients for this population. Survey participants were recruited via email to patients registered on the LC database as well as through multiple social media channels. Survey questions consisted of multiple choice, rating, and open-ended questions. Skipping logic was integrated into the surveys; therefore, respondents were only asked questions relevant to them.

A brief summary of the patient demographic characteristics for survey respondents is provided in Table 4. A total of 114 patients responded to both surveys (107 without, and 7 with pola-BR experience). The majority of patients lived in Canada (82%), were female (53%) and were greater than 60 years of age (48%).

Table 4: Demographic Characteristics of Survey Respondents

Patient Characteristics	Survey 1: Patients without pola-BR Experience (n = 107)	Survey 2: Patients with pola-BR experience (n = 7)
Age		
<20	2	0
20-39	12	0
40-59	32	0
≥60	51	4
Skipped	10	3
Gender		
Female	60	0
Male	37	4
Skipped	10	3
Country		
Canada	87	7
USA	8	0
Other	2	0
Skipped	10	0

From the patient perspective the most debilitating physical symptoms associated with DLBCL and treatment included fatigue, enlarged lymph nodes, drenching night sweats, weight loss, loss of appetite, flu-like symptoms, and persistent cough. Aside from the physical effects of the disease and treatment, DLBCL patients also experienced mental and emotional stress including fear of disease recurrence, memory loss, anxiety, problems concentrating, difficulty sleeping, loss of sexual desire, stress of diagnosis, and depression. Overall, 86% of patients reported symptoms that negatively impact their quality of life (QoL). LC noted that, given the age of patients with DLBCL in the surveys, the disease and associated treatments can have a severe impact on daily life. fifty-five percent of respondents reported a negative impact on their ability to work and cited early retirement and no finances or income as major sources of life-altering stress and limitation.

Chemoimmunotherapy with R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) was the most commonly reported first-line treatment option, which was received by 83% of respondents as first-line therapy. Other options (second line or beyond) included ASCT or allogeneic stem cell transplants. The most commonly side effects of DLBCL treatment reported by more than 50% of responders included hair loss, fatigue, memory problems/confusion, neutropenia, and nausea. Patients stated that their

associated fatigue so is impactful that they are unable to exert themselves beyond the minimum and do very little around the house in order to ensure they have enough energy for work.

Respondents with pola-BR experience noted that the dosing schedule of pola-BR was better than other chemotherapy treatments as the number of treatments was reduced. The side effect profile of pola-BR was also noted to be no worse than currently available treatments for DLBCL, with patients noting that side effects were minimal compared to the results obtained. The most commonly reported side effects were nausea and fatigue. Patients also noted that these AEs are also the most difficult side effects to tolerate in the DLBCL treatment. Despite this, patients rated "fewer side effects" as the least important outcome when they were asked about their expectations regarding a new treatment option, whereas improved survival and remission were the most important treatment values. Patients noted that they would be willing to accept treatments with undesirable side effects if recommended by their physician. Overall, patients considered pola-BR to be an acceptable treatment option, offering improved overall physical and mental well-being.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

From the patients' perspective, the most commonly reported symptoms affecting QoL at the time of their diagnosis included lack of energy or fatigue (69%), enlarged lymph nodes (48%), night sweats (36%), weight loss (29%), loss of appetite (25%), flu-like symptoms, and persistent cough (18% each). Other symptoms including itching, chest pain, and trouble breathing affected ≥10% of patients' QoL.

A total of 86% of respondents indicated that at least one symptom had negatively impacted their QoL. With regards to their disease and treatment, the following symptoms were reported to have a negative impact on mental and emotional well-being and QoL: fear of disease recurrence (67%), memory loss (39%), anxiety/worry (38%), problems concentrating (38%), difficulty sleeping (29%), loss of sexual desire (26%), stress of diagnosis (19%), and depression (16%).

Patients with DLBCL also noted that the disease had had a negative impact on different aspects of their day-to-day life. Ability to work and family obligations were cited as the aspects of daily life that have been negatively impacted the most, affecting 55% and 45% of respondents, respectively. Other aspects of daily life that are negatively impacted include personal image (39%), intimate relations (30%), friendships (24%) and ability to attend school (3%).

The following quotes from patients with DLBCL demonstrate the impact of the disease on QoL, particularly daily activities and mental/emotional health status:

"[Fear of disease recurrence] is very high and consumes a lot of my thought process almost every day. Even after two years since my Chemo treatments finished and I had a complete response."

"I retired early due to memory loss, lack of concentration and ongoing depression."

"It affected our personal lives my husband had to stay home from work to help me. We had no income. Very stressful. Our community did a couple benefits which helped us pay our bills. Big life changer for sure."

"It has limited my work options; had to transition to work at home and changing the type of work which is not meeting my prior financial income. It has limited my ability to do routine daily chores around the home at times and I can only perform limited exercise due to fatigue."

3.1.2 Patients' Experiences with Current Therapy

A total of 103 respondents indicated their prior experience with treatments for DLBCL. All respondents had received, or were currently receiving at least one line of therapy, with of half of them receiving ≥2 or > 3 lines of treatment (48% and 8%, respectively). Chemoimmunotherapy consisting of R-CHOP was the most commonly reported first-line treatment among respondents (83%). Of

those who received more than one line of treatment, 24% had undergone an ASCT and 5% had undergone an allogeneic stem cell transplant.

Table 5 lists the most common treatment-related side effects reported by 103 respondents, Notably, hair loss fatigue, memory problems or confusion, neutropenia, and nausea were reported by more than half of the respondents.

Table 5: Treatment Related Side-Effects

Side effects from treatment (103 respondents)					
Side effect (n)	**% of respondents**	**Side effect (n)**	**% of respondents**	**Side effect (n)**	**% of respondents**
Hair loss (90)	87%	Mouth sores (45)	43%	Trouble breathing (23)	22%
Fatigue (87)	84%	Thrombocytopenia (37)	36%	Cough (23)	22%
Memory problems or confusion (70)	68%	Infections (34)	35%	Skin rashes/severe itching (22)	21%
Neutropenia (67)	65%	Anemia (32)	31%	Loss of menstruation (18)	17%
Nausea (61)	59%	Diarrhea (27)	26%	Irregular heartbeat (15)	15%
Constipation (49)	48%	Pain (27)	26%	Viral reactivation (7)	7%
Peripheral neuropathy (48)	47%	Other (24)	23%	Bowel obstruction (7)	7%

The side effects reported as most difficult to tolerate by 85 respondents included fatigue (41%), nausea/vomiting (19%), chemo-brain (15%), and hair loss (9%).

With regards to the impact of treatment on QoL and daily life, patients indicated that fatigue and other side-effects had the most significant negative impact on their QoL (Table 6). Patients also noted that the number of clinic visits, infusion time and reactions, as well as number of infections negatively impacted their QoL. Patients indicated that DLBCL treatment also had a very significant impact on ability to work, travel, participate in daily activities, as well as affecting relationships with family and friends (Table 7).

Table 6: Impact of Treatment on Quality of Life

Impact of treatment on quality of life (101 respondents)			
Treatment aspect	**Weighted average**	**Significant negative impact (rating = 4-5)**	**Number of responses**
Fatigue	3.6	59%	101
Side-effects	3.4	53%	100
# of clinic visits	2.3	21%	100
Infusion time	2.3	20%	98
Infusion reaction	2.2	19%	99
# of infections	1.9	19%	98

Table 7: Impact of Treatment on Daily Living

Impact of treatment on daily living (95 respondents)			
Activity	**Weighted average**	**Significant negative impact (rating = 4-5)**	**Number of responses**
Work	4.0	61%	94
Travel	3.9	64%	94
Activities	3.9	69%	94
Intimate relations	3.3	45%	92

Impact of treatment on daily living (95 respondents)			
Activity	**Weighted average**	**Significant negative impact (rating = 4-5)**	**Number of responses**
Family	2.9	36%	91
Friendships	2.5	23%	93
School	2.1	6%	85

Notably, the following quotes indicate the impact of treatment on QoL and daily life:

"I needed to make extra visits to emergency or to the clinic between treatments as a result of fever. Eventually I was given neupogen injections after treatments to keep my white blood cells at a better level (these were daily in my home for several days - impact, had to be home)"

"Learning to not to push myself with physical activity ie yard work, house reno etc. Not taking on extra duties at work, and possibly retiring early in age"

"There is always some stress getting time off work to attend check-ups with oncologist. I am tired after work so I do very little during the work week to make sure I will have enough energy for my job."

Given that patients' work lives are significantly impacted by their disease and treatment, the resulting financial implications lead to mental and emotional hardship, and uncertainty, as evidenced by the following patient quotations:

"Had to give up a new career and job to have treatment"

"I was unable to continue working so I had to retire early, and therefore I lost my salary and health benefits"

When asked about the financial implications of treatment, close to half of the 85 respondents from Canada (47%) reported that their absence from work or school impacted them financially (Table 8). A number of respondents also indicated that there were no additional financial implications (24%) of DLBCL treatment.

Table 8: Financial Implications of Treatment

Financial implications of treatment for DLBCL patients in Canada (85 Canadian respondents.)		
Financial impact	**% of respondents**	**Number of respondents**
Absence from work or school	47%	40
Cost of medications	33%	28
None	24%	20
Travel	13%	11
Other	13%	11
Accommodation	8%	7
Drug administration supplies	4%	3
Clinical trial charges	0%	0

3.1.3 Impact on Caregivers

None to report. There were no caregiver respondents to the survey. One patient quote indicated that their husband had to stay home from work to help, impacting their income.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Respondents were asked about the most important factors they valued in a new drug or therapy for DLBCL. The top-rated factors were longer survival and longer remission than current therapies, rated "extremely important" by 89% and 86% of patients,

respectively; followed by better QoL, rated “extremely important” by 76% of patients. Fewer side effects were rated as the least important outcome, overall (rated “extremely important” by 55% of patients). As many as 46% of survey respondents indicated that they would be willing to tolerate the side effects of a new treatment if they were short term events. Half of the respondents (50%) indicated that they would choose a doctor-recommended treatment with known side effects, even if they were potentially serious. The majority of the remaining respondents were unsure (46%).

3.2.2 Patient Experiences to Date

As noted above, only seven respondents indicated that they had experience with pola-BR for DLBCL. Patients in the second survey were diagnosed with DLBCL between 2009 and 2018, and most received CHOP-R as first-line therapy. Other therapeutic agents received by patients in this survey included SCT, CDOP ± R (cyclophosphamide, doxorubicin, vincristine, prednisone with or without rituximab), GDP ± R (Gemcitabine, Cisplatin, and Dexamethasone with or without rituximab), radiation therapy, HDT (high-dose therapy) regimen, auto-transplant, and CAR T-cell therapy. All patients received pola-BR in 2020, with the majority receiving treatment through a clinical trial, and the rest accessing pola-BR through a private program. All patients except one were currently in remission at the time of the survey.

Below are some patient comments regarding their experience with pola-BR:

“I’ve had so many treatments that didn’t work, but this one finally did*!”* and *“pola-BR was the best thing that could have happened to me; I am so happy to have been able to receive it.”*

“With every cycle of pola-BR, I felt better and better. I can finally breathe again.” and *“I am now doing everything I used to, golfing, fishing, and gardening. My two daughters are so incredibly happy to have their dad still in their life.”*

“The side effects related to this treatment are so minimal compared to the result obtained.”

“My previous chemo treatment was not effective at treating my lymphoma.”

Two of the seven patients did not experience any side effects with pola-BR. Nausea and fatigue were the most commonly reported side effects of pola-BR therapy, which are common with all chemotherapy regimens. Other side effects experienced while taking pola-BR included neutropenia, thrombocytopenia, low blood pressure, loss of taste, rash and peripheral neuropathy. Only one patient required hospitalization to manage side effects and two patients experienced nausea that lasted longer than two months. One patient commented: *“The side effects were not as bad compared to other chemotherapies and treatments for DLBCL that I had in the past.”*

Questions aimed at rating the impact of pola-BR on QoL were answered by three patients. Responses suggested that treatment with pola-BR did not have a significant negative impact on patient QoL, with the most negative impact arising from travel to treatment centers, low activity levels, and treatment-related fatigue (weighted average of 2.3; where 1 = no negative impact, and 5 = significant negative impact). Despite this, one patient commented the following: *“This [pola-BR] was 1 treatment every 3 weeks. Not bad compared to other chemotherapy treatments where I had to go in 3 times a week for treatment.”*

Four of five patients stated their physical health and QoL improved with pola-BR treatment. Three respondents indicated their mental health improved by being able to do things they were not able to do before and while on treatment, and two stated their mental health remained unchanged with pola-BR therapy. One patient commented: *“I like being occupied and doing a lot, and this treatment gave me back the ability to do this.”*

Overall, when asked about pola-BR, patients described their experience as good to excellent, and would take the treatment again if it was necessary. All patients reported that they would recommend pola-BR as a therapy to others with DLBCL, citing *“I have already told other patients in my support group about this therapy”*, and *“Yes, would recommend this to other patients, very much so! pola-BR treats cancer well and I don’t have cancer anymore, I am physically and mentally well.”*

3.3 Companion Diagnostic Testing

None to report. There is no companion diagnostic test for pola-BR.

3.4 Additional Information

None to report.

4 Summary of Provincial Advisory Group (PAG) Input

The PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the CADTH website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pola-BR for R/R DLBCL:

Clinical factors:

- Numerous clinical eligibility criteria
- Criteria for discontinuation of therapy
- Sequencing with other therapies including CAR-T

Economic factors:

- BR is not funded across all jurisdictions

Please see below for more details.

4.1 Currently Funded Treatments

There is no SOC for R/R DLBCL. Among transplant-eligible patients with R/R DLBCL, systemic chemotherapy with or without rituximab with plans to proceed to high-dose chemotherapy and ASCT is an option.

In transplant ineligible patients with R/R DLBCL who failed to respond to upfront chemotherapy regimens, or for those who relapsed after ASCT, there are various alternate chemotherapies with or without rituximab available including R-GDP, PEP-C (prednisone, etoposide, procarbazine and cyclophosphamide), R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin), R-DICEP, (rituximab, dose-intensive cyclophosphamide, etoposide, cisplatin) and R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone). Other therapies (e.g., lenalidomide, brentuximab vedotin, ibrutinib) may be used in exceptional circumstances and/or experimental settings. PAG noted that not all agents are funded across all jurisdictions.

PAG acknowledged the possibility that CAR T-cell therapy may be a relevant comparator provided patients do not receive prior allogenic SCT, have no active Central Nervous System (CNS) disease, are not HIV-positive, and if the reimbursement request is intended for the use of pola-BR after two or more lines of systemic treatment. PAG noted that CAR T-cell therapy may be offered as an alternate line of treatment.

The GO29365 phase Ib/II trial assessed polatuzumab vedotin combined with bendamustine and obinutuzumab (BG) and pola-BR compared to BR alone. PAG recognizes that the trial includes data on polatuzumab vedotin in combination with BG, however, the reimbursement request submitted by the sponsor is for pola-BR. Furthermore, PAG raised the relevance of BR as a comparator as BR is not a standard treatment or publicly funded regimen for R/R DBLCL in Canada. PAG seeks an additional comparison of pola-BR to other chemoimmunotherapies (e.g., R-chemotherapy) used in Canada and to CAR T-cell therapies.

4.2 Eligible Patient Population

The reimbursement request is for pola-BR for the treatment of adult patients with R/R DLBCL, NOS, who are not eligible for ASCT and have received at least one prior therapy. In view of the characteristics of the patient population and exclusion criteria in the phase Ib/II trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with pola-BR.

- Pediatric patients
- Patients with prior ASCT

- Patients who progressed on prior treatment with CAR T-cell therapy
- Subgroups: efficacy in patients who failed prior ASCT vs patients who were not eligible

PAG identified additional exclusion criteria in the study, notably patients with transformed follicular lymphoma to DLBCL, patients with CNS lymphoma and HIV-related aggressive histology lymphoma. PAG would like to know if all these criteria need to be met for eligibility to pola-BR reimbursement.

If pola-BR was recommended for reimbursement, PAG noted that patients currently on alternate therapies for R/R DLBCL who are not progressing as well as patients who just started second line therapy would need to be addressed in a time-limited basis.

PAG noted potential indication creep to using pola-BR in R/R DLBCL as a bridge to a SCT or CAR-T, R/R DLBCL who are not ineligible for transplant, previously untreated DLBCL patients in first line, and other aggressive NHL histologies (e.g., Burkitt, Primary Mediastinal B Cell Lymphoma, Grey Zone Lymphoma).

4.3 Implementation Factors

Polatuzumab vedotin is available in 140 mg single-use vials. The recommended dose of polatuzumab vedotin is 1.8 mg/kg administered as an IV infusion every 21 days in combination with BR for 6 cycles. pola-BR can be administered in any order on day 1 of each cycle. The recommended dose of bendamustine is 90 mg/m^2/day on day 1 and 2 when administered with polatuzumab vedotin and rituximab. The recommended dose of rituximab is 375 mg/m^2 on Day 1 of each cycle. Polatuzumab vedotin is an IV drug that would be administered in an outpatient chemotherapy center; however, in some areas, some patients may need to travel far to an outpatient chemotherapy center, which would be a barrier for these patients. Moreover, as polatuzumab vedotin dosing is weight-based, PAG has concerns for incremental costs due to drug wastage, specifically in smaller centers where vial sharing may be difficult.

PAG seeks advice on treatment duration, discontinuation criteria as well as feasibility of combining polatuzumab vedotin with other chemotherapies or chemoimmunotherapies. PAG noted polatuzumab vedotin as an add-on to chemoimmunotherapy which implies additional resource requirements for drug preparation and administration (e.g., increased nursing resources, chair utilization), monitoring of infusion site reactions and adverse effects (e.g., peripheral neuropathy and tumour lysis syndrome). Additional resources would be required to monitor, manage and treat AEs, and to support increased frequency of clinic visits, bloodwork, preparation of supportive drugs such as G-CSF and ophthalmologist consults. There are some patients that may require the prophylactic use of G-CSF.

While there is a concentration range for polatuzumab vedotin of 0.72 to 2.7 mg/mL in the product monograph, PAG noted the need to determine the bag size for a target range of usual doses to ensure these are within this range. In addition, needle and syringe are outlined in the product monograph for preparation. PAG is seeking clarity on whether this is compatible with needle-less systems or closed system transfer devices. Furthermore, PAG noted an added workload on the pharmacy of patients that require transportation of the prepared solution. In the product monograph, infusion reactions can occur within 24 hours after infusion. While no monitoring system is required, PAG recognizes that patient education would be needed so that patients are informed of what to do if they experience a reaction after they leave the cancer centre. PAG is seeking clarity that standard management for tumor lysis syndrome applies in this setting.

PAG noted that since obinutuzumab was an option in the phase Ib/II study trial, PAG is seeking clarity on whether BG is an option for patients who experienced severe infusion-related reactions in response to rituximab.

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the place in therapy and sequencing with pola-BR including the scenarios below:

- Options after failure of pola-BR including anti-CD19 CAR-T
- Use of pola-BR as bridge to CAR-T. If appropriate, can bendamustine be omitted to avoid depleting T-cells?
- Number and types of prior therapies that should be attempted before offering pola-BR

- If BR is not tolerated, switching to polatuzumab vedotin plus other chemoimmunotherapies

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of three joint clinician inputs were provided: two clinicians provided input on behalf of CCO Hematology DAC, 20 individual clinicians provided input on behalf of the BC Cancer Agency and UBC, and three on behalf of Lymphoma Canada (LC).

Inputs received from registered clinicians indicate that there is currently no SOC regimen for transplant ineligible R/R DLBCL patients, as there have been no randomized trials that establish the superiority of one regimen over another for this patient population. Treatment options for these patients include sequential single agent chemotherapy drugs, or chemotherapy combinations, which are mostly palliative. Steroids and/or radiation may be offered in the palliative setting, mainly for symptom control. The clinicians noted that the most frequently used treatment in the R/R setting is platinum-based combination chemotherapy, and that this option is generally unsuitable for older patients or those with comorbidities as it is often too intensive and toxic. The registered clinician input suggested that many patients in the R/R setting have already received and failed platinum-based regimens, and therefore require novel options. The addition of novel agents to chemotherapy may be difficult due to overlapping toxicities, and access is often restricted to clinical trials. Clinicians providing input anticipated that pola-BR would represent a new SOC. The clinician group inputs also noted other places in the treatment algorithm where pola-BR is anticipated to be used beyond the funding request. In the absence of universally established SOC, and based on its efficacy, tolerability, and potential for long term durable disease control, pola-BR is believed to provide clinicians with a therapeutic option for patients with R/R DLBCL who are not eligible for ASCT and have failed on at least one prior therapy. The clinicians also remarked on the possibility of serving as a bridge to ASCT or CAR T-cell therapy as opposed to standard platinum-based chemotherapy (i.e., R-GDP). They also noted that pola-BR could possibly replace conventional palliative chemotherapy following ASCT relapse.

