Summary Report of Benefit-Risk Assessment

POLIVY POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 140MG

NEW DRUG APPLICATION

Active Ingredient(s)	Polatuzumab vedotin
Product Registrant	ROCHE SINGAPORE PTE LTD
Product Registration Number	SIN16007P
Application Route	Full Evaluation
Date of Approval	04 September 2020

Table of Contents

A INTRODUCTION

Polivy is indicated in combination with bendamustine and rituximab for the treatment of relapsed/refractory diffuse large B-cell lymphoma who are not eligible for haematopoietic cell transplant.

The active substance, polatuzumab vedotin, is a CD79b-targeted antibody-drug conjugate (ADC) that preferentially delivers an anti-mitotic agent (monomethyl auristatin E [MMAE]) to B cells, which results in anti-cancer activity against B-cell malignancies.

Polivy is available as powder for concentrate for solution for infusion supplied in single-dose 20 ml vials that deliver 140 mg of polatuzumab vedotin. Other ingredients are succinic acid, sodium hydroxide, sucrose and polysorbate 20.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, Polatuzumab Vedotin, is manufactured at [redacted]. The drug product, Polivy Powder for Concentrate for Solution for Infusion 140mg, is manufactured at [redacted].

Drug substance:

The drug substance, Polatuzumab Vedotin is an antibody-drug conjugate that contains a humanised immunoglobulin G1 (IgG1) anti-CD79b monoclonal antibody (polatuzumab antibody intermediate) and an antimitotic agent, monomethyl auristatin E (MMAE), linked through a protease-cleavable linker, maleimidocaproyl-valine-citrulline-paminobenzyloxycarbonyl (mc-vc-PAB). The antimitotic agent and linker are referred to as the linker-drug, vcMMAE.

Adequate controls have been presented for the cell substrate, polatuzumab antibody intermediate, linker drug intermediate vcMMAE and raw materials. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance intermediates and drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity and potency testing is presented.

The stability data is adequate to support the approved storage condition and shelf life. The drug substance is stored in stainless steel storage tanks. The drug substance is approved for storage at -20°C with a shelf life of 36 months.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity and potency testing is presented.

The stability data submitted is adequate to support the approved shelf-life of 24 months at 2-8°C. The reconstituted drug product can be stored at 2°C - 8°C for up to 72 hours or at ≤ 25°C for 24 hours. The container closure system is a USP type I glass vial.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of polatuzumab vedotin (pola) in combination with bendamustine (B) and rituximab (R) for the treatment of relapsed refractory diffuse large B-cell lymphoma (R/R DLBCL) who are not eligible for haematopoietic cell transplant was based on one pivotal study, GO29365.

Study GO29365 was a Phase Ib/II, multicentre, open-labelled study that evaluated safety and efficacy of polatuzumab vedotin in combination with BR (pola-BR) in patients with R/R DLBCL who were ineligible for haematopoietic stem cell transplant. The study consisted of two stages with a Phase Ib safety run-in stage followed by a Phase II expansion stage of the study once the patients in each cohort had cleared safety during the observational period. This study was nested in an umbrella trial where the activity of polatuzumab vedotin (in combination with BR or BG[Bendamustine and obinutuzumab]) in both DLBCL and follicular lymphoma (FL) was studied.

A total of 80 R/R DLBCL patients were randomised in the Phase II stage in a 1:1 ratio to receive either 1.8mg/Kg pola in combination with BR or BR alone for a period of six 21-day cycles. The primary efficacy endpoint was complete response (CR) at primary response assessment (6-8 weeks after Cycle 6 Day 1 or last dose of study medication) as measured by Positron Emission Tomography and Computed Tomography (PET-CT) scans and as determined by an Independent Review Committee (IRC) using Modified Lugano 2014 Response Criteria. The key secondary endpoints included CR at the time of primary response assessment based on PET-CT as determined by investigator, objective response rate (ORR), best overall response (BOR) at the time of primary response assessment and PFS (IRS). Overall survival, event free survival and PFS (by investigator) were the exploratory endpoints.