All three clinician groups indicated that they had prior experience with pola-BR. The LC and BC Cancer Agency/UBC clinicians noted that pola-BR has a similar side-effect profile to BR, except for a higher incidence of neutropenia. Clinicians from LC also noted that severe neuropathy (grade 2 or higher) would be a contraindication for polatuzumab. Overall, it was believed that pola-BR is a more favourable option in R/R DLBCL over platinum-based regimens. Regarding retreatment with pola-BR, all three clinician groups were unaware or uncertain of the availability of evidence at this time.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s)

All three groups of clinicians noted that there is no SOC for R/R DLBCL. For patients eligible for transplant, current treatment options include the following:

- Systemic chemotherapy with or without rituximab with plans to proceed to high-dose chemotherapy and ASCT

For transplant-ineligible patients who do not respond to upfront chemotherapy regimens or those who relapsed following ASCT, current treatment options include the following:

- R-GDP, PEP-C, R-DHAP, R-DICEP, and R-CEOP; all with or without rituximab
    - The team from the BC Cancer Agency and UBC noted that platinum-based combinations such as GDP are used primarily as a bridge to transplant (usually unsuitable for older patients or those with comorbidities)

CAR T-cell therapy may be a relevant comparator provided patients do not receive prior allogenic stem cell transplant, have no active CNS disease, are not HIV-positive, and if the reimbursement request is intended for the use of pola-BR after two or more lines of systemic treatment. Clinicians from LC indicated that CAR T-cell therapy may be offered in some academic centers, but this option is not realistic for many Canadian patients.

In the palliative setting, LC clinicians noted that steroids and/or radiation may be offered mainly for symptom control. The group of clinicians from CCO noted that there were no additional regimens currently funded in Ontario.

Groups from the BC Cancer Agency and UBC, and LC noted that there is an unmet need in R/R DLBCL, and current options only offer minimal PFS, and a number of toxicities.

5.2 Eligible Patient Population

All three groups of clinicians reported that that the R/R DLBCL indication for pola-BR aligns with clinical practice. Of note, the LC group believed that approximately two thirds of patients in clinical practice would meet the eligibility criteria defined in the trial, as about one third of patients would be palliative, and excluded based on poor performance status, co-morbidities or having CNS disease. The BC Cancer Agency and UBC group indicated that despite this being the first and only pivotal, randomized trial to include patients with R/R DLBCL who are considered transplant ineligible by the treating physician or experienced treatment failure with prior ASCT, the large majority of R/R DLBCL patients are unfit to receive an ASCT due to age, comorbidities, performance status, or chemotherapy-insensitive disease. Transplant ineligible patients, or those who become ineligible due to salvage chemotherapy insensitivity or those who relapse following transplant have very limited treatment options ranging from palliative care to conventional chemotherapy. There is no standard treatment approach in this setting across Canada, and patient outcomes remain poor, with a median OS of approximately six months.

Unanimously, the clinician groups agreed that there was an unmet need in the population of patients who received frontline R-CHOP (or similar), as approximately 40% of patients progress following this therapy. Secondly, patients that have serious comorbidities and are not candidates for ASCT or CAR T-cell therapy, or patients who have relapsed after ASCT or CAR T-cell therapy are suitable for pola-BR. It was stated by the BC Cancer Agency and UBC clinicians that pola-BR would provide clinicians with a much-needed tolerable therapeutic option that can provide durable disease control and improve OS in this unfortunate patient population.

The clinicians from CCO stated that there would be no specific subgroups in which to extend or limit the new treatment; however, the LC clinicians noted that there are subgroups of patients who require adequate tumor control as a bridge to a more potentially curative therapy. For instance, some patients have obtained complete remissions with pola-BR (on compassionate use program), which was used as a bridge to either CAR T-cell therapy or allogeneic stem cell transplant after a failure to CAR T-cell therapy. Technically these patients still meet the eligibility criteria for pola-BR, but these patients were not studied in the original trial (e.g., CAR T-cell therapy failures).

5.3 Relevance to Clinical Practice

All groups of clinicians reported that they had prior experience administering the treatment under review in the context of clinical trials and compassionate use programs.

The BC Cancer Agency and UBC clinicians highlighted that compared to BR, pola-BR resulted in clinically relevant improvements in long term durable control, with longer PFS (median, 9.5 vs. 3.7 months; HR 0.36; 95% CI, 0.21-0.63; $P < 0.001$) and OS (median, 12.4 vs. 4.7 months; HR 0.42; 95% CI, 0.24-0.75; $P = 0.002$). Nearly 20% of patients treated with pola-BR achieved prolonged disease control extending beyond two years, suggesting it may provide a potential bridge to an ASCT or CAR T-cell therapy which has been approved in the third-line setting. The LC clinicians agreed and suggested that one big advantage of pola-BR over cellular therapy is that it is “off the shelf” and not “customized”, therefore it can be administered in a timely manner, similar to other antibody drug conjugates.

Clinicians from both the BC Cancer Agency and UBC, and LC indicated that pola-BR is safe and well tolerated, having a similar side-effect profile to the comparator of BR, with the exception of a higher incidence of neutropenia. While higher rates of cytopenias were observed with pola-BR compared to BR alone, this did not result in an increased risk of infection or need for transfusion. The clinicians noted that in patients with baseline cytopenias, reducing the dose of bendamustine from 90 mg/m^2 to 70 mg/m^2 may be necessary to avoid grade 3 or 4 cytopenias, that would lead to treatment delays. LC clinicians believed that this approach should be tried before reducing the dose of polatuzumab. The clinicians noted that the majority of peripheral neuropathies observed are low grade and transient and are resolved in most patients. The clinicians from LC noted that while it has not been a significant issue, severe neuropathy (grade 2 or higher) would be a contraindication to give polatuzumab. Conversely, the clinicians from CCO or BC Cancer Agency and UBC did not identify any specific contraindications associated with pola-BR treatment.

Overall, the safety and tolerability profile of the triplet pola-BR combination was found to be acceptable within the context of this heavily pre-treated population of patients with R/R DLBCL.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

Input received from the clinician groups indicated that there is no defined SOC for transplant ineligible R/R DLBCL. Patients may receive conventional salvage regimens such as R-GDP, sequential single agent therapy, other combination therapies, radiation therapy or supportive care with palliative intent.The clinicians added that enrolment into a clinical trial of novel agents is often the preferred treatment option for these patients due to the limited therapeutic options.

Clinicians from CCO believed that pola-BR would constitute a new SOC if available for funding. The BC Cancer Agency/UBC and LC indicated that availability of pola-BR would provide Canadian clinicians with a definitive and desirable therapeutic option for patients who are considered ineligible for ASCT or have failed conventional care, and may also serve as a potential bridge to ASCT or CAR T-cell therapy.

The clinicians from LC also believed that the following scenarios where pola-BR would be useful in R/R DLBCL patients following treatment with R-CHOP:

- In patients not fit for ASCT but still fit to receive chemotherapy, pola-BR would replace less effective conventional chemotherapy regimens (e.g., R-GDP).
- In patients fit for ASCT or CAR T-cell therapy, but there is an inadequate response to second line therapy (e.g. R-GDP), pola-BR would be an option as 3rd line.
- In patients with relapsed DLBCL after ASCT or who are ineligible for ASCT/CAR T-cell therapy, pola-BR would replace conventional palliative chemotherapy.

5.5 Companion Diagnostic Testing

Clinicians providing input indicated that there is no companion diagnostic testing for pola-BR. The group from CCO noted that CD79b, which is part of standard testing, should be considered by pERC

5.6 Implementation Questions

5.6.1 If pola-BR were funded, what would be the treatment algorithm for R/R DLBCL patients who are not eligible for ASCT?

Based on its efficacy, tolerability, and potential for long term durable disease control, the three clinician groups agreed that pola-BR is a much-needed treatment option for patients with R/R DLBCL who are not eligible for ASCT and have received at least one prior therapy. Clinicians from CCO noted that for those not eligible for ASCT, it is possible that they may be suited to CAR T-cell therapy.

All three groups of clinicians agree that pola-BR could be used in patients who are ineligible for ASCT as bridge to CAR T-cell therapy or as salvage chemotherapy, although this was not tested in the trial. The BC Cancer Agency and UBC noted that this may be the case as CAR T-cell therapies have been approved in the third-line setting based on single-arm studies for the treatment of patients who had failed two or more lines of prior therapies. Clinicians from CCO noted that the number of cycles used may be limited due to bendamustine and the ability to collect T-cells. The BC Cancer Agency also noted that most patients treated with CAR T-cell therapy cell therapy will ultimately relapse and require additional options.

The LC clinicians indicated that post-R-CHOP failure, pola-BR would replace less effective conventional chemotherapy regimens (i.e., R-GDP). The group also noted that pola-BR could be potentially used in patients fit for ASCT or CAR T-cell therapy with inadequate response to second line therapy and potentially as a bridge to ASCT, which was allowed on trial. Lastly the LC clinicians noted that pola-BR could be used relapsed DLBCL post-ASCT to replace conventional palliative chemotherapy or as a third-line option following inadequate response to second line therapy or first salvage chemotherapy.

5.6.2 What evidence is available to use pola-BR for retreatment?

Clinician groups from CCO and LC stated that to their knowledge, there was no data supporting re-treatment with pola-BR.

5.7 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

The primary objective of this systematic review was to assess the efficacy and safety of pola-BR for the treatment of adult patients with R/R DBCL, NOS, who are not eligible for ASCT and have received at least one prior therapy.

The following supplemental issues relevant to the CADTH review and to the PAG were identified while developing the review protocol:

Supplemental Issue 1: In the pivotal trial, GO29365, a liquid formulation of polatuzumab vedotin was studied in the randomized cohort comparing pola-BR to BR in R/R DLBCL patients. However, as the study was ongoing, a lyophilized formulation of polatuzumab vedotin was developed to improve product stability, which is the commercialized formulation that is approved by Health Canada. Two non-randomized, single-arm cohorts with lyophilized formulations of pola-BR were added to the study, Arm G and Arm H, which included patients with R/R DLBCL. A summary of the efficacy and safety of the lyophilized formulation cohorts, Arms G and H, are reported in section 7.1.

Supplemental Issue 2: No standard treatment exists for the indication under review, and there are a wide variety of relevant comparators used in Canadian clinical practice that are selected based on individual patient characteristics. In the absence of a direct treatment comparison with these relevant comparators, the sponsor submitted a MAIC that compared the efficacy of pola-BR to R-GemOx, pixantrone, tisagenlecleucel (CAR T-cell therapy), and axicabtagene ciloleucel (CAR T-cell therapy). Refer to section 7.2 for the summary and critical appraisal of the MAIC.

Supplemental Issue 3: To address the absence of direct comparisons with relevant comparators, the sponsor also submitted a PSWA that compared the efficacy of pola-BR to standard treatments using IPD from the Alberta Oncology Outcomes (O2) RWD in transplant-ineligible patients with R/R DLBCL. Refer to section 7.2.2 for the summary and critical appraisal of the PSWA. Refer to section 7.3 for the summary and critical appraisal of the PSWA.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria outlined in Table 9 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 9: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of pola-	Adult patients with R/R DLBCL, not otherwise specified **Subgroups:** • Transplant ineligible patients who relapsed/ are refractory to first line treatment • Patients non-responsive to salvage chemotherapy who	pola-BR	Single agent**: • Etoposide • Cyclophosphamide • Gemcitabine • Bendamustine Radiation Alternate salvage: • R-DHAP† • R-GDP‡	Efficacy outcomes: • **OS** • PFS • **ORR** • Time to response • DOR • **HRQoL** Harms outcomes: • AEs • SAEs

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
BR should be included.	therefore did not undergo ASCT • Patients who relapsed post-transplant • IPI score • Type of initial chemotherapy • Number of prior lines • Time from prior therapy to relapse • ECOG PS • Molecular or genetic factors (e.g. BCL6 gene)		• R-ICE‡ • R-DICEP • R-CEOP • R-GemOx Conventional salvage: • DHAP • ICE • GDP • PEP-C** • MEP CAR T-cell therapy Dexamethasone/etoposide Lenalidomide Ibrutinib BR	• Withdrawal due to AEs • AEs of clinical interest: infection, thrombocytopenia, anemia, gastrointestinal bleeding, peripheral neuropathy • Deaths

ASCT=autologous stem cell transplantation; BR = bendamustine and rituximab; CAR T-cell therapy=Chimeric Antigen Receptor T-Cell therapy; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GDP=gemcitabine + dexamethasone + cisplatin; IPI = International Prognostic Index; MEP=methotrexate + etoposide + cisplatin; ORR = objective response rate; PEP-C=prednisone + etoposide + procarbazine + cyclophosphamide; Pola = polatuzumab vedotin; R-CEOP=rituximab+cyclophosphamide+etoposide+vincristine+prednisone; R-DHAP=rituximab + dexamethasone + cisplatin + cytarabine; R-DICEP=rituximab+ dose-intensive cyclophosphamide + etoposide + cisplatin; R-GDP= rituximab + gemcitabine + dexamethasone+ cisplatin; R-ICE=rituximab+ ifosfamide + carboplatin + etoposide

Note: CGP discussed that treatment for R/R DLBCL varies widely across the country and is specific to patient characteristics.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

*** CGP noted these regimens may be used more often in elderly patients and/or patients with several comorbidities in Canadian clinical practice.*

† CGP noted these regimens may not be used as often in Canadian clinical practice.

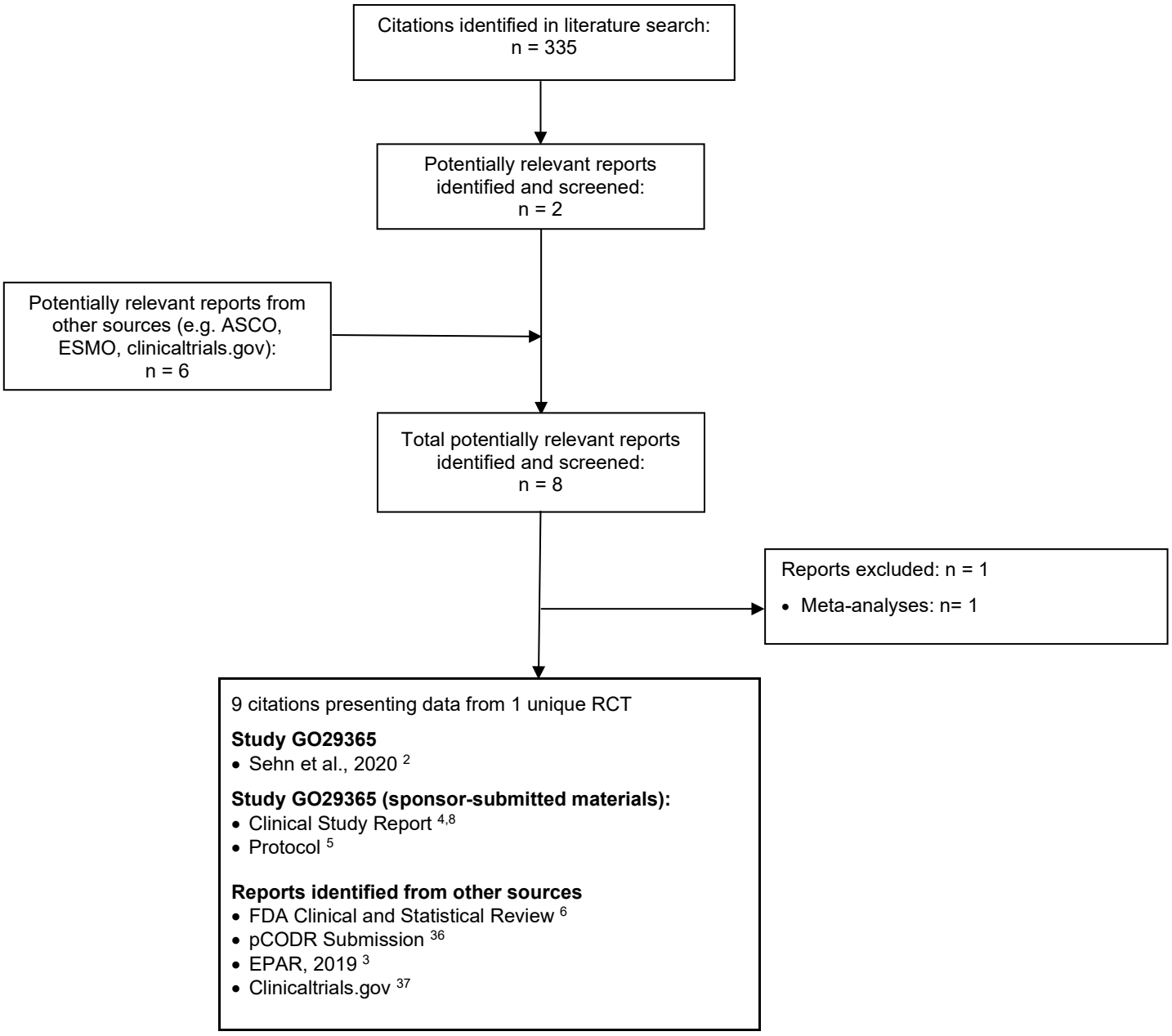
‡ CGP noted these regimens are used more often in fitter patients in Canadian clinical practice.

6.3 Results

6.3.1 Literature Search Results

Of the two potentially relevant studies identified, one study was included in the CADTH systematic review [2] and one study was excluded.[35] This study was excluded because it was a meta-analysis.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to the GO29365 trial were also obtained through requests to the Sponsor by CADTH. [38]

6.3.2 Summary of Included Studies

One clinical trial, GO29365, met the selection criteria of the systematic review.[2] Key characteristics of the GO29365 trial, including study design, eligibility criteria, interventions, and trial outcomes, are summarized in Table 10.

6.3.2.1 Detailed Trial Characteristics

Table 10: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: GO29365[2] NCT02257567 **Characteristics:** Phase Ib/II, open-label trial with randomized and non-randomized cohorts *Phase II randomization (arms C and D):* N randomized = 80 (40 randomized to pola-BR and 40 to BR) N treated = 78 (39 treated with pola-BR and 39 with BR) **Settings:** 54 centres in 12 countries (Canada, US, France, Spain, Australia, Czech Republic, Italy, Turkey, Great Britain, Hungary, Germany, Korea, and Netherlands) **Patient enrollment dates:** *Phase II randomization (arms C and D):* Oct 15, 2014 to Sep 2016 **Primary data cut-off:** Apr 30, 2018 **Updated analysis:**	**Key Inclusion Criteria:** • ≥ 18 years old • Biopsy confirmed R/R DLBCL (excluding transformed lymphoma) • ≥ 1 prior line of therapy • ECOG PS 0 to 2 • Grade ≤ 1 peripheral neuropathy • Transplant ineligible or treatment failure with prior ASCT • Life expectancy ≥ 24 weeks • Patients who received prior bendamustine, response duration must have been > 1 year for patients who relapsed after a prior regimen • At least one bi-dimensionally measurable lesion on imaging scan defined as > 1.5 cm in dimension • Adequate hematologic function unless inadequate function is due to underlying disease, such as extensive bone marrow involvement or hypersplenism secondary to the involvement of the spleen by the lymphoma • Agreement to use highly effective contraception • Negative serum pregnancy test **Key Exclusion Criteria:** • Active HBV, HCV or HIV • Treatment with RT, ChT, IT, IST or any investigational agent for cancer within 2 weeks of cycle day 1 • Ongoing CS use > 30 mg daily prednisone or equivalent other than for lymphoma symptom control • ASCT or CAR T-cell therapy within 100 days of cycle 1 • Prior allogeneic SCT • History of transformation of indolent disease to DLBCL	**<u>Phase II randomization (arms C and D):</u>** **Intervention:** pola-BR Pola 1.8 mg/kg IV on Day 2 of cycle 1 then on Day 1 of subsequent cycles Bendamustine 90mg/m2/day on days 2 and 3 of cycle 1 then days 1 and 2 of subsequent cycles Rituximab 375 mg/m2 on day 1 of each cycle **Comparator:** BR Bendamustine 90mg/m2/day on days 2 and 3 of cycle 1 then days 1 and 2 of subsequent cycles Rituximab 375 mg/m2 on day 1 of each cycle	**<u>Phase II randomization (arms C and D):</u>** **Primary:** • IRC-assessed CR rate (PET-CT) **Secondary:** • INV-assessed CR and IRC- and INV-assessed ORR rate based on PET-CT • CR and ORR based on CT only, IRC and INV-assessed • BOR at any assessment by PET-CT or CT only, • INV-assessed BOR by PET-CT or CT only, IRC-assessed • DOR based on PET-CT or CT only, IRC-assessed • PFS based on PET-CT or CT only, IRC-assessed • PROs measuring peripheral neuropathy symptom severity and symptom interference using TINAS **Exploratory:** • DOR, PFS, EFS based on PET-CT or CT only, INV-assessed • OS

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
January 2nd, 2020 **Funding:** Hoffman-La Roche	• Primary or secondary CNS lymphoma • History of severe allergic or anaphylactic reactions for murine mAbs or known sensitivity or allergy to murine products • Grade 3b follicular lymphoma • Vaccination with a live vaccine within 28 days prior to treatment • Significant uncontrolled concomitant diseases such as significant CVD (such as NYHA class III or IV cardiac disease, MI < 6 months, unstable arrythmias, and unstable angina) or pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm) • Patients with suspected or latent TB • Known infections with HTLV-1 virus • Recent major surgery		• Biomarker evaluation of efficacy by cell of origin • Safety

ASCT=autologous stem cell transplantation; BR=bendamustine rituximab; ChT=chemotherapy; CNS=central nervous system; CR=complete response; CS=corticosteroid; CT=computed tomography; DLBCL=diffuse large B cell lymphoma; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; EOT=end of therapy; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INV: Investigator; IST=immunosuppressive therapy; IT=immunotherapy; ORR=objective response rate; PET=positron emission tomography; PFS=progression-free survival; Pola=polatuzumab; R/R=relapsed/refractory; RT=radiation therapy; SCT=stem cell transplantation

Sources: FDA Clinical Review, 2019[6]; EPAR, 2019 [3]; Study Protocol, 2014 [5]; Clinicaltrials.gov [37]; Clinical Study Report, 2020 [4]

a) Trials

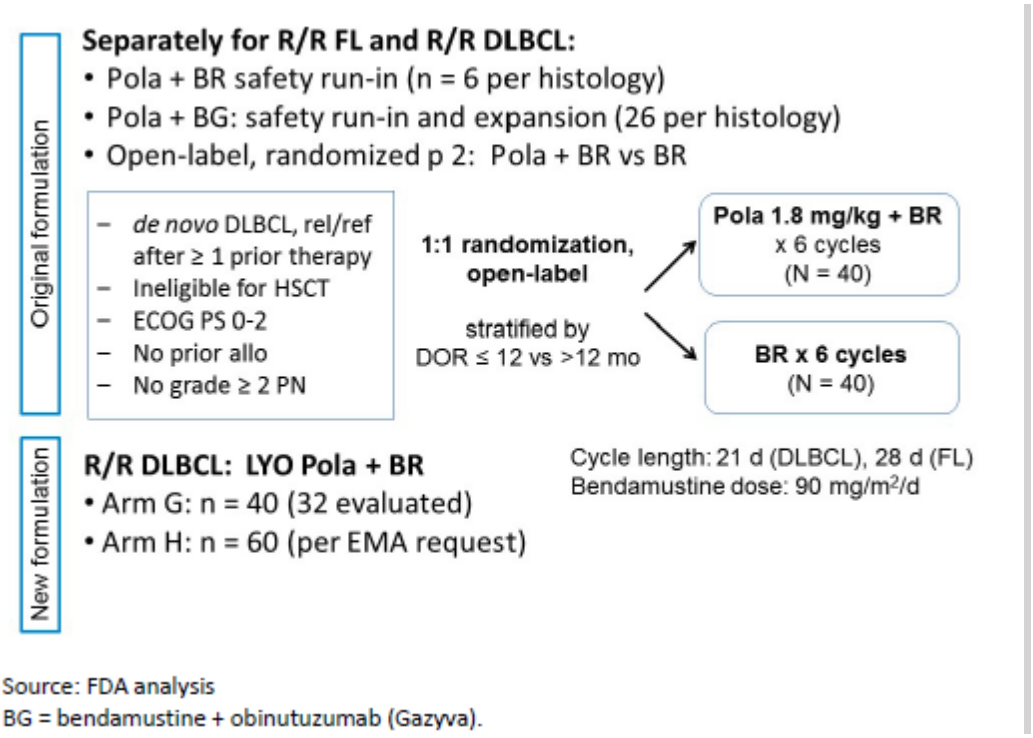
Trial Design

One sponsor-funded, international (54 centres across 12 countries including 4 Canadian sites with 44 Canadian patients), open-label clinical trial met the inclusion criteria. Study GO29365 is an ongoing Phase Ib/II study that enrolled patients with R/R DLBCL after at least one prior regimen. This study had several different arms, as shown in Figure 2, some of which included patients with FL, or combined polatuzumab with obinutuzumab plus bendamustine, which were not considered relevant to this review. [7] This review focused on the phase II randomization cohort that compared, in a 1:1 randomized fashion, R/R DLBCL patients who received pola-BR (arm C) with those who received BR (arm D) alone, for six cycles. The study is scheduled to end once all patients enrolled in the study have had at least two years of follow up from the time of treatment completion or have discontinued the study, with the results of the final analysis planned to be published in 2022. [5,38]

Screening was performed within 28 days of the first dose of study drug, unless otherwise indicated. All screening evaluations had to be completed before eligibility was confirmed. Screening evaluations included a general medical history and baseline conditions, concomitant medications, ECOG PS, IPI score assessment, a complete physical, as well as vital signs, ECG, a clinical response assessment of the tumor (conducted by physical exam) and a PET-CT scan. Lab values were also taken, including hematology, serum chemistry, coagulation panel, viral serology, Serum IgA, IgG, IgM, a pregnancy test, bone marrow biopsy and aspirate, tumour tissue sample for exploratory biomarker analyses, and a tissue sample and pathology report for central pathology review. [5]

Key inclusion criteria included: at least 1 prior line of therapy, transplant ineligible or had treatment failure with prior ASCT, and an ECOG PS of 0 to 2. Patients with primary or secondary CNS lymphoma were excluded. Randomization was performed using an interactive voice/web response system and was stratified by DOR to prior therapy (≤ 12 months versus > 12 months).[5] There were no pre-specified subgroup analyses however a post hoc analysis was provided in the primary trial publication.

Figure 2: Overview of the GO29365 Phase Ib/II Trial Design



Source: FDA Clinical Review, 2019 [6]

Reprinted from FDA Clinical Review, 2019 [6]

Disease Assessments

Tumour response was assessed by physical exam, CT scans, PET scans, and bone marrow examinations.[2] PET-CT scans were required at screening, an interim response assessment after cycle 3, and at the EOT visit. The EOT visit took place between six and eight weeks after the last dose of study treatment. CT scans without PET were to be obtained every six months until approximately two years after the EOT visit, or until progressive disease (PD) or patient withdrawal. Tumor response was assessed by the investigator and an IRC.[5] The IRC was composed of board-certified radiologists and an oncologist with experience in malignant lymphoma and assessed all patients for response on the basis of imaging results and bone marrow biopsy results. The modified Lugano Response Criteria were used to assess overall response. The IRC assessment was conducted using the modified Lugano Response Criteria applied separately for PET-CT and CT scans, as well as an overall tumor response and progression assessment integrating both the radiographic and clinical data findings separately for PET-CT and CT assessments.[4] A full tumour assessment, including radiographic assessment, had to also be performed at any time disease progression or relapse were suspected.[5]

As part of the tumour assessment by the investigator, physical examinations were to include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Targeted physical exams were conducted on Day 1 of each cycle, as well as the treatment completion visit, the EOT visit, the discontinuation visit, and during the follow-up period. Bone marrow examinations were required at screening for staging, and repeat bone marrow examinations were required for patients with bone marrow infiltration at screening who may have achieved a CR at the EOT visit and in patients with a PR and continued bone marrow involvement to confirm a CR at a later timepoint.[5]

Treatment Discontinuation

Study treatment was to be permanently discontinued in the event of:[5]

- Grade 3 or 4 hematologic toxicity that did not resolve to Grade 2 or lower and delayed treatment by over 14 days despite administration of growth factors
- Grade 2 or higher non-hematologic toxicity that did not resolve to Grade 1 or baseline value and delayed treatment by over 14 days
- Hepatitis B reactivation (rising HBV-DNA viral load exceeding 100 IU/mL) despite starting appropriate antivirals
- Disease progression
- Any dose delay of 4 weeks or greater
- Pregnancy

Polatuzumab vedotin was permanently discontinued in the event of Grade 4 peripheral neuropathy, grade 3 peripheral neuropathy that resulted in treatment delay of 14 days or more and did not improve to Grade 1 or less within 14 days, or recurrence of a Grade 2 or higher peripheral neuropathy at the reduced dose. Rituximab was to be discontinued in the event of a life-threatening (Grade 4) infusion-related reaction or an immunoglobulin E (IgE)-mediated anaphylactic reaction, recurrence of Grade 3 infusion-related symptoms at re-challenge, regardless of timing, or if the patient had Grade 3 wheezing, bronchospasm, or generalized urticarial at the first occurrence.[5]

Study Outcomes

All efficacy analyses were performed on the ITT population, which included all randomized patients analyzed according to their treatment assignment.[2] The primary outcome of the phase II portion of the study was IRC-assessed CR rate at the EOT using the modified Lugano Response Criteria as measured by PET-CT scan. If no scans were performed, the IRC considered the patient missing or unevaluable and the patient was treated as a non-responder. The modified Lugano criteria were:

- Assessment of CR based solely on imaging without confirmatory bone marrow testing was classified as a PR for patients with bone marrow involvement or unknown status at baseline
- A PR required a partial metabolic response by (18F) fluorodeoxyglucose PET and either a CR or PR by CT; otherwise, the response was classified as stable disease (SD). However, because of an error, IRC had the PR modification, but the investigator did not, and thus response were assessed slightly differently by investigator and IRC. Thus, only IRC-assessed outcomes are reported in this report.

Secondary outcomes relevant to the review included the following IRC-assessed outcomes:[5]

- CR rate at EOT based on CT only
- Objective response rate (ORR)
- Best overall response (BOR)
- Duration of response (DOR)
- Progression-free survival (PFS)

ORR was defined as patients with either a CR or a PR at the time of EOT based on PET-CT. BOR was defined as patients with either a CR or PR while on study based on PET-CT or CT only. DOR was defined as the time from first occurrence of a documented CR or PR to disease progression, relapse or death from any cause PR based on PET-CT or CT only (only patients who experienced a CR or PR were included in this analysis).[5]

PFS was defined as the period from randomization until the date of disease progression, relapse or death from any cause, whichever occurs first. For PFS, patients who did not have documented disease progression or death had observations censored on the date of the last tumour assessment, or, if no tumour assessments were performed after the baseline visit, at the time of randomization. Two sensitivity analyses of IRC-assessed PFS were conducted using alternative censoring rules including:[3]

- For patients who had missed one or more assessments before their recorded event of PD or death, data were censored at the date of the last non-missing assessment prior to the event; and

- For patients who started a new anticancer therapy prior to PD were censored at the date of the last non-missing disease assessment before starting a new anticancer therapy

Exploratory outcomes included OS, which was defined as date of randomization until the date of death from any cause.[5] For OS, patients for whom death had not been documented had observations censored on the last date at which they were known to be alive.

Peripheral neuropathy is a recognized AE of polatuzumab vedotin therapy, and thus patients were assessed for signs of neuropathy by the investigator, using the Total Neuropathy Score, and by the patient reported TINAS. The TINAS assessments included subjective sensory symptoms, motor symptoms, and autonomic symptoms and objective pinprick sensitivity, vibration sensitivity, strength testing and deep tendon reflex testing. The TINAS is an 11-item questionnaire that assesses severity of neuropathy-related symptoms on a scale from 0 (symptom not present) to 10 (symptom is as bad as the patient can imagine). The questionnaire was completed using an electronic device, once weekly by patients over the course of study treatment, and weekly for the first two months following the study period, then monthly for the next 10 months.[5] For the TINAS score, when patients did not complete individual TINAS items, missing data was derived using scoring instructions provided by the designer of the instrument.[4] A prorated total score was calculated if at least 50% of items were answered, using the following formula:

Prorated total score = ([Sum of total scores] x [total number of items])/[number of items answered] [4]

The safety-evaluable population included all patients who received at least one dose or more of any study treatment.[2] The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to assess and grade AEs. With respect to safety, TEAEs were defined as those that are new or worsened from baseline grade or are unknown to have worsened from baseline.[7] The AE reporting window was 90 days after the last study drug after which SAEs or AESI were reported.[5] Prespecified AESI per protocol included drug induced liver injury, infections, tumor lysis syndrome, and second malignancies.

Statistical Analyses

The primary analysis data cut-off was April 30th, 2018, which occurred after all treated patients had one year of follow-up after the preliminary response assessment.[3] Updated analyses with longer term efficacy results were also provided by the sponsor with a data cut-off of January 2nd, 2020.[4]

There was no pre-specified statistical hypothesis testing for the phase II randomized portion of GO29365. [3] The sponsor assumed a 40% CR rate in the BR group and a 25% increase in CRs in the pola-BR group. The assumption of a 40% response rate in BR was based on the literature and the opinion of clinical experts, while the 65% in the pola-BR group was based on the fact that with the 40% assumption in the BR group, the 95% exact Clopper-Pearson CI of the observed CR rate in the pola-BR group will rule out 40% if the increase in CRs is at least 25%. [38]Using a 95% exact Clopper-Pearson CI, the sponsor arrived at a 95% CI for the difference in CRs between groups of 3.8% to 46.2%. It was also estimated that with 40 patients in each group there was an 87% chance of observing at least one AE with a true incidence of at least 5%. The sponsor also assumed a margin of error of +/- 17% based on a sample of 40 patients per group.[3] Time to event outcomes such as OS and PFS were summarized descriptively using Kaplan-Meier methodology to estimate median 1-year and 2-year PFS and 95% CIs using Greenwood's formula.[5] There was no pre-specified alpha control plan, p-values are provided for descriptive purposes only. Median DOR was estimated, along with the corresponding 95% CI using the method of Brookmeyer and Crowley.[5] No formal comparisons of median DOR across treatment groups was conducted.

The analysis populations for the randomized phase II R/R DLBCL portion included the ITT population, which consisted of all patients randomized to treatment (N=80).[2] All patients in the ITT population were analyzed according to the treatment arm (pola-BR: N=40 and BR: N=40) to which they were randomized. The safety-evaluable analysis set included all patients who received at least one dose of any study treatment (=78), and patients were analyzed according to actual treatment received (pola-BR: N=39 and BR: N=39).

For the purposes of this report the expanded safety population (N=84) was also reviewed, which included an additional 6 R/R DLBCL patients from the phase IB safety run-in portion who were treated with pola-BR, resulting in a total of 45 patients in the pola-BR group and 39 patients treated with BR from the randomized phase II portion. [6]

A post-hoc exploratory multiple Cox regression analyses were performed for PFS and OS and prognostic factors included in final models were selected based on a statistical threshold of P = 0.2.[3] Prognostic factors for PFS included Ann Arbor Stage, baseline ECOG and IPI, and for OS it was Ann Arbor Stage, baseline ECOG and bulky disease and IPI.

Additionally, the FDA conducted their own re-analysis, using their own methods for adjudicating outcomes like ORR, DOR and PFS.[7] See Table 11 for details. The FDA re-analysis resulted in more cases of PD (and fewer cases of stable disease) and a smaller number of 'not evaluable' cases. The FDA also conducted a Bayesian analysis with uniform priors to further characterize the magnitude and uncertainty of the treatment effect for CR.[6]

Table 11: Differences in the Approach of FDA Re-Analysis of Efficacy Outcomes from the GO29365 Trial

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.

Source: FDA Clinical Review, 2019 [6]

Reprinted from FDA Clinical Review, 2019 [6]

Protocol Amendments

Protocol amendments were implemented after the first patient had been dosed, and are summarized in Table 12 below:[3]

Table 12: Summary of Protocol Amendments in the GO29365 trial

Amendment Number (Date) No. Patients recruited prior to the amendment	Amendment summary
Amendment 1 (April 27, 2015) 9	After first 9 patients in Cohort 1A of safety run-in were enrolled, the following changed were implemented: • All patients in the run-in were to receive the polatuzumab vedotin 1.8mg/kg dose, while originally the design called for a dose escalation to 2.4 mg/kg. This amendment was due to a partial clinical hold being placed on this higher dose by the FDA. • Adoption of the new Lugano 2014 response criteria for NHL, which had been published after finalization of the first protocol, for evaluation of CR using PET.
Amendment 2 (September 14, 2015) 1	After 1 patient in the BR groups of the randomized phase II portion had been dosed, the following was implemented: • Modification of the Lugano Response Criteria to include requirement for bone marrow examinations for all patients (DLBCL as well as FL) at screening for staging. • Response was assessed by the IRC and investigator on the basis of physical examinations, CT scans, PET scans, and bone marrow examinations using the modified Lugano criteria. • Updated eligibility to exclude patients with secondary, as well as primary and CNS lymphoma and exclude all patients eligible for ASCT. • Include gastrointestinal perforations as an identified risk associated with obinutuzumab treatment. • Updated guidelines for monitoring HBV reactivation for patients with occult or prior HBV infection (negative HBsAg and positive HBcAb), for pregnancy prevention for women of childbearing age and for men (extension of period of contraception) and for the pregnancy test for all women of childbearing age.
Amendment 3 (July 11, 2017) NR	• Inclusion of second malignancies as an AESI/non-serious expedited AE requiring expedited reporting, and to require indefinite reporting of second malignancies (even if the study has ended) for patients in the obinutuzumab cohorts.
Amendment 4 (November 16, 2017) NR	• Added additional cohort of 20 to 30 patients (Arm G) with R/R DLBCL who will receive a new lyophilized formulation of polatuzumab vedotin in combination with BR, in order to gain clinical experience with respect to pharmacokinetics and safety. • Introduced analysis of PFS and DOR by IRC for the DLBCL cohorts as requested by the FDA.
Amendment 5 (May 31, 2018)	• Expansion of Arm G to include 10 more patients with R/R DLBCL with one prior line of therapy (i.e. second line) to evaluate the efficacy of pola-BR, using the lyophilized formulation of polatuzumab vedotin.

Amendment Number (Date) No. Patients recruited prior to the amendment	Amendment summary
NR	• Added analysis of IRC-assessed BOR for the DLBCL cohorts
Amendment 6 (October 2, 2018) NR	• Added a new arm (Arm H) to the phase II new formulation cohort that enrolled approximately 60 patients with R/R DLBCL who will receive the new lyophilized formulation, as above, in order to gain supportive clinical experience of the combination of pola-BR with this formulation. Objectives, study description and exploratory biomarker assessments were updated for the new formulation cohort (Arm H), inclusion criteria for HHV8-positive DLBCL, not otherwise specified, was deleted. Pharmacokinetic sampling and Anti-Drug Antibody Schedule for patients treated with the new formulation (Arm H) of polatuzumab vedotin was added. • Additional important requirements included update of the Statistical Considerations and Analysis Plan for the new formulation cohort, including the rationale for sample size and pooled efficacy analysis plan (Arms G and H). Updated the secondary objectives for Arm G of the new formulation cohort to include investigator-assessed DOR, PFS, EFS, and OS.