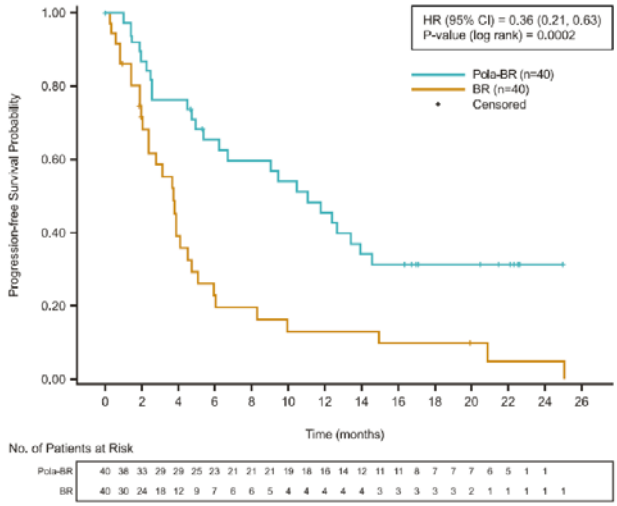
Discontinuations were lower in pola-BR arm compared to BR arm and more patients in pola-BR arm completed treatment compared to BR arm (45% vs 22.5%). There were imbalances observed in the baseline characteristics with higher proportion of older patients (≥65 years)(65% vs 57.5%), high risk DLBCL (42.5% vs 22.5%), bulky disease (37.5% vs 25%), extranodal involvement (72.5% vs 67.5%) and those with ECOG 2 (20% vs 15%) in the BR arm compared to pola-BR arm and these imbalances might bias in favour of the pola-BR arm.

On the other hand, pola-BR arm had higher proportion of difficult to treat subjects including those who failed prior bone marrow therapy (25% vs15%) or salvage therapy (30% vs 22.5%) compared to BR arm. About 70% of patients in both arms had two or more prior lines of therapies. Most patients at baseline (97.3%) were categorized as DLBCL “not otherwise specified” (NOS) based on the 2016 World Health Organization (WHO) classification and included 45.1% activated B-cell (ABC) type and 38.9% germinal centre B-cell-like (GCB type).

The primary efficacy endpoint of CR rate at the primary response assessment based on PET-CT, as determined by the IRC, was statistically significantly higher (95% CI: 2.6%, 40.2%; p=0.0261, Cochran-Mantel-Haenszel [CMH] chi-square) in the pola-BR arm (40.0% [16/40]; 95% CI: 24.9%, 56.7%) than the BR arm (17.5% [7/40], 95% CI: 7.3%, 32.8%). The key secondary endpoints also supported the primary efficacy endpoint with higher investigator determined CR rate (42.5% vs. 15.0%), IRC determined ORR (45.0% vs. 17.5%) and investigator assessed BOR (CR: 57.5% vs. 20.0%; ORR: 70.0% vs. 32.5%). The median DOR as determined by IRC was not estimable (95% CI: 8.8, NE) for pola-BR and 7.7 months (95% CI: 3.2, 18.9) for BR (stratified HR 0.40 [95% CI: 0.16, 1.01]).

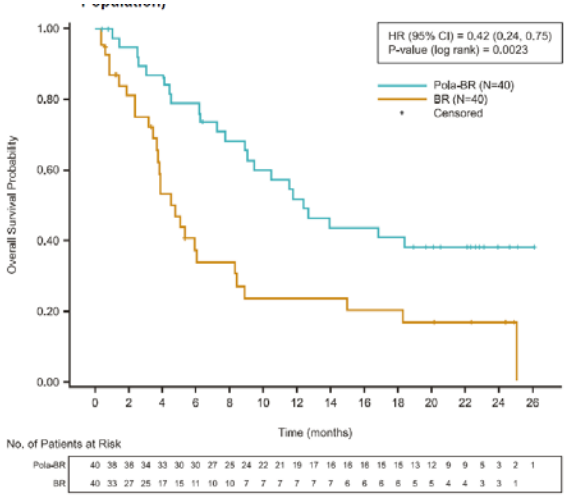
There was 7.4 months improvement in median PFS as determined by IRC in patients treated with pola-BR compared to BR,11.1 months (95% CI: 6.2, 13.9) vs. 3.7 months (95% CI: 2.4, 4.5), with a 64% reduction in the risk of progression or death (stratified HR of 0.36; 95% CI: 0.21, 0.63; p-value=0.0002). The Kaplan-Meier (KM) curves separated in favour of pola-BR quite early within the first month.