AESI = adverse event of special interest; ASCT = autologous stem cell transplant; BOR = best overall response; BR = bendamustine combined with rituximab; CNS = central nervous system; CR = complete response DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EFS = event-free survival; FDA = Food and Drug Administration; HBV = hepatitis B virus; IRC = independent review committee; NHL = Non-Hodgkin's lymphoma; OS = overall survival; PFS = progression-free survival; pola = polatuzumab vedotin; R/R = relapsed or refractory

Source: EPAR, 2019 [3]

Funding

This study was funded by the sponsor, F. Hoffman La Roche Ltd.[2] The lead investigator Dr. Sehn has received honoraria and has had a consulting/advisory role with a number of companies including Genentech and F. Hoffman-La Roche Ltd. and has received research funding from F. Hoffman La-Roche Ltd.

b) Populations

The baseline characteristics of the study groups in the Study GO29365 are summarized in Table 13. Study GO29365 randomized 80 patients, with 40 patients assigned to pola-BR and 40 patients assigned to BR. [3,7] The population enrolled were predominantly male (66%), white (71%), and had a median age of 68 years. Most patients (80%) had an ECOG performance status of 0 or 1. Per the inclusion criteria, patients were required to have DLBCL NOS, however there was 1 patient (3%) with FL and 1 patient (3%) with Burkitt's lymphoma that were enrolled. With respect to prior therapy, 80% were considered refractory, 84% had a DOR of 12 months or less, and 20% were considered to have failed HSCT.[6]

Differences in baseline characteristics between pola-BR and BR of greater than 10% were observed for race (white: 65% versus 78%, respectively), primary reason for HSCT ineligibility (age: 33% versus 48% and failed prior HSCT: 25% versus 15%, respectively), outcome of last therapy (refractory: 75% versus 85% respectively), disease features at baseline (bulky disease: 25% versus 38%, respectively), and IPI risk at baseline (High: 23% versus 43%).[6]

Table 13: Baseline Characteristics in the Phase II Randomized R/R DLBCL Portion GO29365 Trial, ITT Population (N = 80)

Characteristics	POLA + BR (n = 40)	BR (n = 40)
Median age (range), years	67 (33 to 86)	71 (30 to 84)
Males, n (%)	28 (70)	25 (63)
Race, n (%)		
• White	26 (65)	31 (78)
• Asian	6 (15)	4 (10)
• Black	3 (8)	0
• Other/unknown	5 (13)	5 (13)
ECOG PS, n (%)		
• 0 or 1	33 (83)	31 (78)
• 2	6 (15)	8 (20)
• Unknown	1 (2.5)	1 (2.5)
Disease characteristics		
Primary reason for HSCT ineligibility, n (%)		
• Age	13 (33)	19 (48)
• Comorbidities	1 (3)	1 (3)
• Inadequate response	12 (30)	9 (23)
• Failed prior HSCT	10 (25)	6 (15)
• Patient refused HSCT	2 (5)	2 (5)
• Other	2 (5)	1 (3)
Time since diagnosis at study entry, median months (range)	0.7 (0 to 20)	0.8 (0 to 15)
Diagnosis by central review, n (%)		
• DLBCL NOS	38 (95)	40 (100)
• ABC	19 (48)	19 (48)
• GCB	15 (38)	17 (43)
• COO unspecified	4 (10)	4 (10)
• FL	1 (3)	0
• Burkitt lymphoma	1 (3)	0
• Other	0	0
Bulky disease (≥ 7.5 cm), n (%)	10 (25)	15 (38)
Ann Arbor Stage III to IV disease, n (%)	34 (85)	36 (90)
Extranodal disease, n (%)	27 (68)	29 (73)
IPI risk at study baseline, n (%)		

Characteristics	POLA + BR (n = 40)	BR (n = 40)
• Low (0 to 1)	9 (23)	3 (8)
• Low intermediate (2)	9 (23)	8 (20)
• High intermediate (3)	13 (33)	12 (30)
• High (4 to 5)	9 (23)	17 (43)
Prior anti-lymphoma therapies		
Prior lines of therapy, median (range)	2 (1 to 7)	2 (1 to 5)
• 1 prior line, n (%)	11 (28)	12 (30)
• 2 prior lines, n (%)	11 (28)	9 (23)
• ≥3 prior lines, n (%)	18 (45)	19 (48)
Prior types of therapies, n (%)		
• Anti-CD20	39 (98)	40 (100)
• Bendamustine	1 (3)	0
• Bone marrow transplant	10 (25)	6 (15)
• Cancer radiotherapy	11 (28)	10 (25)
Outcome of prior therapy, n (%)		
• Refractory to last therapy	30 (75)	34 (85)
• DOR to last therapy ≤12 months	34 (85)	33 (83)
• HSCT failure	10 (25)	6 (15)
Time from last anti-lymphoma therapy, median, days (range)	131 (17 to 11744)	82.0 (21 to 2948)
Disease features at baseline		
CD79b detectable by IHC		
Evaluated, n (%)	31 (78)	31 (78)
• Detectable, n	31	30
• Undetectable, n	0	1
CD79b H score, among cases evaluated, n (%)		
• > 0	31/31 (100)	30/31 (97)
• 1+ (> 0 but < 200)	6 (19)	12 (39)
• 2+ (200 to 299)	9 (29)	9 (29)
• 3+ (300+)	16 (52)	9 (29)

ABC = activated B-cell; COO = cell of origin; DLBCL=diffuse large B cell lymphoma; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL= follicular lymphoma; GCB = germinal centre B cell like; HSCT = hematopoietic stem cell transplantation; IHC = immunohistochemistry; IPI = international prognostic index; NOS = not otherwise specified

Sources: EPAR, 2019 [3]; FDA Clinical Review, 2019 [6]

c) Interventions

Treatment

Pola-BR was compared to BR, and all patients received up to six cycles of treatment (21 days per cycle).[7] Polatuzumab vedotin was administered at a dose of 1.8 mg/kg IV on Day 2 of Cycle 1, then on Day 1 of each subsequent cycle. The first cycle was a 90-minute infusion, with antipyretic and antihistamine premedication, and subsequent infusions were administered over 30 minutes, if tolerated. Rituximab was administered 375 mg/m^2 intravenously on Day 1 of each cycle and bendamustine 90 mg/m^2/day on days 2 and 3 of cycle 1, then days 1 and 2 of each subsequent cycle.

Treatment Modification Guidelines

Patients who developed Grade 2 to 3 peripheral neuropathy had all treatments delayed. Polatuzumab vedotin was held until improvement to Grade 1 or less, and if this had not happened by Day 14, polatuzumab vedotin was permanently discontinued. If the patient did recover to Grade 1 or less, then the dose of polatuzumab vedotin was permanently reduced to 1.4 mg/kg. If a prior dose reduction to polatuzumab vedotin 1.4 mg/kg had already occurred, then polatuzumab was to be discontinued. Patients who developed Grade 4 peripheral neuropathy were to discontinue polatuzumab.[6] Patients developing Grade 3 or 4 neutropenia or thrombocytopenia who recovered by Day 7 to an absolute neutrophil count (ANC) greater than 1000/uL or platelets greater than 75, resumed treatment without modification. For those with protracted cytopenias, no dose reductions of polatuzumab were permitted, but bendamustine dose was reduced to 70 mg/m^2 then 50 mg/m^2, followed by discontinuation of all treatment. No dose modifications to rituximab were allowed.[5]

G-CSF was optional prior to amendment 5, and herpesvirus and pneumocystis jiroveci pneumonia prophylaxis during and for six months after treatment, were optional prior to amendment 5.[6]

Treatment Exposure

At the time of the primary/interim analysis data cut-off (April 30th, 2018), the median number of completed cycles was 5 (range = 1 to 6) in the pola-BR group and 3 (range = 1 to 6) in the BR group in the safety evaluable population as shown in Table 14 (N = 78). [2] Double the proportion of patients completed six cycles of treatment with pola-BR (46.2%) compared to BR (23.1%). The median dose intensity of polatuzumab vedotin in the pola-BR group was 93% (range = 58 to 109). The median dose intensity of BR in the pola-BR and BR groups were comparable, as shown in Table 14. In the expanded safety evaluable population (N = 84), treatment exposure was similar with the same median number of cycles completed in both treatment groups as the safety evaluable population.[6] A total of 49% of patients completed 6 cycles in the pola-BR group and 23% in the BR group in the expanded safety evaluable population, which was highly consistent to the safety evaluable population. There was no change in the median number of completed cycles at the time of the longer term follow up, and a small increase in the median dose intensity for pola-BR (94% [range: 58 to 113] and for BR (96% [range: 64 to 103]).[4]

A higher proportion of patients discontinued treatment due to AEs in the pola-BR group compared to the BR group (33.3% versus 10.3%, respectively; however more patients in the BR group discontinued due to PD compared to the pola-BR group (53.8% versus 15.4%, respectively). Few patients required a dose reduction of polatuzumab in the pola-BR group and a comparable number of patients required a dose reduction of bendamustine in the pola-BR and BR groups. A higher proportion of patients in the pola-BR group had to delay treatment for AEs (53.8%) compared to those in the BR group (38.5%).[2]

Table 14: Summary of Treatment Exposure in the Phase II Randomized R/R DLBCL Portion, Safety Evaluable Population (N = 78)

Treatment Exposure	pola-BR (n = 39)	BR (n = 39)
Median number of cycles completed (range)	5 (1 to 6)	3 (1 to 6)
Completed 6 cycles, n (%)	18 (46.2)	9 (23.1)
Median dose intensity, % (range)		
• Pola	93 (58 to 109)	NA
• Bendamustine	91 (84 to 98)	93 (63 to 102)
• Rituximab	91 (70 to 103)	93 (45 to 101)
Discontinued treatment, n (%)		
• AEs	13 (33.3)	4 (10.3)
• PD	6 (15.4)	21 (53.8)
• Lack of efficacy	1 (2.6)	1 (2.6)
• Other	1 (2.6)	4 (10.3)
Dose reductions, n (%)		
• Pola	2 (5.1)	
• Bendamustine	5 (12.8)	4 (10.3)
AE leading to dose delay, n (%)	21 (53.8)	15 (38.5)

AE = adverse event; BR = bendamustine combined with rituximab; PD = progressive disease; Pola = polatuzumab vedotin

Source: Sehn et al., 2020 [2]

Subsequent Therapies

Data on subsequent therapy were provided for those who responded to therapy in the pivotal trial publication. Of the 7 patients in the pola-BR group who had an ongoing DOR of greater than 20 months and remained in complete remission at last follow-up, 1 received consolidative ASCT, while the others received no additional therapy.[2] Of the 2 patients in the BR group who remained in follow-up without progression, both receiving consolidative therapy, one ASCT and the other radiation.

After a request for additional data from the sponsor, data was provided for new anti-lymphoma treatments initiated after discontinuation of study drug. No patients treated with pola-BR and 2 patients treated with BR went on to receive CAR-T.[38] Two patients in each of the pola-BR (both allogenic) and BR groups (one allogenic, one autologous) received a subsequent SCT following treatment with study drug. Other therapies received in the pola-BR group included gemcitabine, dexamethasone, and cisplatin (n = 3); dexamethasone, cytarabine, and cisplatin (n = 2); and lenalidomide (n = 2). In the BR group, other therapies included GemOx (n = 3), bendamustine (n = 2), and lenalidomide (n = 1).[38]

d) Patient Disposition

Patient disposition details are shown in Table 15. A total of 96 patients were screened for eligibility, and 16 (17%) were screen failures.[2] Reasons for failing screening included not meeting eligibility criteria (11%), withdrawal of consent (2%), unacceptable laboratory value (1%), and death (1%).

At the time of the primary, there were 73% of patients in the pola-BR group and 90% of patients in the BR group who discontinued the study, and the most common reason for this was death, in 58% of pola-BR and 70% of patients in the BR group. For both treatment groups the most common cause of death was due to PD and AEs, with a higher proportion of patients dying due to PD

(42.5% vs. 35%) and AEs (27.5% vs. 22.5%) in the BR group compared to the pola-BR group, respectively. A total of 11 (28%) patients were alive in the pola-BR group and 4 (10%) patients were alive in the BR group. [2]

Protocol deviations occurred in 20% of patients in the pola-BR group and 12.5% of patients in the BR group, as shown in Table 16 below. The most common protocol deviations in the pola-BR group were 'signed informed consent' and 'primary assessment not done within 6 to 8 weeks of last dose', each occurring in 6.5% of patients.[3]

Table 15: Patient Disposition in the Phase II Randomized R/R DLBCL Portion of the GO29365 Trial

	POLA + BR	BR
Screened, n	96	
Randomized, n	40	40
Randomized and treated, n	39	39
On study		
Discontinued study, n (%)	29 (73)	36 (90)
• Death	23 (57.5)	28 (70)
○ AEs	9 (22.5)	11 (27.5)
○ Progressive disease	14 (35)	17 (42.5)
• Withdrawal by patient	5 (12.5)	5 (12.5)
• Progressive disease	0	2 (5)
• Physician decision	0	1 (2.5)
• Other	1 (2.5)	0
Alive at follow-up	11 (27.5)	4 (10)

AE: Adverse Event; BR = bendamustine combined with rituximab; Pola = polatuzumab vedotin

Source: Sehn et al., 2020 [2]

Table 16: Protocol Deviations in the GO29365 Trial, Expanded Safety Population (N = 84)

	POLA + BR (n = 46)	BR (n = 40)
At least 1 major protocol deviation, n (%)	9 (20)	5 (12.5)
• Signed informed consent	3 (6.5)	1 (2.5)
• Patient received prohibited concomitant medications	1 (2.2)	0
• Primary assessment not done withing 6 to 8 weeks of last dose	3 (6.5)	1 (2.5)
• Interim assessment performed outside of Cycle 3 Day 15 to Cycle 4 Day 1	2 (4.3)	1 (2.5)
• Dose not modified following specific toxicity	0	1 (2.5)
• Bone marrow biopsy > 3 months before Cycle 1 Day 1	0	1 (2.5)

BR = bendamustine combined with rituximab; Pola = polatuzumab vedotin

Source: Clinical Study Report (Interim), 2019

e) Limitations/Sources of Bias

IRC was used to carry out assessment of objective responses, which helps to reduce bias.

There was no blinding in the included trial. This is less likely to have biased findings for clinical outcomes such as mortality, PFS and objective response, and more like to have biased patient reported outcomes and assessment of harms. The only patient-reported outcome was TINAS, which was used to assess the impact of neuropathy. The results of this assessment may have been biased by lack of blinding, considering the fact that neuropathy is a known AE of polatuzumab vedotin. AEs may have been more likely to be assigned a different stage by investigators based on whether they were experienced by patients in the pola-BR or BR groups, and patients may have been more or less likely to report AEs if they knew whether they were receiving pola-BR or BR.

There was no pre-specified statistical hypothesis for the primary outcome, or for the CR rate difference between groups. Additionally, there were no adjustments made for multiple statistical comparisons, therefore the analysis of any of secondary outcomes, which are primary interest for this review, are at risk of Type 1 error. Given that the study had a small sample size and was not powered to detect differences between treatment groups on these key primary and secondary outcomes, there is considerable uncertainty in the reported results of key outcomes of interest such as PFS and OS.

There were imbalances in baseline characteristics for numerous parameters, and the size of these imbalances is difficult to place into perspective given the small sample size in the study. Some of the imbalances included refractory to prior therapy (75% pola-BR versus 85% BR), bulky disease at baseline (25% pola-BR versus 38% BR), IPI risk score of 'high' (23% versus 43%). [3,6] Notably, the majority of imbalances in baseline characteristics had the potential to bias results in favour of pola-BR, which further contribute to uncertainty in the reported primary and secondary outcomes. The sponsor assessed these outcomes in multiple Cox regression models and found that these baseline imbalances did not appear to impact the efficacy results.

The combination of bendamustine and rituximab is not a relevant comparator for the Canadian setting (see Section 7 for a comparison and critical appraisal of pola-BR to relevant comparators in Canadian practice). The lyophilized formulation of pola-BR, which is the formulation that will be used in Canada, was not studied in the randomized phase II portion of the GO29365 trial (liquid formulation was studied). Instead, it was added as two single arms to GO29365 as a protocol amendment. After conducting a comparative analysis of pharmacokinetics, the FDA reviewers concluded that there were no meaningful differences between the lyophilized formulation and the liquid solution, however this appears to have been based on modelling and was limited to pharmacokinetics.[6] Albeit a naïve comparison, the CR across the pooled Arm G and H was 40%, and this was consistent with CR of 40% observed with pola-BR in the double-blind phase.[4]

HRQoL was not assessed in the included study. The only patient-reported outcome was TINAS, used to assess the impact of neuropathy, a known AE of polatuzumab vedotin. This analysis had some limitations, including the fact that baseline data was only available for half of the patients, and there was a large amount of attrition that occurred during the study, and eventually only 29% of patients were continuing to be adherent to the questionnaire.

Subgroup analyses appear to have been conducted post hoc, rather than being pre-planned, thus these analyses should not be used to draw any conclusions about the efficacy of pola-BR in these subgroups. Subgroups identified in the systematic review protocol to be of interest included transplant ineligible patients who relapsed/are refractory to first line treatment, patients non-responsive to salvage chemotherapy and who therefore did not undergo ASCT, and patients who relapsed post-transplant, and therefore no data is available in these subgroups.

Different definitions were used for IRC and investigator assessed objective responses therefore it was not possible to determine concordance between the two. Since the primary outcome focused on IRC assessment this does not impact any conclusions that can be made about efficacy. In their clinical review, the FDA noted that the ORR (BOR) of 25% observed in the BR group of GO29365 was lower than ORR for various studies of BR in DLBCL reported in the literature. In these studies, the ORR ranged from 46% to 63%, suggesting that BR may have underperformed in GO29365, although there are limitations with such a naïve analysis, including differences in study design and baseline characteristics of the study populations. [6]

The sponsor analysis of several different outcomes did not follow FDA recommendations. These differences between the sponsor and FDA recommendations are summarized in table 11. In many cases the sponsor analysis resulted in a reduced number of

progression events, as they counted these as 'not evaluable'. This approach by the sponsor mainly impacted outcomes that rely upon progression events, such as PFS. The results of the FDA adjudicated analysis are presented at the end of the efficacy results section.

The sponsor, F. Hoffman La-Roche Ltd., funded the trial and was involved in several aspects of the study conduct, including the study design, data analysis, data interpretation, and writing of the reports. The extent to which the sponsor's involvement may have influenced the results and reporting of the trial is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

At the time of the primary, the median duration of follow-up in GO29365 was 22.3 months, with a data cut-off of April 30, 2018.[2] At the time of the updated analysis, the median duration of follow-up was 42.2 months, with a data cut-off of January 2nd, 2020.[4] A summary of the key efficacy outcomes can be found in Table 17. In the systematic review protocol, time to response and HRQoL were identified as outcomes of interest, however these outcomes were not assessed in the included trialand thus, are not reported.

Table 17: Summary of Efficacy Outcomes in the GO29365 Trial, ITT Population (N = 80)

	POLA + BR N = 40	BR N = 40
Primary outcome: CR Rate at EOT based on PET-CT, n (%)		
Complete response, IRC, n (%)	16 (40)	7 (18)
Difference between groups, % (95% CI)	22% (3 to 41)	
Secondary outcomes		
IRC-Assessed CR rate at EOT based on CT		
Complete response, IRC, n (%)	9*(23)	1*(3)
Difference between groups, % (95% CI)	20.0% (95% CI: 5.5 to 35.1)	
IRC-Assessed ORR at EOT		
Objective response, EOT, n (%)	18 (45)	7 (18)
Partial response, n (%)	2 (5)	0
Stable disease, n (%)	6 (15)	1 (3)
Progressive disease, n (%)	8 (20)	10 (25)
Missing or Not evaluable, n (%)	8 (20)	22 (55)
-no EOT scan performed due to AE	3(8)*	0
-no EOT scan for IRC	1(3)*	0
-no scans in study, withdrew from study	2 (5)*	2(5)*
-EOT scan unavailable by IRC	1(3)	0
-EOT CT performed without PET	1(3)	0
-clinical progression, no scan performed	0	14(35)*
-no EOT scan performed, interim scan PD by INV and SD by IRC	0	4(10)*
-no EOT scan performed; death from AE	0	2(5)*
IRC-Assessed BOR		
Objective response, BOR, n (%)	25 (63)	10 (25)

	POLA + BR N = 40	BR N = 40
Complete response, n (%)	20 (50)	9 (23)
Partial response, n (%)	5 (13)	1 (3)
Stable disease, n (%)	5 (13)	9 (23)
Progressive disease, n (%)	6 (15)	8 (20)
Missing or Not evaluable, n (%)	4 (10)	13 (33)
IRC-Assessed DOR		
Patients with an event, IRC, n (%)	13/25 (52)	8/10 (80)
Median (95% CI), months	12.6 (7.2 to NE)	7.7 (4.0 to 18.9)
HR (95% CI)	0.47 (0.19, 1.14)	
IRC-Assessed PFS		
Events by IRC assessment, n (%)	25 (63)	32 (80)
Median (95% CI), months	9.5 (6.2 to 13.9)	3.7 (2.1 to 4.5)
HR (95% CI)	0.36 (0.21, 0.63)	
OS		
Deaths, n (%)	23 (58)	28 (70)
Median (95% CI), months	12.4 (9.0 to NE)	4.7 (3.7 to 8.3)
HR (95% CI)	0.42 (0.24, 0.75)	

AE = adverse event; BOR = best overall response; CI = confidence interval; CR = complete response; CT = computed tomography; DOR = duration of response; EOT = end of treatment; HR = hazard ratio; IRC = independent review committee; NE = not evaluable; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; PR: Partial Response; SD = stable disease

*HR assessed using a Cox proportional hazards model

* n/% values estimated

Sources: EPAR, 2019 [3], Sehn et al., 2020 [2]

Efficacy Outcomes

Primary Outcome – IRC-Assessed CR Rate by PET-CT at EOT

The CR rate at EOT, by IRC assessment using PET-CT, was the primary outcome. At the time of the primary, CRs occurred in 16 (40%) of patients in the pola-BR group and in 7 (18%) of patients in the BR group, for a difference between groups of 22% (95% CI: 3% to 41%). [2,3]

Secondary Outcomes

IRC-Assessed CR Rate at EOT based on CT Only

The CR rate at EOT by IRC assessment using CT only was much lower than reported when using PET-CT for both treatment groups.[3] At the time of the primary/interim analysis, the CR rate in the pola-BR group was 22.5% compared to 2.5% in the BR group. However, the difference in CR rate between treatment groups as assessed by CT alone was 20.0% (95% CI: 5.5 to 35.1), which was consistent with the difference based on PET-CT assessment.[3]

IRC-Assessed ORR at EOT

The IRC-assessed ORR at EOT was 45% (n=18) in the pola-BR group and 17.5% (n=7) in the BR group. PRs were observed in 2 patient (5%) in the pola-BR group and no patients in the BR group at EOT.[2] Results of a Bayesian analysis, reported in the FDA Statistical Review, estimated a magnitude of treatment effect for CRs of 21%, meaning that the difference in CRs between pola-BR and BR is likely higher than 21%, on average. [6]

IRC-Assessed BOR

BOR was also reported, and there were more patients with a best response of CR in the pola-BR group (50%) compared to the BR group (23%). PRs occurred in 5 patients (12.5%) in the pola-BR group and 1 patient (2.5%) in the BR group. The ORR based on best response was 62.5% with pola-BR and 25% with BR. [2] Results for BOR were unchanged at the time of the longer term follow up.[4]

IRC-Assessed DOR

At the time of the primary/interim analysis, the median DOR by IRC was 12.6 months (95% CI: 7.2 to NE) with pola-BR and 7.7 months (95% CI: 4.0 to 18.9) with BR for a HR of 0.47 (95% CI: 0.19 to 1.14).[2] The CI of the HR suggests that the difference in DOR may not be significant between pola-BR and BR, although there was no formal prespecified statistical testing of the difference between treatment groups and there were only a small number of patients included in the analysis, and thus, there is uncertainty in the reported results of DOR. Of the 25 patients in the pola-BR group who had an IRC-assessed BOR of CR or PR, 16 (64%) had a DOR of at least 6 months compared to 3 patients (30%) in the BR group. There were 12 patients in the pola-BR group (48%) and 2 (20%) of patients in the BR group who had a DOR of at least 12 months.[6] The median DOR at the time of the updated analysis was 10.9 months (95% CI: 5.7 to 40.7) with pola-BR and 10.2 months (95% CI: 4.0 to 19.6) with BR, for a HR of 0.60 (95% CI: 0.25, 1.43). [4]

IRC-Assessed PFS

Median PFS by IRC was 9.5 months (95% CI: 6.2 to 13.9) with pola-BR and 3.7 months (95% CI: 2.1 to 4.5) with BR, representing a HR of 0.36 (95% CI: 0.21 to 0.63), or a 64% reduction in risk of either progression or death.[2] Similar to DOR, given the limitations of the analyses (small sample size, lack of prespecified statistical testing and control for multiple comparison), these results are uncertain. Please see Figure 3A for the Kaplan-Meier curves.

At the time of the updated analysis, PFS by IRC was 9.2 months (95% CI: 6.0 to 13.9) with pola-BR and 3.7 months with BR (95% CI: 2.1 to 4.5) for a HR of 0.38 (95% CI: 0.22 to 0.65), indicating little change from the original analysis.[4]

Exploratory Outcomes

OS

Median OS was 12.4 months (95% CI: 9.0 to NE) with pola-BR and 4.7 months (95% CI: 3.7 to 8.3) with BR. This corresponds to a HR of 0.42 (95% CI: 0.24, 0.75), or a 58% reduction in risk of death.[2] Similar to the reasons identified in the DOR and PFS section, these results are uncertain and are considered exploratory. Please see Figure 3C for the Kaplan-Meier curves. Results from the longer term follow-up were unchanged.[4]

Subgroup analyses were conducted post hoc, and this data is presented in Figure 3.[2] All subgroup analyses are limited by small sample sizes. There did not appear to be any differences in response based on subgroups identified to be of interest to this review including IPI score (≥3 versus <3), ECOG PS (≥2 versus 0 or 1), prior lines of anti-lymphoma therapy (≥2 versus 1) and DOR to prior anti-lymphoma therapy (>12 months versus ≤12 months).

Figure 3: Kaplan-Meier analysis of PFS and OS and subgroup analysis

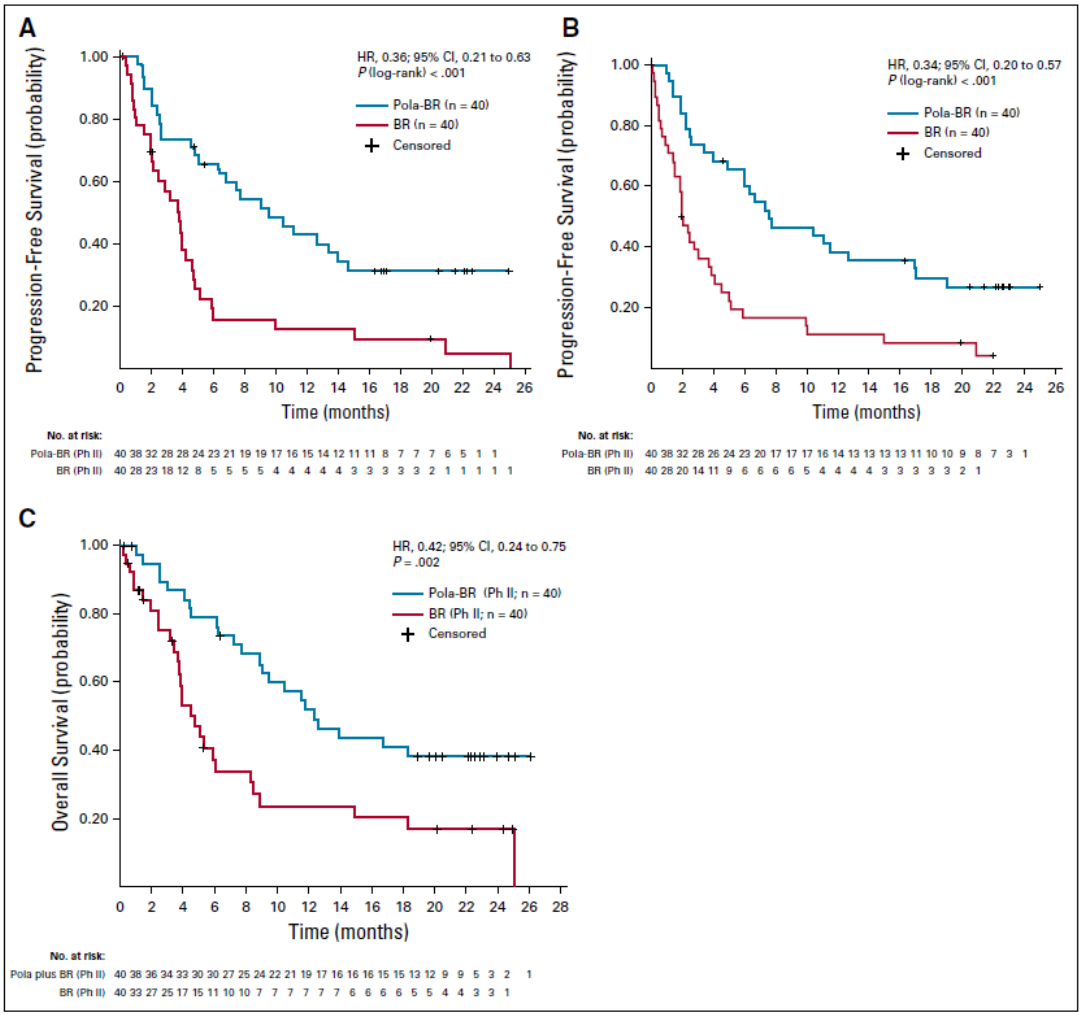


FIG 2. (A) Progression-free survival by independent review committee. (B) Progression-free survival by investigator. (C) Overall survival of polatuzumab vedotin combined with bendamustine-rituximab (pola-BR) compared with bendamustine-rituximab (BR). (D) Forest plot of overall survival according to clinical and biologic characteristics. Values are based on an unstratified analysis. WHO classification was by central pathology review that incorporated results from NanoString Technologies for cell-of-origin determination when available. ABC, activated B-cell–like; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; GCB, germinal center B-cell–like; IPI, International Prognostic Index; ph, phase; ref, refractory; yr, year.

Source: Sehn et al., 2020 [2]

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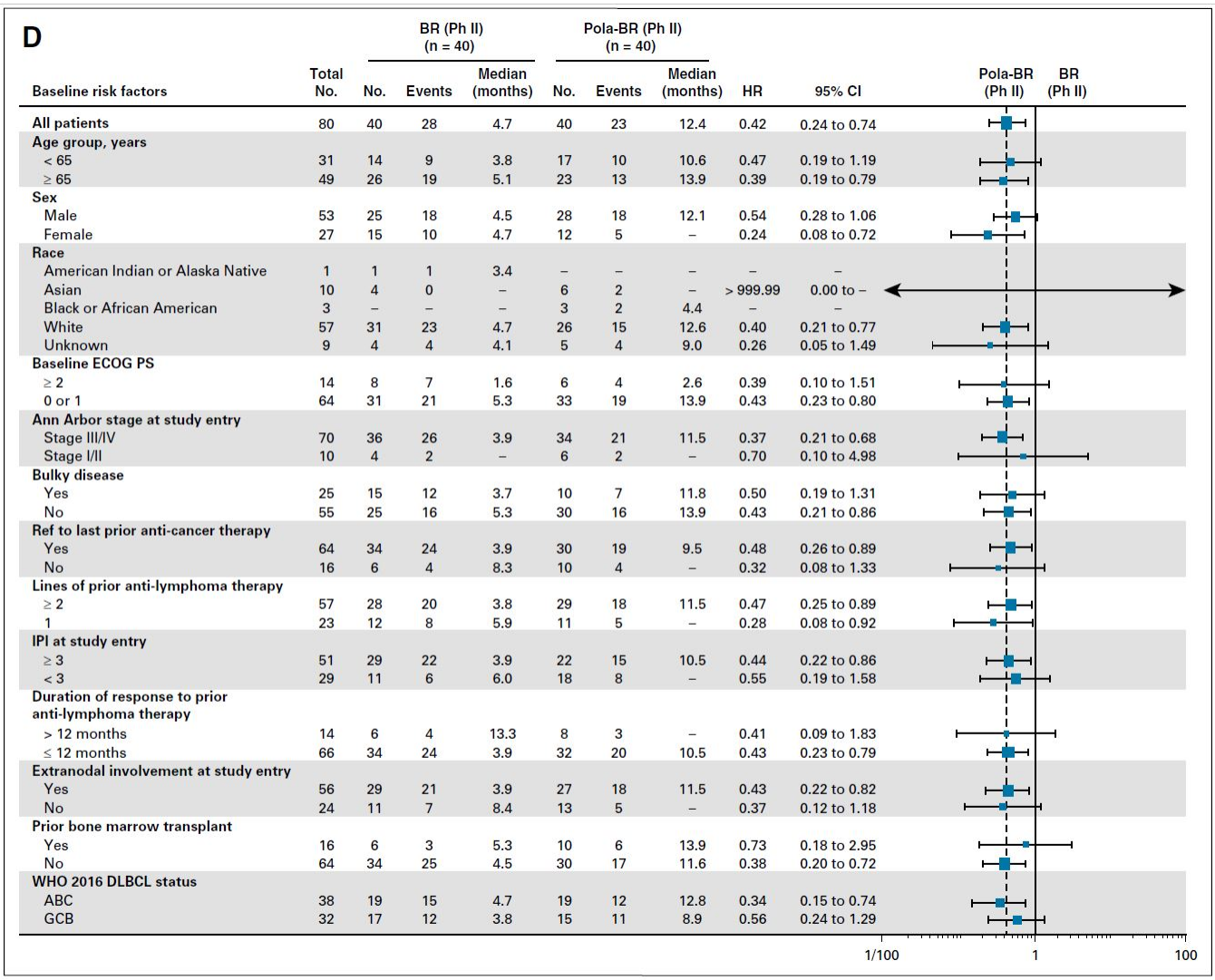

Source: Sehn et al., 2020 [2]

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Post-hoc Multiple Cox Regression Analyses Adjusting for Prognostic Factors

In a post hoc multiple Cox regression analysis, the impact of various prognostic factors on PFS and OS were reported (see Table 18). The results of these individual stratified analyses were generally consistent with that of the primary analyses, with the exception of high IPI scores (4 or 5) at baseline, which appeared to reduce the impact of pola-BR on OS, with a HR of 0.54 (95% CI: 0.30, 0.97) and on IRC-assessed PFS, a HR of 0.45 (95% CI: 0.25, 0.80).[3] In the overall population, the HR for OS was 0.42 (95% CI: 0.24, 0.74) and for PFS was 0.36 (95% CI: 0.21, 0.61). These were analyzed using Multiple Cox regression, adjusting for Ann Arbor stage, ECOG PS, and bulky disease (OS) and for Ann Arbor stage and ECOG PS and IPI score (for both).[2]

Table 18: Stratified Multiple Cox Regression Analyses for Time-To-Event Endpoints Adjusted for Potential Prognostic Factors

	Outcome	Pola BR vs BR HR (95% CI)
Adjusting for		
Bulky disease	OS	0.45 (0.25, 0.80)
	PFS-INV	0.36 (0.21, 0.61)
	PFS-IRC	0.38 (0.22, 0.67)
Refractory to last anti-lymphoma therapy	OS	0.44 (0.25, 0.67)
	PFS-INV	0.36 (0.21, 0.61)
	PFS-IRC	0.39 (0.22, 0.68)
Previous bone marrow transplant	OS	0.44 (0.25, 0.77)
	PFS-INV	0.35 (0.20, 0.58)
	PFS-IRC	0.37 (0.21, 0.64)
Age (< 65 years, ≥ 65 years)	OS	0.42 (0.24, 0.74)
	PFS-INV	0.34 (0.20, 0.57)
	PFS-IRC	0.36 (0.21, 0.61)
IPI high (4 or 5)	OS	0.54 (0.30, 0.97)
	PFS-INV	0.41 (0.24, 0.71)
	PFS-IRC	0.45 (0.25, 0.79)

BR = bendamustine combined with rituximab; CI = confidence interval; HR = hazard ratio; INV = investigator assessment; IPI = international prognostic index; IRC = independent review committee; OS = overall survival; PFS = progression-free survival; pola = polatuzumab vedotin

Source: EPAR, 2019 [3]

FDA-Adjudicated Outcomes

There was no difference between the primary analysis conducted by the sponsor and the FDA-adjudicated analysis for CR rate (see Table 11 for a list of differences between the methods used for the FDA analysis versus those used by the sponsor). BOR was also similar between the primary analysis by the sponsor and the FDA adjudicated analysis, and DOR was the same.[6]

An FDA adjudicated analysis found PFS by IRC to be 7.6 months with pola-BR and 2.4 months with BR, for a HR of 0.29 (95% CI: 0.16 to 0.52). The smaller numbers for PFS were due to the FDA counting more 'not evaluable' events as progression events (see Table 11).[66]

Harms Outcomes

In this section, harms are presented for the safety evaluable population (N = 78) in Table 19, and for the expanded safety evaluable population (N= 84) in Table 20.

AEs

In the safety evaluable population, overall, 100% of patients in the pola-BR group and 97% of patients in the BR group experienced an AE. Grade 3 or 4 AEs occurred in 84% of patients in the pola-BR group and 72% of patients in the BR group, a clear numerical difference between groups. [8] Anemia was the most common AE that occurred in the pola-BR group (54% versus 26% in BR [grade 3

or 4: 28% versus 18%]) followed by neutropenia (54% versus 39% [grade 3 or 4: 46% versus 33%]) and thrombocytopenia (49% versus 28% [grade 3 or 4: 41% versus 23%]) and peripheral neuropathy (44% versus 8% [no grade 3 or 4]). Diarrhea was also a common AE with pola-BR (39% versus 28% [grade 3 or 4: 3% in each group]).[2] All of these AEs occurred numerically more frequently in the pola-BR group than in the BR group. These findings were consistent with that of the expanded safety evaluable population (see Table 20) and in the updated analysis.[4]

SAEs

In the safety evaluable population, SAEs occurred in 64% of patients on pola-BR and 62% on patients on BR, thus there was no clear difference in groups for the risk of SAEs. The most common SAEs with pola-BR were pneumonia (8% versus 8% in BR), febrile neutropenia (10% versus 10%) and pyrexia (10% versus zero), thus pyrexia was numerically more common in the pola-BR group than in the BR group.[3] These findings were consistent with that of the expanded safety evaluable population (see Table 20) and the updated analysis.[4]

Mortality

In the safety evaluable population, there were nine deaths (23% of patients) with pola-BR that were described as AEs and 11 deaths (28%) with BR alone. With pola-BR, two patients died due to pneumonia, while with BR alone, 3 deaths occurred due to sepsis/septic shock, and two deaths occurred due to multiple organ dysfunction syndrome. [8] There were no additional deaths in the expanded safety evaluable population and two additional deaths in the pola-BR group in the updated analysis.[4]

Discontinuations Due to AEs

In the safety evaluable population, there were numerically more treatment discontinuations due to AEs with pola-BR than with BR, occurring in 33% of pola-BR and 15% of patients in the BR group; 31% of patients in the pola-BR group discontinued polatuzumab vedotin. Dose modifications/interruptions occurred with 72% of patients in the pola-BR group and 49% of BR alone.[8] These results were consistent with that of the expanded safety evaluable population (see Table 20) and the updated analysis of safety.[3]

AESI

Peripheral neuropathy was a protocol-defined notable harm, and the percentages of patients with peripheral neuropathy are reported above. Peripheral neuropathy was also assessed using the TINAS instrument. There was a significant amount of missing baseline data (29% of patients) and less than 50% of patients filled out the questionnaire, with decreased participation over time. Fewer than 25% of the remaining adherent patients continued the assessment after week 29. When the data was presented in linear plots, there appears to be higher scores in the pola-BR groups and scores remained flat in the BR group, however the significant amount of missing data limits confidence in this analysis.[3] Other protocol-defined harms of special interest such as neutropenia, thrombocytopenia, infections and peripheral neuropathy are reported above.

The sponsor identified additional AESI including tumour lysis syndrome, hepatoxicity and second malignancies. At the time of the updated analysis, secondary malignancies were reported in two patients (5.1% of patients) in each of the pola-BR and BR groups. Two patients in the pola-BR group and one patient in the BR group had a serious malignancy

Table 19: Harms (safety evaluable population, N = 78)

	Pola-BR (n = 39)*		BR (n = 39)*	
Adverse Event	**All Grades, No. (%)**	**Grades 3-4, No. (%)**	**All Grades, No. (%)**	**Grades 3-4, No. (%)**
Blood and lymphatic system disorders				
Anemia	21 (53.8)	11 (28.2)	10 (25.6)	7 (17.9)
Neutropenia	21 (53.8)	18 (46.2)	15 (38.5)	13 (33.3)
Thrombocytopenia	19 (48.7)	16 (41.0)	11 (28.2)	9 (23.1)
Lymphopenia	5 (12.8)	5 (12.8)	0	0
Febrile neutropenia	4 (10.3)	4 (10.3)	5 (12.8)	5 (12.8)
GI disorders				
Diarrhea	15 (38.5)	1 (2.6)	11 (28.2)	1 (2.6)
Nausea	12 (30.8)	0	16 (41.0)	0
Constipation	7 (17.9)	0	8 (20.5)	1 (2.6)
General disorders and administration site conditions				
Fatigue	14 (35.9)	1 (2.6)	14 (35.9)	1 (2.6)
Pyrexia	13 (33.3)	1 (2.6)	9 (23.1)	0
Metabolism and nutrition disorders				
Decreased appetite	10 (25.6)	1 (2.6)	8 (20.5)	0
Peripheral neuropathy				
Peripheral neuropathy†	17 (43.6)	0	3 (7.7)	0

NOTE. Shown are all-grade adverse events occurring in ≥ 20% of patients and grade 3-4 adverse events in ≥ 10% of patients (safety-evaluable). Preferred terms are shown within each System Organ Class with the exception of peripheral neuropathy.

Abbreviations: BR, bendamustine-rituximab; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab.

*One patient in each group did not receive the study treatment and so was excluded from the safety-evaluable population.

†Includes peripheral motor neuropathy, peripheral sensory neuropathy, decreased vibratory sense, hypoesthesia, paresthesia.