Kaplan-Meier Plot of Progression-Free Survival (IRC-assessed) in patients with R/R DLBCL treated with Pola-BR or BR (Randomized Phase II; ITT Population):



At the time of the clinical cut-off (22.5 months follow-up), a total of 51 patients with R/R DLBCL in the randomized Phase II had died (28 patients [70.1%] in the BR arm and 23 patients [57.5%] in the pola-BR arm) with the relative risk of death reduced by 58% in patients treated with pola-BR compared to BR (stratified HR : 0.42; 95% CI: 0.24, 0.75; p< 0.0023). Median overall survival was 12.4 months (95% CI: 9.0, not estimable) in patients in the pola-BR arm compared to 4.7 months (95% CI: 3.7, 8.3) in the BR arm.

Kaplan-Meier Plot of Overall Survival in patients with R/R DLBCL treated with Pola-BR or BR (Randomized Phase II; ITT Population):



Additional sensitivity analysis using multivariate regression models and propensity score analyses considering the imbalances in baseline covariates that could potentially impact prognosis was done for the four efficacy endpoints (CR, BOR, PFS and OS). The results from the sensitivity analysis was consistent with the primary analysis. Furthermore, subgroup analyses by baseline risk factor for PFS and OS consistently showed that the efficacy was consistent in the subgroups which were not balanced across the arms.

Summary of key efficacy results (Study GO29365)

	BR (N=40)	**Pola-BR (N=40)**
Primary efficacy endpoint		
CR by PET (IRC)		
n (%)	7 (17.5%)	16 (40.0%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(24.9, 56.7)
95% CI) (Wilson); p-value (CMH chi-square)	22.5 (2.62, 40.2); p<0.0261	
Secondary efficacy endpoints		
Objective response (CR/PR) by PET (IRC)		
n (%)	7 (17.5%)	18 (45.0%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(29.3, 61.5)
95% CI) (Wilson); p-value (CMH chi-square)	27.5 (7.2, 45.0); p<0.0069	
Complete Response by PET (Investigator's assessment)		
n (%)	6 (15.0%)	17 (42.5%)
95% CI for response rate (Clopper-Pearson)	(5.7, 29.8)	(27.0, 59.1)
95% CI) (Wilson); p-value (CMH chi-square)	27.5 (7.7, 44.7); p<0.0061	
Complete Response at PRA by CT alone (IRC)		
n (%)	1 (2.5%)	9 (22.5%)
95% CI for response rate (Clopper-Pearson)	(0.06, 13.2)	(10.8, 38.5)

95% CI) (Wilson); p-value (CMH chi-square)	20.0 (5.5, 35.1); p<0.0078	
Complete Response by CT (INV)		
n (%)	2 (5.0%)	8 (20.0%)
95% CI for response rate (Clopper-Pearson)	(0.6, 16.9)	(9.1, 35.7)
Best overall response by PET-CT or CT (CR/PR) (INV)		
n (%)	13 (32.5%)	28 (70.0%)
95% CI for response rate (Clopper-Pearson)	(18.6, 49.1)	(53.5, 83.4)
95% CI) (Wilson); p-value (CMH chi-square)	37.5 (15.6, 54.7); p<0.0006	
Duration of response (DOR) (IRC)		
Patients with event, n (%)	8/10 (80.0%)	11/23 (47.8%)
median DOR (95% CI)	7.7 (3.2, 18.9)	NE (14.9, NE)
HR (95% CI); stratified p-value (log-rank)	0.40 (0.16, 1.01); p<0.0462	
Progression-free survival (PFS) (IRC)		
Patients with event, n (%)	31 (77.5%)	25 (62.5%)
median PFS (95% CI)	3.7 (2.4, 4.5)	11.1 (6.2, 13.9)
HR (95% CI); stratified p-value (log-rank)	0.36 (0.21, 0.63); p<0.0002	
Duration of response (INV)		
Patients with event, n (%)	11/13 (84.6%)	17/28 (60.7%)
median DOR (95% CI)	4.1 (2.6, 12.7)	10.3 (5.6, NE)
HR (95% CI); stratified p-value (log-rank)	0.44 (0.20, 0.95); p<0.0321	
Progression-free survival (INV)		
Patients with event, n (%)	35 (87.5%)	27 (67.5%)
median PFS (95% CI)	2.0 (1.5, 3.7)	7.6 (6.0, 17.0)
HR (95% CI); stratified p-value (log-rank)	0.34 (0.20, 0.57); p<0.0001	
Event-free survival (EFS)		
Patients with event, n (%)	38 (95.0%)	29 (72.5%)
median EFS (95% CI)	2.0 (1.5, 3.1)	6.4 (4.0, 11.1)
HR (95% CI); stratified p-value (log-rank)	0.34 (0.20, 0.57); p<0.0001	
Overall Survival (OS)		
Patients with event, n (%)	28 (70.0%)	23 (57.5%)
OS (95% CI)	4.7 (3.7, 8.3)	12.4 (9.0, NE)
HR (95% CI); stratified p-value (log-rank)	0.42 (0.24, 0.75); p<0.0023	