Source: Sehn et al., 2020 [2]

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Table 20: Harms (expanded safety evaluable population, N =84)

	POLA + BR N=45		BR N=39	
Adverse events	*All grades*	*Grades 3-4*	*All grades*	*Grades 3-4*
Patients with any AE, n (%)	45/45 (100)	38/45 (84)	38/39 (97)	*28/39 (72)*
SAEs, patients, %				
Blood and lymphatics				
Anemia	47%	24%	26%	18%
Neutropenia	47%	40%	39%	33%
Thrombocytopenia	47%	38%	28%	23%
Lymphopenia	11%	11%	0	0
Leukopenia	11%	7%	13%	8%
Febrile neutropenia	11%	11%	13%	13%
Gastrointestinal disorders				
Diarrhea	38%	4%	28%	5%
Nausea	33%	0	41%	0
Constipation	18%	0	21%	3%
Vomiting	18%	2%	13%	0
Abdominal pain upper	11%	2%	5%	0
Abdominal pain	11%	4%	10%	3%
General disorders/administrative site conditions				
Fatigue	41%	4%	36%	3%
Pyrexia	33%	2%	23%	0
Asthenia	11%	0	15%	0
Chills	11%	0	8%	0
Infections and infestations				
Pneumonia	16%	7%	10%	0
Metabolism and nutrition disorders				
Decreased appetite	27%	2%	21%	0
Hypoalbuminemia	13%	2%	5%	0
Hypokalemia	16%	7%	8%	3%
Hypocalcemia	11%	2%	3%	0
Nervous system disorders				
Peripheral neuropathy	20%	0	3%	0
Peripheral sensory neuropathy	13%	0	0	0
Dizziness	13%	0	8%	0

	POLA + BR N=45		BR N=39	
Other				
Cough	16%	0	21%	0
Weight decreased	16%	3%	8%	3%
Pruritus	13%	0	10%	3%
Infusion-related reactions	33%	7%	23%	10%
SAEs, n (%)	**N=45**		**N=39**	
Any SAE n (%)	29/45 (64)		24/39 (62)	
Pneumonia	4/45 (9)		3/39 (8)	
Febrile neutropenia	5/45 (11)		4/39 (10)	
Pyrexia	4/45 (9)		0	
Sepsis	2/45 (4)		2/39 (5)	
Anemia	2/45 (4)		1/39 (3)	
Thrombocytopenia	2/45 (4)		1/39 (3)	
Mortality				
Fatal adverse events, n	9/45		11/39	
AE resulting in treatment modification or discontinuation	**N=45**		**N=39**	
Discontinuation of any treatment, n (%)	14/45 (31)		6/39 (15)	
polatuzumab vedotin	12/45 (27)		0	
Dose reduction, n (%)	8/45 (18)		4/39 (10)	
Dose delay/interruption, n (%)	23/45 (51)		15/39 (38)	
Cause of treatment discontinuation				
Neutropenia +/or thrombocytopenia	8/14		2	
Fatal adverse event	3		2	
Pneumonitis	1		0	
Muscle atrophy	1		0	
Infection	1		1	
Hypoxia	0		1	
Notable harms				
Infections, n (%)	24 (53)		20 (51)	
Serious infections	29%		31%	
Fatal infections	9%		10%	

AE=adverse event; SAE=serious adverse event

Source: EPAR, 2019 [3]; FDA Clinical Review [7]

6.4 Ongoing Trials

Table 21 lists one ongoing trial of polatuzumab vedotin in patients with R/R DLBCL. The trial is a phase III RCT evaluating polatuzumab in combination with GemOx compared to rituximab/gemcitabine/oxaliplatin in patients with R/R DLBCL.[39] This study did not meet the inclusion criteria of the systematic review, however it is a treatment combination that is of interest to clinicians.

Table 21: Ongoing Trials of Polatuzumab Vedotin in DLBCL

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study POLARGO **Characteristics:** Phase III OL RCT N= 216 (planned) **Settings:** 27 sites; 6 countries (not Canada) **Patient Enrolment Dates:** Start: December 2, 2019; Enrollment ongoing **Funding:** Sponsor funded	**Key Inclusion Criteria:** **Inclusion Criteria:** • DLBCL NOS or history of indolent disease to DLBCL • Relapsed (recurred following a response that lasted ≥6 months from completion of last line of therapy) OR • Refractory (progressed during therapy or progressed <6 after prior therapy • ≥1 line of prior systemic therapy • May have undergone HSCT (chemo followed by consolidative autologous HSCT is counted as 1 line of therapy) • Local therapies (e.g. radiation) not counted as a line of therapy • At least 1 bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension • ECOG of 0, 1, or 2 • Adequate hematologic function **Key Exclusion Criteria:** • History of allergy to mAbs • PN >Grade 1 by NCI CTCAE v5.0 • Prior use of pola or a GEM-based Pt-based agent combination • Recent participation in a clinical trial or • RT, ChT, IT, or IST within 2 weeks • Planned autologous or allogenic SCT at time of recruitment • Primary or secondary CNS lymphoma • Richter's transformation or prior CLL • Abnormal lab values or health conditions assessed by INV, any known conditions preventing adherence to protocol, or active infection	Pola 1.8 mg/kg IV + rituximab 375 mg/m^2 IV on day 1+ gemcitabine 1000 mg/m^2 IV + oxaliplatin 100mg/m^2 IV on day 2 versus rituximab 375 mg/m^2 IV on day 1+ gemcitabine 1000 mg/m^2 IV + oxaliplatin 100mg/m^2 IV on day 2 Each cycle consists of 21 days with up to 8 cycles of treatment	Stage 2: **Primary**: OS **Secondary:** • OR (IRC using PET-CT); also assessed by investigator using Response alone • CR (IRC using PET-CT); also, INV-assessed using Response (not including PET) • PFS • DOR • EORTC QLQ-C30 • FACT-Lym • Change in PN using FACT/GOG-Ntx12 • AEs • Patients with peripheral neuropathy

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Vaccination with a live vaccine within 4 weeks prior to treatment • Major surgery within 6 weeks of start of Cycle 1 other than for diagnosis • Any other contraindications • Pregnant or breastfeeding • Women of childbearing potential must have negative pregnancy test within seven days of initiating study drug		

BR=bendamustine rituximab; CTCAE=common terminology criteria for adverse events; ChT=chemotherapy; CLL=chronic lymphocytic leukemia; CNS=central nervous system; CR=complete response; CT=computed tomography; DLBCL=diffuse large B cell lymphoma; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQC30=European organization for research and treatment of cancer quality of life questionnaire core 30; FACT-Lym=functional assessment of cancer therapy – lymphoma; FACT/GOG-Ntx12=functional assessment of cancer therapy/gynecologic oncology group neurotoxicity 12 item scale; Gem=gemcitabine; INV=investigator assessed; IRC=independent review committee; IST=immunosuppressive therapy; IT=immunotherapy; IV=intravenous; kg=kilogram; mAbs=monoclonal antibody; mg=milligram; NCI=National Cancer Institute; NOS=not otherwise specified; OL=open label; OR=objective response; PET=positron emission tomography; PFS=progression-free survival; Pola=polatuzumab; Pt=platinum; RCT=randomized controlled trial; RT=radiation therapy; SCT=stem cell transplantation.

Source: Clinicaltrials.gov [39]

7 Supplemental Questions

The following supplemental question were identified during development of the review protocol as relevant to the CADTH review of pola-BR for the treatment of R/R DLBCL patients:

Supplemental Issue 1: In the pivotal trial, GO29365, a liquid formulation of polatuzumab vedotin was studied in the randomized cohort comparing pola-BR to BR in R/R DLBCL patients. However, as the study was ongoing, a lyophilized formulation of polatuzumab vedotin was developed to improve product stability, which is the commercialized formulation that is approved by Health Canada. Two non-randomized, single-arm cohorts with lyophilized formulations of pola-BR were added to the study, Arm G and Arm H, which included patients with R/R DLBCL. A summary of the efficacy and safety of the lyophilized formulation cohorts, Arms G and H, are reported in section 7.1.

Supplemental Issue 2: No standard treatment exists for the indication under review, and there are a wide variety of relevant comparators used in Canadian clinical practice that are selected based on individual patient characteristics. In the absence of a direct treatment comparison with these relevant comparators, the sponsor submitted a MAIC that compared the efficacy of pola-BR to R-GemOx, pixantrone, tisagenlecleucel (KYMRIAH®; CAR T-cell therapy), and axicabtagene ciloleucel (YESCARTA®; CAR T-cell therapy). Refer to section 7.2 for the summary and critical appraisal of the MAIC.

Supplemental Issue 3: In the absence of direct comparisons with relevant comparators, the sponsor also submitted a PSWA that compared the efficacy of pola-BR to standard treatments using IPD from the Alberta O2 RWD in transplant-ineligible patients with R/R DLBCL. Refer to section 7.2.2 for the summary and critical appraisal of the PSWA. Refer to section 7.3 for the summary and critical appraisal of the PSWA.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Review of Efficacy and Safety from Non-randomized Groups in GO29365

7.1.1 Objective

In the pivotal trial, GO29365, a liquid formulation of polatuzumab vedotin was studied in the randomized cohort comparing pola-BR to BR in R/R DLBCL patients. However, as the study was ongoing a lyophilized formulation of polatuzumab vedotin was developed to improve product stability, which is the commercialized formulation that is approved by Health Canada. Two non-randomized, single-arm cohorts with lyophilized formulations of pola-BR were added to the study, Arm G and Arm H, which included patients with R/R DLBCL. A summary of the efficacy and safety of the lyophilized formulation cohorts, Arms G and H, are reported in this section.

7.1.2 Summary

Two open-label, single-arms with lyophilized versions of polatuzumab vedotin were added to the study, Arm G (N=40 planned, N=42 enrolled) and Arm H (N=60 planned, N=64 enrolled), both in patients with R/R DLBCL. Arm G was planned to include 10 patients who had one prior line of therapy, and Arm H had at least 30% with one prior line of therapy. The primary objective of Arm G was to assess the pharmacokinetics and safety of the lyophilized formulation of polatuzumab vedotin, while the primary objective of Arm H was to assess efficacy (CR rate by PET-CT at EOT, by IRC). The secondary efficacy objectives of Arm G included CR rate and ORR (CR or PR) at EOT, using PET-CT determined by investigator and IRC, the same outcomes assessed by CT only, BOR (CR or PR achieved at any point over the duration of the study) using PET-CT or CT by investigator and IRC, DOR, PFS based on PET-CT or CT determined by investigator and IRC, and OS. Secondary efficacy objectives for Arm H were similar to Arm G, although the CR rate at the time of EOT by PET-CT was investigator only, as the primary outcome assessed using IRC.[4]

The baseline characteristics of the lyophilized cohorts are presented in Table 22. The median age of 70 years was similar in the lyophilized cohorts compared to the RCT arms of the study (69 years). There was an even split of males (49%) and females (51%) in the lyophilized cohorts, which was different than the RCT component of the study, which had 66% males. The majority of patients were white in the lyophilized cohorts (78%) and in the RCT component of the study (71%). Most patients in the lyophilized cohort had an ECOG performance status of 0 or 1 (87%), as was the case in the RCT component (80%). With respect to prior therapy,

76% were refractory to their last prior lymphoma therapy (versus 80% in the RCT phase), 13% had ECOG PS of 2 (versus 18% in the RCT phase) and 26% had bulky disease (versus 31% in the RCT phase).

Table 22: Baseline Characteristics from Lyophilized Cohorts

Characteristics	Pooled LYO Arms G and H N=106
Median age, years (range)	70.0 (64 to 75)
Males, n (%)	52 (49)
Race, n (%)	
• White	83 (78)
• Asian	8 (8)
• Black	1 (1)
• Other/unknown	14 (13)
ECOG at baseline	
• 0	30 (28)
• 1	62 (59)
• 2	14 (13)
Disease characteristics	
• Primary reason for HSCT ineligibility	
• Age	46 (44)
• Comorbidities	4 (4)
• Inadequate response to salvage therapy	13 (12)
• Failed prior transplant	30 (29)
• Other	8 (8)
• Performance Status	4 (4)
Diagnosis by central review	
• DLBCL NOS	
• ABC	50 (48)
• GCB	42 (40)
• NOS	3 (3)
• -+EBV, NOS	3 (3)
• High grade with rearrangements	5 (5)
• T cell histocyte rich	1 (1)
Prior lines of therapy, mean (SD)	2.3 (1.3)
• Refractory to first prior anti-lymphoma therapy	73 (69)
• Refractory to last prior anti-lymphoma therapy	81 (76)
• Refractory to last prior anti-CD20	74 (70)

Characteristics	Pooled LYO Arms G and H N=106
• Time from last anti-lymphoma therapy, days mean (SD)	368.6 (907.7)
• Received prior bendamustine	0
Disease features at baseline	
• Bulky disease	28 (26)

DLBCL=diffuse large B cell lymphoma; EBV=Epstein Barr Virus; ECOG=Eastern Cooperative Oncology Group; GCB=germinal centre B cell like; HSCT=hematopoietic stem cell transplantation; NOS=not otherwise specified; SD=standard deviation

Source: Clinical study report, 2020 [4]

Efficacy

Key efficacy outcomes for the pooled cohort receiving lyophilized formulation are presented in Table 23. The data cut-off for efficacy and harms was January 2, 2020, with a median duration of follow-up of 19.4 months in Arm G and 8.8 months in Arm H, both of which were shorter than the primary long term analysis of the RCT phase (42.2 months). Deaths occurred in 48% of patients across both arms, for a median survival of 11.0 months (95% CI: 8.3, 14.2). Median PFS was 6.1 months (95% CI: 5.1, 8.0) across both arms. CRs were observed in 40% of patients by the end of the treatment period, using independent review by PET. The median DOR was 6.2 months (95% CI: 5.4, 11.6) across both arms.[4] The median PFS and median DOR were all numerically lower in pooled results from Arms G and H than they were with the pola-BR group in the RCT phase. Arms G and H of study GO29365 are still ongoing, while the RCT phase of GO29365 has been completed.

Harms

Key harms data for the pooled cohort receiving lyophilized formulation are presented in Table 24. Across Arms G and H, 99% of patients experienced at least one AE, 77% of AEs were grade 3 or 4. Common AEs included neutropenia (31% in Arms G and Arm H [27% were grade 3 or 4]), and this was consistent with the RCT phase. Other common AEs were thrombocytopenia (18% [14% grade 3 or 4]) and anemia (26% [8% grade 3 or 4]).[4]

SAEs were reported in 51% of patients. Febrile neutropenia was the most common SAE (9% of patients), followed by sepsis (8% of patients) and pyrexia (7%). Febrile neutropenia (11%) was the most common SAE in the RCT phase. There were seven patients who had an AE resulting in death, and sepsis was the most common reason for death, occurring in four patients. Pneumonia was the most common reason for death in the RCT phase.[4]

There were 15% of patients who discontinued polatuzumab vedotin due to an AE (compared to 33% in the RCT phase). Dose interruptions of polatuzumab vedotin occurred in 42% of patients. Notable harms such as infection, anemia, thrombocytopenia, and neutropenia are described above.

Table 23: Efficacy (Cohorts Receiving Lyophilized Formulation)

	Pooled LYO Arms G and H N=106
End of therapy PET, IRC assessed, n (%)	
Objective response, IRC, n (%)	45 (43)
Complete response, IRC, n (%)	42 (40)
Partial response, n (%)	3 (3)
Stable disease, n (%)	4 (4)
Progressive disease, n (%)	19 (18)
Not evaluable or missing, n (%)	38 (36)

	Pooled LYO Arms G and H N=106
Duration of response	
Patients with an event, IRC, n (%)	22 (37)
Median (95% CI) duration of response, months	6.21 (5.39, 11.60)
Progression-free survival	
Events by IRC assessment, n (%)	64/106 (60)
Median [95% CI] progression-free survival, months	6.11 (5.09, 7.95)
Survival	
Deaths, n (%)	51/106 (48)
Median (95% CI) OS, months	11.01 (8.28, 14.19)

AE=adverse event; CI=confidence interval; CT=computed tomography; PFS=Progression-Free Survival; HR=hazard ratio; IRC=independent review committee; LYO: lyophilized; NE=not evaluable; OS=Overall Survival; PET=positron emission tomography; PR: Partial Response; SD=stable disease

Source: Clinical study report, 2020 [4]

Table 24: Harms (Pooled Lyophilized Formulation Safety Population)

	Pooled LYO Arms G and H N=106	
Adverse events	*All grades*	*Grades 3-4*
Any AE, n (%)	105 (99)	82 (77)
SAEs	***All grades***	***Grades 3-4***
Diarrhea	36 (34)	NR
Neutropenia	33 (31)	29 (27)
Thrombocytopenia	19(18)	15 (14)
Anemia	27 (26)	8 (8)
Peripheral neuropathy	15 (14)	NR
SAEs, n (%)		
Any SAE, n (%)	54 (51)	
Febrile neutropenia	9 (9)	
Sepsis	8 (8)	
Pyrexia	7 (7)	
Pneumonia	5 (5)	
Back pain	3 (3)	
Dehydration	3 (3)	
Neutropenic sepsis	2 (2)	
Respiratory tract infection	2 (2)	
Septic shock	2 (2)	
Urinary tract infection	2 (2)	

	Pooled LYO Arms G and H N=106
Diarrhea	2 (2)
Vomiting	2 (2)
Tumour lysis syndrome	2 (2)
Atrial fibrillation	2 (2)
Mortality	
Fatal AEs, n	7 Sepsis (4) Hydrocephalus (1) Pneumonia (1) Death (1)
AE resulting in treatment modification or discontinuation	
Discontinuation of polatuzumab, n (%)	16/106 (15)
Dose reduction	1 (1)
Drug interruption (delay/withhold dose)	44 (42)

AE=adverse events; LYO=lyophilized; SAE=serious adverse event

Source: Clinical study report, 2020 [4]

Critical Appraisal

There was no comparator group for the arms that studied the lyophilized formulation of polatuzumab vedotin in combination with bendamustine and rituximab. This introduces the potential for bias in the reporting of AEs, as patients were aware that they were receiving active drug. Although more objective outcomes such as survival, PFS and objective response are less likely to be biased by patient knowledge of their assigned treatment, the knowledge that they were receiving active drug may have influenced their willingness to persist with therapy. The FDA conducted a pharmacokinetic comparison of the solution and the lyophilized formulation and found no difference between the two.

There were differences in baseline characteristics between the pooled lyophilized cohorts and the RCT phase. There were fewer males in the lyophilized cohort than in the RCT phase (49% versus 66%), a higher percentage of white patients (78% versus 71%), and fewer patients with bulky disease (26% versus 31%). These differences, and the shorter follow-up time of 19.4 months in the lyophilized cohort versus 42.2 months in the RCT cohort make it difficult to compare results between the lyophilized and RCT cohorts and may perhaps explain any differences seen in efficacy and harms between the cohorts.

7.2 Summary and Critical Appraisal of Submitted Indirect Comparisons

Polatuzumab vedotin has been approved by Health Canada for the treatment of DLBCL. There is currently no direct evidence comparing polatuzumab vedotin to current standards of care used in Canada. Given that other treatments are already on the market and there is an absence of head-to-head studies, the objective of this section it to critically appraise the manufacturer submitted ITCs that assesses the comparative efficacy of polatuzumab vedotin to other available treatments. Additionally, these results are used as inputs to inform the submitted pharmacoeconomic model.

7.2.1 Methods

Objectives and rationale for manufacturer's ITC

The primary objective of the sponsor's ITC was to compare the efficacy, in terms of OS and PFS, associated with polatuzumab vedotin relative to other first-line treatments for DLBCL. The sponsor submitted two overlapping but distinct unpublished reports. The first was a large systematic review and ITC feasibility assessment with a MAIC.

Systematic Literature Review and ITC feasibility

Systematic Literature Search

This systematic literature review (SLR) that was conducted by the sponsor aimed to identify all existing RCTs and comparative observational studies that evaluated pola-BR and relevant comparators for the first-line treatment of DLBCL. The search strategy included disease, study design, and intervention search terms and was limited to only English studies. Relevant studies were identified through searches of EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials. Comparators were selected by reviewing international treatment guidelines, this also included potentially emerging therapies. The initial search was conducted in September 2018 and extended multiple times up to March 2020. Major hematology and oncology conference abstracts and trial registries (Clinicaltrials.gov and WHO Clinical trials registry) were searched to identify unpublished studies.

Eligibility Criteria and Study Selection

Studies were eligible for inclusion based on the population, intervention, comparators, outcomes, and study design (i.e. PICOS) criteria outlined in Table 25. All eligibility criteria were defined a priori. Studies were RCTs and comparative observational studies that included one of the interventions of interest, irrespective of blinding status or other RCT characteristics. This SLR allowed inclusion of unpublished trial inclusion. Studies were screened based on titles and abstracts. Full-text articles of studies deemed eligible according to the full paper review. Full text articles were screened twice.

Table 25: Population, Interventions, Comparisons, Outcomes and Study Design Criteria for Study Inclusion

Criteria	Monotherapy
Population	• Adult patients (≥18years) with R/R DLBCL who are receiving second or third line (or beyond) therapy • Subgroups of interest includes: • SCT ineligible • Failed transplant patients • Duration of response to prior therapy: ≤12 months vs. >12 months • Disease burden: high vs. low • Age (≤60 vs. >60) • Stage of Disease (I–II vs. III–IV) • Prior systemic therapy • Refractory vs. relapse • Extranodal-site involvement (0–1 vs. 2–4) • ECOG Score
Interventions	Polatuzumab vedotin in combination with bendamustine plus rituximab
Comparators	Licensed or investigational pharmaceutical treatment available for R/R DLBCL patients: • Bendamustine+/–rituximab • Brentuximab vedotin • CEPP (Cyclophosphamide, Etoposide, Procarbazine) +/– rituximab • CEOP (Cyclophosphamide, Etoposide, Vincristine) +/– rituximab • DA-EPOCH (Cyclophosphamide, Doxorubicin, Etoposide, Vincristine) +/– rituximab • GDP (Cisplatin, Dexamethasone, Gemcitabine) +/–rituximab • Carboplatin, Dexamethasone, Gemcitabine +/– rituximab • GemOx (Gemcitabine, Oxaliplatin) +/– rituximab • Gemcitabine + vinorelbine +/– rituximab • Lenalidomide +/– rituximab • Rituximab • Ibrutinib • Pixantrone +/– rituximab • CAR-T (Axicabtagene ciloleucel or Tisagenlecleucel)

Criteria	Monotherapy
	• MOR208 • Venetoclax • Apatinib • DHAP (dexamethasone, cytarabine, cisplatin) +/– rituximab • ICE (ifosfamide, etoposide, carboplatin) +/– rituximab • MINE (mesna, ifosfamide, mitoxantrone, etoposide) +/– rituximab • ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) +/– rituximab • IME (ifosfamide, mitoxantrone, etoposide) +/– rituximab • IVE (ifosfamide, epirubicin and etoposide) +/– rituximab • CEPP • R+/–PECC (Rituximab-Prednisone, Etoposide, Chlorambucil, Lomustine) • BSC/placebo
Outcomes	Efficacy: • OS • PFS • TTP • EFS • DOR • Response rates (CR, PR, SD) • Any response rates reported as PET-CR (i.e. metabolic CR) or using older criteria (e.g. CRu), or a mixture of various different criteria ([Cheson et al. 2007]), Lugano [Cheson et al. 1999], modified Lugano [Cheson et al. 2014]) • ORR • DCR Safety • All-grade treatment related AE • Treatment related Grade 3, 4 or 5AEs • Treatment related SAEs • Tolerability: dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs) HRQoL and PRO measures (e.g. EORTC QLQ-C30)
Study design and factors	• RCTs, any duration (irrespective of blinding) • Prospective single arm studies • Comparative observation studies
Language	English Language
Search Period	Initial Search in September 2018 and refreshed in March 2020

Source: Adopted from manufacturer's submitted ITC [9]

Data Extraction

The data extraction protocol is unclear, specifically the number of independent reviewers that carried out the data extraction process and the initial scans. Data were extracted in duplicate for study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies.

Quality Assessment of Included Studies

The risk of bias associated with included RCTs was assessed using the Cochrane Risk of Bias tool and the results of these assessments were presented. This approach was based on guidance provided by the Centre for Reviews and Disseminations for assessing the quality of studies included in SLRs and assessed the likelihood of selection, performance, and attrition and detection bias. This information was not used later in analyses.

Indirect Comparison Feasibility Assessment Methods

An ITC feasibility assessment was undertaken to explore the plausibility of conducting a formal synthesis of evidence identified from the SLR. In order to complete the feasibility analysis, a network-building exercise was conducted to assess whether a connected network of evidence could be constructed. This assessment was also supplemented with the addition of potential studies not meeting the SLR inclusion criteria.

7.2.2 Results of Systematic Review

The systematic review identified a total of 3,618 unique publications. Overall, 39 studies (from 124 publications) met the criteria for inclusion for the core comparators. Of those that met inclusion criteria 11 were RCTs and 28 were single arm trials. Importantly, only one study was double blinded. The majority of trials were observational studies with no comparator. A total of 39 studies included a total of 4,104 subjects with sizes ranging from 14 to 429 (Table 26). The median follow-up across studies was 24 months and ranged from 3 to 65 months.

Table 26: Studies Included in Systematic Review

Study name (Primary reference)	Dates of study	Study design (Blinding)	Study location or region	Interventions	No. of patients randomised/ enrolled	Median follow-up (months)
Aribi et al. 2010	2005-2008	RCT (single-blind)	Algeria	ESHAP vs GDP	96	13
Avilés et al. 2010	2009	RCT	Mexico	ESHAP vs R-ESHAP	100	64.5
EudraCT	2017	RCT (Open label)	Multinational (Canada included)	Lenalidomide vs IC	111	NR
NCT01679119	2011-2013	RCT (Open label)	Multinational (Canada included)	Inotuzumab ozogamicin plus rituximab vs investigator choice (BR or rituximab plus gemcitabine)	338	15.4
NCT00088530	2004-2008	RCT (Open label)	Multinational (No Canada)	Pixantrone vs Comparator	140	18
PIX306	X	RCT (Open label)	Multinational (No Canada)	Pixantrone + Rituximab vs Gemcitabine + Rituximab	312	24

Study name (Primary reference)	Dates of study	Study design (Blinding)	Study location or region	Interventions	No. of patients randomised/ enrolled	Median follow-up (months)
GO29365, NCT02257567	2014-2018	RCT (Open label)	Multinational (Canada included)	pola-BR vs BR	80	22.3
El Gnaoui et al. 2007	2002-2005	Observational	France	R-GemOx	33	28
Lakshmaiah et al. 2015	2011-2012	Observational	India	Lenalidomide	15	24
López et al. 2008	2004-2006	Observational	Spain	R-GemOx	32	13
NCT00616	2003-2009	Observational	France	R-GemOx	48	65
ZUMA-1	2015-2016	Observational	US/Israel	Axicabtagene ciloleucel (Yescarta)	77	8.7
NCT01111	2010-2011	Observational	Japan/Korea	BR	59	4.7
Papageorgiou et al. 2005	X		Greece	Gemcitabine plus vinorelbine	22	44
NCT02030834	2014-2017	Observational	US	Tisagenlecleucel	14	28.6
JULIET, NCT02445248	X	Observational	Multinational (Canada included)	Tisagenlecleucel (Kymriah)	115	3
Vacicra 2014	2008-2011	Observational	US	BR	59	36
Wiermik 2008	2005-2006	Observational	US	Lenalidomide	26	3.7
Witzig et al. 2011	2006-2008	Observational	Multinational (no Canada)	Lenalidomide	217	9.2
Zinzani 2011	2009	Observational	Italy	Lenalidomide and Rituximab	23	16
Gisselbrecht et al. 2010	2003-2007	RCT (Open label)	Multinational (no Canada)	R-ICE vs R-DHAP	400	27
Fayad et al. 2015	2007-2009	RCT (Double-blind)	Multinational (no Canada)	Dacetuzumab + R-ICE vs R-ICE + Placebo	151	27

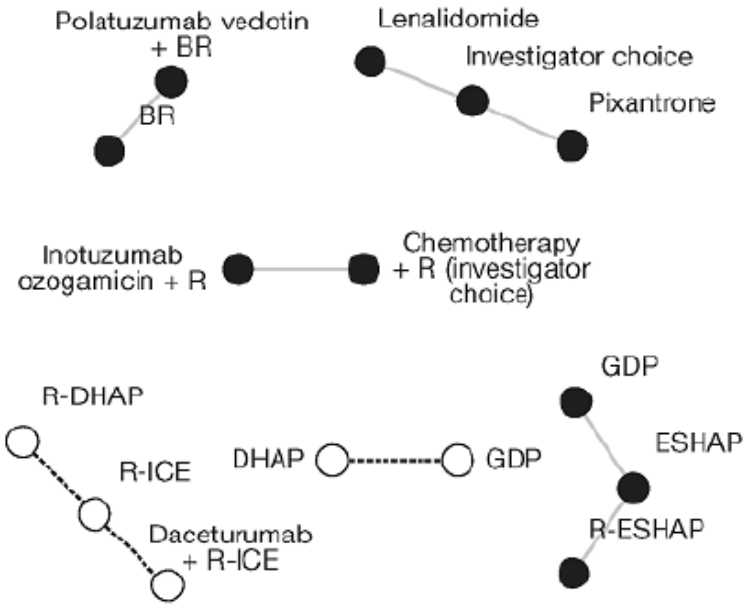
Study name (Primary reference)	Dates of study	Study design (Blinding)	Study location or region	Interventions	No. of patients randomised/ enrolled	Median follow-up (months)
Kuruvilla et al. 2015	2003-2011	RCT (Open label)	USA/Australia/Canada	GDP vs DHAP	429	53
Chiappella et al. 2019	2013-2018	RCT (Open label)	Unclear	Bortezomib-R-DHAP vs R-DHAP	108	15.9
Bartlett et al. 2017	2013-2014	Observational	USA	Brentuximab vedotin	55	NR
Davids et al. 2017	2011-2014	Observational	USA/Australia	Venetoclax	106	24
Gumenyuk et al. 2016	2007-2015	Observational	Italy	R-IEV	42	36
Hertzberg et al. 200	NR	Observational	Australia	ICE	38	11
Jacobsen et al. 2015	2011-2013	Observational	US	Brentuximab vedotin	49	4.6
Jurczak et al. 2018	2013-2014	Observational	Multinational (no Canada)	MOR208	35	21
Jerkeman et al. 2004	2000-2002	Observational	Sweden/Finland	ICE	40	NR
Jermann et al. 2004	1998-2001	Observational	Switzerland	Rituximab–EPOCH regimen	50	33
Martin et al. 2008	2000-2007	Observational	Spain	R-ESHAP	163	29
Ma et al. 2019	2017-2019	Observational	NR	Apatinib	32	8.6
Proctor et al. 2001	NR	Observational	UK	IVE	61	NR
Tobinai et al. 2004	1999-2000	Observational	Japan	Rituximab	68	6
Wang et al. 2013	2008-2011	Observational	US	Lenalidomide and rituximab	45	29
Wilder, Ogden, and Jain 2001	1993-1996	Observational	US	EPOCH	93	NR
(Zelenetz et al. 2003	NR	Observational	NR	ICE	222	60

Source: Adopted from manufacturer's submitted ITCs [9]

Network Feasibility Analysis

The investigators conducted an ITC feasibility assessment by constructing a network using the evidence identified in the SLR. They concluded that since much of the comparator evidence arises from single arm studies, a network-based ITC would not be feasible. Only 9 trials would be included and produced a disconnected network - see Figure 4. Even expanded inclusion outside of the SLR did not produce a connected network. These results were used to support the need for an MAIC analyses.

Figure 4: Network of Evidence



Source: Adopted from manufacturer's submitted ITC [9]

7.2.3 Matching-Adjusted Indirect Comparison (MAICs)

Trials and Comparisons Included in the MAIC

A comparison of included trials in the MAIC is presented in Table 27. The report carries out a number of MAICs to compare pola-BR to other therapies using results reported in single-arm trials. The justification for using an MAIC approach was based on the network feasibility assessment which showed a lack of a common comparator between studies of pola-BR and other therapies. Thus, MAICs were carried out for each comparison using an unanchored approach. They used individual patient characteristics from patients in the GO29365 study to generate weights for patients in order to mimic the baseline summary statistics reported in the other trials. Details on how the studies and which comparators were selected were not provided. Using a propensity score model with a

predefined list of variables, weighting was performed and weighted treatment estimates for the outcomes are then reported. MAICs were used to compare pola-BR to four treatments:

- R-GemOx (NCT0016)
- Pixantrone (PIX301)
- Kymriah (JULIET)
- Yescarta (ZUMA-1)

Table 27: Comparison of Included Trials in MAIC

Characteristics	pola-BR (GO29365)	R-GemOx (NCT0016)	Pixantrone (PIX301)	Kymriah (JULIET)	Yescarta (ZUMA-1)
Years	2014-2018	2003-2009	2004-2008	--	2015-2016
Location	Global	France	Global	Global	US/Israel
Design	RCT (Open label)	Observational (Open-Label)	RCT (Open label)	Observational (Open-Label)	Observational (Open-Label)
Size (n)	80	48	140	167	81
Intervention(s)	• Polatuzumab vedotin: 1.8 mg/kg Bendamustine:90mg/m^2 • Rituximab: 375mg/m^2 • Bendamustine:90mg/m^2 • Rituximab: 375mg/m^2	• Rituximab 375 mg/m^2, gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2	• Pixantrone dimaleate: 85 mg/m² • Comparator: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone or gemcitabine	• single dose of tisagenlecleucel (median, 3.0×10^8 [range, 0.1-6.0×10^8] CAR-positive viable T cells)	• Axi-cel at a target dose of 2×10^6 CAR T cells per kilogram of body weight (on day 0)
Median Follow-up (months)	22.3	65	18	>3	8.7
Inclusion	• Transplant ineligible R/R DLBCL patients • Patients could have had prior autologous but not allogeneic transplant • ECOG PS of 0, 1, or 2 • Adequate hematologic function unless inadequate function is due to underlying disease, such as extensive bone marrow involvement or hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator	• Patients with age between 18 and 75 years old and had R/R CD20-positive DLBCL that had been diagnosed in accordance to the World Health Organization classification at the time of enrollment • Patients were required to be: • (i) in first or second relapse, • (ii) previously treated with a chemotherapy regimen containing anthracycline, with or without rituximab, and • (iii) not eligible for high-dose therapy.	• Patients aged ≥18 years diagnosed with de novo DLBCL, DLBCL transformed from indolent lymphoma, or grade 3 follicular lymphoma who relapsed after at least one standard rituximab-containing multi-agent regimen	• Patients with DLBCL were eligible if they had measurable disease after primary and salvage therapies • relapsed or residual disease after ASCT, or were not eligible for autologous or allogeneic stem-cell transplantation and eligible if they had CD19+ DLBCL and a limited prognosis (<2 years of anticipated survival), and a partial response to or stable disease after the most recent therapy	• Age ≥18 years • ECOG performance status 0-1, and refractory disease defined as progressive disease or stable disease as best response to last line of therapy, or disease progression ≤12 months after ASCT).
Exclusion	• Patients with history of severe allergic or anaphylactic reactions to humanized or murine	NR	• Primary refractory de novo DLBCL and grade 3 FL,	• Pregnant or lactating women. The safety of this	• History of malignancy other than nonmelanoma

Characteristics	pola-BR (GO29365)	R-GemOx (NCT0016)	Pixantrone (PIX301)	Kymriah (JULIET)	Yescarta (ZUMA-1)
	monoclonal antibodies (MAbs, or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products • Transplant eligible patients were also excluded • History of other malignancy that could affect compliance with the protocol or interpretation of results and Known history of HIV and hepatitis C • Women who were pregnant or lactating		defined as progression within 12 weeks of the last cycle of the first-line treatment regimen, was an exclusion criterion	therapy on unborn children is not known. Female study participants of reproductive potential must have a negative serum pregnancy test at enrollment. A urine pregnancy test will be performed within 48 hours before infusion. • Uncontrolled active infection. • Active hepatitis B or hepatitis C infection. • Concurrent use of systemic steroids. Recent or current use of inhaled steroids is not exclusionary. For additional details regarding use of steroids • Any uncontrolled active medical disorder that would preclude participation as outlined.	skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years • History of allogeneic stem cell transplantation • Prior CAR therapy or other genetically modified T cell therapy

ASCT= autologous stem cell transplant ECOG PS= Eastern Cooperative Oncology Group Performance Status; RCT=randomized controlled trial

Comparison of Included Studies for MAIC

The MAIC used 5 separate studies to compare to polatuzumab vedotin. The comparators included R-GemOx [40], pixantrone [41] Kymriah (JULIET) [32] and Yescarta (ZUMA-1).[42] The studies differed from each other in notable ways. Most notable to the heterogeneity of the studies was the designs, inclusion/exclusion criteria, and the median follow-ups. Firstly, only 2 of the study arms were clinical trials, with the other 3 were observational studies. Secondly, important differences in the inclusion/exclusion criteria related to diagnosis and disease progression may lead to systematic differences between populations. Specifically, the inclusion of those with refractory disease was different between some arms and the polatuzumab vedotin study. In some comparisons, this meant exclusion of patients from the polatuzumab vedotin study to allow for comparison. Thirdly, the median follow-up time between studies ranged widely from 3-65 months highlight the differences in study designs.

Matching of Comparator Groups for MAIC

The MAICs were conducted in line with the methodology described in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document 18. Study-specific weights were derived to match the R/R DLBCL patients of the GO29365 study who received pola-BR with those populations reported in the single-arm studies separately. Patient baseline characteristics from the GO29365 study were weighted according to the patient baseline characteristics from each of the comparisons of interest separately using pre-selected prognostic factors. These factors were age at baseline >60 years or median age, ECOG PS score, refractory to last line of treatment, number of prior treatment lines, and prior SCT.

The sponsor did not specify how these prognostic factors were identified (i.e., based on expert opinion or literature review). In addition, no search was conducted for potential effect modifiers and thus, no such factors were included in the propensity score model. Importantly, due to major inclusion differences between PIX301 and GO29365, the sample of patients was substantially reduced, and as a result, the investigators conducted separate MAICs for each prognostic factor. See Table 28 for matched comparison across all the different groups.

Table 28: Comparison of Matched Population Characteristics to POLA-BR Population for each MAIC Analysis

Characteristics	pola-BR	R-GemOx (NCT0016)	pola-BR	Pixantrone (PIX301)	pola-BR	Kymriah (JULIET)	pola-BR	Yescarta (ZUMA-1)
Number	65	49	21	70	78	165	66	81
Age at baseline > 60 years or median (IQR)	80%	69%	86%	51%	65.1 (12.1)	55.9 (12.9)	63.2 (11.8)	57.1 (10.6)
ECOG PS score > 2	10.8%	22%	62%	63%	66.7%	53.3%	68.2%	64%
Refractory patients	76.9%	12%	90%	57%	82.1%	58.2%	97.0%	78%
Number of prior treatment lines > 1 or 2	56.9%	14%	3 (25)	3 (2-9)	69.2% *	96.4% *	80.3% *	98% *
Prior Stem Cell Transplant	15.4%	35%	38%	16%	19.2%	43.6%	22.7%	23%

**Greater than 2. Adopted from Submitted Sponsor Report*

Outcomes

CR was selected as the primary focus of the comparison. Reported CR were taken from the relevant published studies.

Analysis Methods

Adjustment for covariates were selected based on factors that could impact outcomes. Effective sample size (ESS) was reported for all weighted analyses. They used patient characteristics age, ECOG performance status, number of prior lines of treatment, prior stem-cell transplant, and refractory disease or early relapse. For the unweighted rates, 95% CIs by Clopper-Pearson exact method were used, and for the unweighted rate differences, 95% CI by Wilson were used. For the weighted rates and rate differences, empirical bootstrapped CIs were used. For the unweighted HRs the 95% Wald CIs were reported. To calculate weighted HR, Wald CIs were constructed using robust variance estimators. Sensitivity analysis were conducted among all the pre-defined prognostic factors of interest when data was available.

MAIC Results

The sponsor performed four independent MAICs based on a comparison of polatuzumab vedotin to the following four comparators: R-GemOx, pixantrone, Kymriah and Yescarta. All analyses leveraged a single-arm study for each comparator. For the MAICs, the pooled pola-BR population consisting of 88 patients (Phase Ib: n=6; randomized Phase II: n=40; and Arm G: n=42) was used in order to increase the pola-BR sample size. This is the ITT population of all patients assigned to pola-BR. The results from the MAIC for unweighted and weighted CR and OS are summarized in Table 29. Pixantrone results were reported weighted estimates for each prognostic factor but did not report overall weighted results. They conducted a number of sub-group analysis when feasible exploring the impact of age, ECOG PS scores, refractory status, prior treatments, and prior SCT. The weighted results showed statistically significant differences in CR between pola-BR and R-GemOx (37.2% ;95% CI 15.2 to 76.1), and Kymriah (23.2%; 95% CI 9.8 to 36.0). Inversely, the results showed no statistical difference between pola-BR and Yescarta for both CR (-6.5%; 95% CI: -25.5 to 13.5) and OS (1.38; 95% CI: 0.57 to 3.31). ESS was low for R-GemOx (9.8), pixantrone (21), Kymriah (14.6) and Yescarta (18.6). Additional sub-population sensitivity analyses across all pre-defined prognostic factors limiting to specific subgroups for comparisons did not find the results shifted in a meaningful way.

Table 29: Summary of MAIC Results

POL-BR Vs.	Groupings/Outcome	Effective Sample Size (ESS)	Estimate
R-GemOx (NCT0016)	1. Unweighted Difference in CR Rate (95% CI)		1.8 (-20.0,16.9)
	2. Weighted Difference in CR Rate (95% CI)	9.8	37.2 (15.9,76.1)
Pixantrone (PIX301)	1. Unweighted Difference in CR Rate (95% CI)	21	46.7 (22.7,67.9)
	Separate MAICs by Individual Pre-Selected Factor		
	a. Age>60	10.6	60.2 (45.3,79.5)
	b. ECOG PS	21.0	46.5 (26.0,70.1)
	c. Refractory Patients	9.1	59.0 (43.0,82.8)
	d. Prior SCT	17.4	52.6 (30.9,76.8)
	2. Unweighted Difference in OS HR (95% CI)	21.0	0.30 (0.12 ,0.76)
	Separate MAICs by Individual Pre-Selected Factor		
	a. Age>60	10.6	0.18 (0.07 ,0.52)
	b. ECOG PS	21.0	0.31 (0.13 ,0.75)
	c. Refractory Patients	9.1	0.18 (0.06 ,0.54)
	d. Prior SCT	17.4	0.23 (0.08 ,0.69)
Kymriah (JULIET)	1. Unweighted Difference in CR Rate (95% CI)		23.2 (9.8, 36.0)
	2. Weighted Difference in CR Rate (95% CI)	14.6	30.0 (10.3 ,45.2)
	3. Weighted Difference in OS HR (95% CI)	14.6	0.54 (0.25 ,1.18)
Yescarta (ZUMA-1)	1. Unweighted Difference in CR Rate (95% CI)		-7.8 (-23.8, 8.5)
	2. Weighted Difference in CR Rate (95% CI)	18.6	-6.5 (-25.5 ,13.5)
	3. unweighted Difference in OS HR (95% CI)		1.46(0.94 ,2.27)
	4. Weighted Difference in OS HR (95% CI)	18.6	1.38 (0.57 ,3.31)

Source: Adopted from manufacturer's submitted ITC [9]

7.2.4 Critical Appraisal

The sponsor submitted an MAIC based on studies selected from a broad SLR. However, due to limitations in the evidence-base the results should be interpreted with caution. This submitted analysis has major limitations that hinder the potential applicability of the comparative results. The major concerns with the submitted report are related to the quality of the analysis, limited control of prognostic factors and effect modifiers, and the heterogeneity of the evidence used. Specifically, differences in design and populations between trials, inclusion of open-label studies and non-comparator trials raise concern of potential issues in the evidence base utilized to conduct the different MAIC. The submitted analysis is unable to overcome the limited evidence base and quality of evidence used.

- The SLR was based on a search of multiple databases over a reasonable period that was updated a number of times to allow for the analysis to remain up-to-date. Overall, the methodology presented is mostly in line with current methodological standards for systematic reviews. Their conclusion that a network analysis would not be feasible is well supported. It is

important to note it is unclear if independent reviewers conducted the analysis and how redundancy was incorporated into the methodology to ensure robustness of results.

- Although a quality assessment of the studies was completed using the Cochrane risk of Bias this information was not applied to ensure inclusion of higher quality trials into the MAIC. It is unclear if this influenced the selection of studies. The quality of included studies is a major concern as the majority of trials were either open-label or did not include a comparator. This lowers the quality of the included studies and raises questions of reduced internal validity of the findings, especially for the outcome of response. Additionally, some of the studies included did have issues full reporting and had evidence of being low-quality studies. The lack of comparators led to an inability to develop a connected network which would allow for a network-based ITC analysis.

- The major concern with the MAIC is that there were large differences in study populations and the use of all non-comparator-based arms. Significant differences were noted in baseline patient characteristics and inclusion criteria, such as ECOG PS, age and balance in sex of patients. Although there were a number of subgroup adjustments conducted, these analyses further reduced an already diminished evidence base, and were largely found to produce wide estimates. This raises concerns around the differences in populations and the control for important prognostic factors and effect modifiers. There were evidence differences between the included trials in their inclusion and exclusion criteria. Specifically, related to the inclusion of patients with refractory disease and previous therapy. These differences are largely unaccounted for in the methodology and may produces systematic differences between populations and introduce bias in the analyses.

- Although the submitted MAIC was broad and extensive in the number of analyses conducted and sub-groups, these still do not overcome the inherent flaw that all evidence was drawn from small open-label non-controlled studies. The ESS ranges from 9 to 21. This greatly reduces the precision and produces wide estimates that are often uninformative. This also increase the likelihood that estimates might be driven by a small (or individual) subset of subjects. Additionally, it is also unclear why the 4 drugs were selected and other comparators which were included in the SLR were not selected.

- For the MAICs conducted for pixantrone specifically, no conclusions can be drawn from these results due to substantial limitations for these analyses. The analysis conducted due to the lack of comparability between trials was unusual since they didn't perform a fully weighted MAIC. Rather the adjustments were made by factor and separate MAICs conducted. This limits the inerrability of the results since they only account for a single factor at a time as it does not allow for the control of multiple factors at once. Also because of major differences between inclusion criteria a portion of the population in the polatuzumab vedotin study was not included further diminishing the sample size included in the analyses.

- Importantly, as is common in the literature the size of all the studies is concerning. The limited sample sizes and complexity of the trials is more likely to lead to conclusions of insufficient evidence to show differences between comparators as wider intervals are common with small sample sizes and high rates of variability. This is not a limitation of the analyses but of the evidence base available. Importantly, this limitation was further pronounced through the weighting process and methods used as discussed above.

- There were only two outcomes reported in this MAIC and no other efficacy, safety or QoL outcomes reported. It is unclear why additional outcomes were not explored given that this information was cited as being collected and included in the methods of the SLR report. Further analysis could have been conducted explore safety and tolerability. These additional analyses would greatly increase the utility of this MAIC especially for inclusion in economic models and comparative studies. This analysis also did not report or conduct any analysis related to safety, specifically tolerability, which is an important consideration when comparing agents within a drug class and indication.

7.2.5 Summary and Conclusions

The applicability of sponsors ITCs is impacted by the limited scope and potential limitations in the submitted analysis. This is largely due to a weak and sparse evidence base. Limitations to the evidence base due to population heterogeneity, limited adjustment for all prognostic factors and effect modifiers, reduced precision due to small samples sizes, and inclusion of open-label non-comparator studies limited the robustness of any possible analysis. Additionally, although MAIC was extensive it was not able to convincingly

overcome the limitations inherent in the evidence base. Overall, the results of this analysis must be interpreted with caution. Little can be elucidated on the comparative efficacy to other products based solely on this submitted ITC analyses.

7.3 Summary and Critical Appraisal of Submitted PSWA

Pola-BR has been approved by Health Canada for the treatment of DLBCL. There is currently no direct evidence comparing pola-BR to current standards of care used in Canada. Given that other treatments are already on the market and there is an absence of head-to-head studies, the objective of this section it to critically appraise the sponsor submitted real-world study that assesses the comparative effectiveness of pola-BR to other available treatments.

7.3.1 Objectives and Rationale for Sponsor's PSWA

The primary objective of the sponsor's PSWA was to compare the effectiveness, in terms of OS and PFS, associated with pola-BR relative to other treatments in R/R DLBCL.The sponsor submitted two overlapping but distinct unpublished reports. The first was a large systematic review and ITC feasibility assessment with a MAIC the second was a RWE study (PSWA) leveraging data from the Alberta O2 RWD.

7.3.2 Methods

In additional to the SLR and ITC report, the sponsor submitted a PSWA leveraging IPD from the Alberta O2 RWD. This submission was also appraised in the context of potential supporting any indirect comparisons.

Data Sources and Patient Population

The submission leveraged data from the GO29365 trial which enrolled patients with histologically confirmed R/R DLBCL with at least one prior therapy. Patients in this trial were ineligible for SCT and had ECOG scores of 0 to 2. These patients were used as the intervention group that received polatuzumab vedotin. For the comparators, the report leveraged Alberta O2 RWD data which includes patients with a broad range of cancer diagnosis. The Alberta data is commonly used to conduct real-world studies on the safety and effectiveness of cancer treatments. Similar inclusion/exclusion criteria for the CO29365 trial were applied to identify similar patients. All patients that met inclusion criteria were included regardless of treatment. Patients included were those that had 1 or 2 previous lines of therapy. No patients with greater than 3 lines of therapy were included. The study cohorts identified were 88 patients in the pola-BR group and 50 patients in the comparator group. The Inclusion and exclusion criteria are summarized in Table 30.[43]

Table 30: Comparison of Inclusion and Exclusion Between Study Arms.

Study Arm	GO29365 Trial	Alberta RWD
Inclusion	• Histologically confirmed R/R DLBCL • If the patient has received prior bendamustine, response duration must have been greater than (>) 1 year (for participants who have relapse disease after a prior regimen • At least one bi-dimensionally measurable lesion on imaging scan defined as >1.5 centimeters (cm) in its longest dimension • Confirmed availability of archival or freshly collected tumor tissue • Life expectancy of at least 24 weeks • ECOG PS of 0, 1 or 2 • Adequate hematological function unless inadequate function	• R/R DLBCL • Patients are transplant-ineligible
Exclusion	• History of severe allergic or anaphylactic reactions to humanized	• Patients that have received bendamustine in the past

Study Arm	GO29365 Trial	Alberta RWD
	or murine monoclonal antibodies or known sensitivity or allergy to murine products • Contraindication to bendamustine, rituximab or obinutuzumab • Prior use of any mAbs, radioimmunoconjugate, or ADC within 4 weeks or 5 half-lives before Cycle 1 Day 1 • Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1 Day 1 • Ongoing corticosteroid use >30mg per day prednisone or equivalent, for purposes other than lymphoma symptom control • Completion of autologous SCT within 100 days prior to Cycle 1 Day 1 • Prior allogenic SCT • Eligibility for autologous SCT • History of transformation of indolent disease to DLBCL • Evidence of significant, uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease or significant pulmonary disease • Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization within 4 weeks prior to Cycle 1 Day 1 • Suspected or latent tuberculosis • Positive test results for chronic hepatitis B infection or for hepatitis C antibody • Known history of HIV seropositive status or known infection with HTLV-1 virus • Women who are pregnant or lactating or who intend to become pregnant within a year of the last dose of study treatment in the rituximab cohort or within 19 months of last dose in the obinutuzumab cohort • Evidence of laboratory abnormalities in standard renal, hepatic or coagulation function tests	• Primary or secondary CNS lymphoma • Treatment with chimeric antigen receptor T-cell (CAR-T) therapy within 100 days prior to Cycle 1, Day 1 • Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1 Day 1

Study Arm	GO29365 Trial	Alberta RWD
	• Treatment with chimeric antigen receptor T-cell therapy within 100 days prior to Cycle 1, Day 1	

ECOG PS= Eastern Cooperative Oncology Group Performance Status
Source: Sponsor submitted Propensity Score Weighted Analysis, [43] Clinicaltrials.gov [39]

Outcomes

The report focused on the estimation of OS and PFS. OS was defined as time from the date of randomization (trial) or start of treatment (RWD) to the date of death. PFS was defined as time from date of randomization (trial) or start of treatment (RWD) to the first occurrence of progression, relapse, or death. Importantly, PFS data may not be complete for all patients in the RWD arm, it was only available for 52% of the RWD cohort. To account for this, use of next line of treatment was used as a proxy of evidence of potential progression. The report suggests that this will likely overestimate the HR.[43]

Analysis

A PSWA was conducted. The propensity score variables were selected in consultation with clinical advisors and data availability. They included R/R category, age, previous therapy, Ann Arbor stage, bulky disease, lactate dehydrogenase (LDH) target, and extra nodal involvement. Propensity scores were developed using a multivariable logistic regression model. The propensity scores were used to conduct an IPTW analysis. Patients with missing information were not included. This is an approach that allows weight based on sets of patients to be applied and distributed and importantly it saves sample size and minimizes loss of eligible patients. Balance between groups was assessed both in the pre- and post-weighting phases and compared using standardized differences.[43]

Kaplan-Meier plots were drawn to summarize survival in the two interventions groups. Both OS and PFS were estimated using a weighted cox proportional hazard models to report HR. Proportional hazard assumptions were assessed based on log-log cumulative hazard plots. Sensitivity analyses were conducted to explore the impact of different propensity score methods, unweighted cox models, and imputation of missing values. Several sensitivity analyses were performed to assess the robustness of the primary analysis: 1) unweighted Cox regression adjusted for the parameters used for propensity score derivation; 2) unweighted Cox regression adjusted for propensity score; 3) doubly robust (applied propensity score methods with multivariable regression adjustments using covariates identified by clinical experts for propensity score estimation); 4) unweighted Cox regression adjusted for the parameters used for propensity score deviation and additionally for time from first-line therapy; 5) missing values in both data sets were imputed with values reflective of the worst-case scenario. In other words, if an individual was missing covariate data, they were assigned a value indicative of the worst outcome; and 6) patients with extreme weights (>4) were removed from the primary analysis. All analysis was conducted using Statistical Analysis System (SAS).[43]

7.3.2 Results

Patient Population

The sponsor performed a PSWA between the Alberta O2 RWD group and pola-BR group from the GO29365 trial. A total of 42 patients in the RWD arm and 91 in the pola-BR arm met the inclusion/exclusion criteria (Table 31). The groups were not well-balanced prior to pre-weighting with major differences in refractory status, age, lines of therapy, and disease characteristics noted. The proportions of patients with refractory disease (72.5% vs. 66.7%), >1 prior lines of anti-lymphoma therapy (45.1% vs. 28.6%), advanced Ann Arbor stage (75.8% vs. 71.4%), mean age (72.5 years vs. 66.7 years), and mean LDH (496.7 U/L vs. 345.8 U/L vs.) were 538 greater in the pola-BR group compared to Alberta O2 RWD. The proportions of patients with bulky disease (26.19% vs. 21.98%) and extra nodal involvement (64.3% vs. 57.1%) were greater in the RWD group compared to the pola-BR group. Post-weighting was better balanced using IPTW but differences in total number of lines (46.5 vs. 41.5) and LDH (532.9 vs. 457.1) remained different between the two study groups.[43]

Table 31: Overview of demographics pre- and post-weighted characteristics

Covariates	Pre-weighted characteristics			Post-weighted characteristics[a]		
	Alberta O2 RWD	Pola+BR Group	SMD[b]	Alberta O2 RWD	Pola+BR Group	SMD[b]
N	42	91	NA	44.3[c]	89.9[c]	NA
Refractory, %	66.67	72.53	**0.13**	74.04	70.77	0.07
Age in years, mean (std dev) median (min – max)	66.76 (12.78)	70.68 (10.68)	**0.34**	68.64 (11.98)	69.59 (11.90)	0.08
Total number of lines of prior anti-lymphoma therapy >1, %	28.57	45.05	**0.34**	46.52	41.48	**0.10**
Ann Arbor Stage III & IV, %	71.43	75.82	**0.10**	75.79	75.33	0.01
Bulky disease, %	26.19	21.98	**0.10**	26.47	23.23	0.08
LDH (U/L), mean (SD) Median (min – max)	345.79 (355.71)	496.69 (488.26)	**0.33**	532.89 (640.17)	457.11 (436.44)	**0.15**
Extra-nodal involvement, %	64.29	57.14	**0.15**	63.15	60.01	0.06

Source: Sponsor submitted Propensity Score Weighted Analysis [43]

Comparative Results

Before weighting, pola-BR was found to have a significant OS (HR 0.51, 95% CI: 0.32-0.82) to Alberta O2 RWD (n = 42) and insufficient evidence in PFS (HR 0.80, 95% CI 0.51-1.24) compared to the Alberta RWD comparator. After IPTW (n = 88.9 for pola-BR; n = 44.3 for Alberta O2 RWD), pola-BR was associated with a statistically significant improvement in OS (HR 0.47, 95% CI 0.29-0.77) and there was insufficient evidence to show a difference in PFS between pola-BR and the comparison group (HR 0.72, 95% CI 0.45-1.16).

A summary of findings is presented in Table 32. For the weighted population, median OS was 13.31 and 5.62 months and median PFS was 6.57 and 3.48 months for pola-BR and the comparison group, respectively. Results of the sensitivity analyses are reported in Table 33. Several sensitivity analyses reported varying estimates of the HR for OS and PFS. However, conclusions from these sensitivity analyses were generally consistent with the findings from the primary analysis for all OS and PFS analyses.

Table 32: Summary of Findings

Analysis	*Outcome*	*Pola-BR*	*RWD*	*HR (95%CI)*
Pre-weighted	OS	13.3 months	6.5 months	0.51 (0.32-0.82)
	PFS	6.6 months	4.2 months	0.80 (0.51-1.24)
Weighted	OS	13.3 months	5.6 months	0.47 (0.29-0.77)
	PFS	6.6 months	3.5 months	0.72 (0.45-1.16)

Source: Sponsor submitted Propensity Score Weighted Analysis [43]

Table 33: Sensitivity Analyses Results

Analysis performed	OS HR (95 % CI)	PFS HR (95% CI)
Primary analysis	0.47 (0.29-0.77)	0.72 (0.45-1.16)
Unweighted and unadjusted Cox regression	0.51 (0.32-0.82)	0.80 (0.51-1.24)
Unweighted Cox regression adjusted for the parameters used for propensity score derivation	0.42 (0.26-0.67)	0.69 (0.44-1.07)
Unweighted Cox regression adjusting for propensity score	0.38 (0.18-0.79)	0.60 (0.29-1.27)
Doubly robust[a]	0.44 (0.27-0.71)	0.75 (0.48-1.18)
Unweighted Cox regression adjusted for the parameters used for propensity score deviation and time from first line	0.49 (0.31-0.78)	0.82 (0.53-1.28)
Missing values imputed with worst-case scenario	0.49 (0.31-0.78)	NR[b]
Primary analysis but excluding patients with extreme weights (>4)	0.46 (0.28-0.74)	0.69 (0.43-1.11)

Source: Sponsor submitted Propensity Score Weighted Analysis [43]

7.3.3 Critical Appraisal

The sponsor submitted PSWA is a novel analysis leveraging Alberta O2 RWD with trial data. This analysis applied methodologies such as IPTW and numerous sensitivity analyses. However, due to limitations in the data available the results should be interpreted with caution. This submitted analysis has major limitations that hinder the potential applicability of the comparative results.

The major concerns with the submitted analysis are related to the size of the cohort used, the ability to efficiently weight between RWD and trial data, the differences between study arms. Specifically, even after IPTW there were important clinical differences between the two study groups. Specifically, LDH and line of prior treatment. Although the submitted analysis was robust, it is unable to overcome these differences which raise concerns in any conclusions of differences.

- Given the small sample sizes in both arms the robustness of any analyses is in question and the ability to properly control for all confounders, regardless of methodology, is likely limited. Most striking is the inability to control for prior treatments in a meaningful manner.
- PFS results should be interpreted with great cuation given issues in the ability to measure PFS. Those results as noted by the manufacoters, must be interpreted with caution. As noted by the sponsor, due to limited data for close to half the population the results may influence the HR estimates.
- In addition to the differences even after weighting, the development of the propensity score was limited by the variables included. Some of these factors are important clinical factors, specifically: ECOG, IPI, refractory to last prior anti-lymphoma treatment, time to relapse and DOR to prior anti-lymphoma therapy <12 months. These important factors, which are likely not balanced between arms may greatly confound any comparisons between arms.
- The comparability of a clinical trial population with extensive inclusion and exclusion criteria to the RWE population raises major concerns of potential healthy-user bias which is more likely to show positive effects for the RCT study arm. The extensive list of

exclusion criteria, with many associated with poor prognosis, may influence the results. There are major concerns when comparing those enrolled in a clinical trial and those seen in routine practice.

7.3.4 Summary and Conclusions

The sponsor also submitted a PSWA to compare OS and PFS between pola-BR in the GO29365 trial and a “basket” of chemotherapy regimens used in the Alberta O2 RWD. This analysis was performed using the IPTW methodology and numerous sensitivity analyses. However, the submitted analysis has major limitations that hinder the potential applicability of the comparative results. The applicability of sponsor’s submitted analysis is impacted by limitations related to the size of the cohort used, the ability to efficiently weight between RWD and trial data, and the differences between study arms. Hence, the results should be interpreted with caution. No firm conclusions can be drawn on the comparative effectiveness of pola-BR based on the submitted PSWA alone.

8 Comparison with Other Literature

None.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Hematology Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on polatuzumab vedotin (Polivy) for R/R DLBCL. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

#	Searches	Results
1	(Polivy* or polatuzumab* or VCMMAE or DCDS4501A or fcu 2711 or fcu2711 or rg 7596 or rg7596 or ro 5541077* or ro5541077* or ACD 79BVCMMAE or ACD79B VCMMAE or ACD 79B VCMMAE or DCDS 4501A or DCDS4501A or KG6VO684Z6).ti,ab,ot,kf,kw,hw,nm,rn.	692
2	1 use medall	153
3	limit 2 to English language	148
4	1 use cctr	71
5	3 or 4	219
6	*polatuzumab vedotin/	97
7	(Polivy* or polatuzumab* or VCMMAE or DCDS4501A or fcu 2711 or fcu2711 or rg 7596 or rg7596 or ro 5541077* or ro5541077* or ACD 79BVCMMAE or ACD79B VCMMAE or ACD 79B VCMMAE or DCDS 4501A or DCDS4501A).ti,ab,kw,dq.	566
8	6 or 7	571
9	8 use oemezd	356
10	limit 9 to English language	337
11	10 not (conference review or conference abstract).pt.	215
12	5 or 11	434
13	remove duplicates from 12	277
14	10 and (conference review or conference abstract).pt.	122
15	limit 14 to yr="2015 -Current"	93
16	13 or 15	370

2. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (searched via Ovid)

3. **Grey literature search via:**
   Clinical trials registries:

   US National Library of Medicine. ClinicalTrials.gov
   https://clinicaltrials.gov/

   World Health Organization

   http://apps.who.int/trialsearch/

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials

   http://www.canadiancancertrials.ca/

   Health Canada's Clinical Trials Database

   https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

   The European Clinical Trials Register

   https://www.clinicaltrialsregister.eu/ctr-search/search

   Search: Polivy/polatuzumab, diffuse large b-cell lymphoma

   Select international agencies including:

   US Food and Drug Administration (FDA)

   https://www.fda.gov/

   European Medicines Agency (EMA)

   https://www.ema.europa.eu/

   Search: Polivy/polatuzumab, diffuse large b-cell lymphoma

   Conference abstracts:

   American Society of Clinical Oncology (ASCO)

   https://www.asco.org/

   European Society for Medical Oncology (ESMO)

   https://www.esmo.org/

   American Society of Hematology (ASH)

   http://www.hematology.org/

   Search: Polivy/polatuzumab, diffuse large b-cell lymphoma — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[44]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974 –) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Polivy/polatuzumab.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of February 18, 2021.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[45] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trials registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, Health Canada Clinical Trials Database, and the European Clinical Trials Registry), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

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