The submitted pivotal study GO29365 had its limitations, as it was a phase Ib/II nested study with a small sample size (n=80). Nevertheless, the results were promising with pola-BR combination demonstrating significant increase in CR compared to the BR treatment in patients with R/R DLBCL, who were ineligible for haematopoietic stem cell transplant. These results were further supported by significant improvement in PFS, and OS. Despite PFS and OS being secondary or exploratory endpoints respectively, the comparative design was

valuable in assessing the add-on benefit of polatuzumab vedotin to bendamustine and rituximab. The other uncertainty about the imbalance in the baseline characteristics was addressed by consistent results observed with the sensitivity analyses considering the baseline characteristics and favourable efficacy in the subgroups which were not balanced across the arms. Overall, the study demonstrated benefit in the proposed patient population.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of pola-BR comprised of a total of 45 safety evaluable R/R DLBCL patients from Study GO29365 who received at least one dose of pola-BR. Similar safety profile was seen for polatuzumab (pola-BR/BG or pola-BG) in an additional 96 patients with R/R Flor R/R DLBCL. The duration of exposure to study treatment was longer (median 5 vs. 3 cycles received) and more patients with R/R DLBCL completed their planned number of treatment cycles (46.2% vs. 23.1%) in the pola-BR arm compared to the BR arm because of fewer early discontinuations due to disease progression.

Overview of Safety Profile: Study GO29365

	Phase Ia	**Phase II**	
AE	**Pola-BR (N=6)**	**BR (N=39)**	**Pola-BR (N=39)**
Any AE	6 (100%)	38 (97.4%)	39 (100%)
Serious adverse events (SAEs) (any)	4 (66.7%)	24 (61.5%)	25 (64.1%)
Discontinuations due to AEs (all)	1 (16.7%)	6 (15.4%)	13 (33.3%)
Deaths (all)	2 (33.3%)	28 (71.8%)	23 (59.0%)

The adverse events (AEs) with a higher incidence in the pola-BR arm compared to the BR arm were neutropaenia (53.8% vs 38.5%), thrombocytopaenia (48.7% vs 28.2%), anaemia (53.8% vs 25.6%), lymphopenia(12.8% vs 0), diarrhoea (38.5% vs 28.2%), vomiting (17.9% vs 12.8%) , upper abdominal pain(12.8% vs 5.1%), pyrexia (33.3% vs 23.1%), chills (10.3% vs 7.7%), pneumonia (12.8% vs 10.3%), hypokalaemia (10.3% vs 7.7%), hypoalbuminemia (12.8% vs 5.1%), peripheral neuropathy (23.1% vs 2.6%), dizziness (12.8% vs 7.7%), peripheral sensory neuropathy (15.4% vs 0), headache (7.7% vs 5.1%), upper respiratory tract infection (5.1% vs 2.6%), decreased appetite (25.6% vs 20.5%), paraesthesia (5.1% vs 0), muscular weakness (5.1% vs 2.6%), hypocalcaemia (7.7% vs 2.6%), hypophosphatemia (5.1% vs 2.6%), dehydration (5.1% vs 0), anxiety (7.7% vs 5.1%), dyspnoea (7.7% vs 5.1%), hypotension (7.7% vs 12.8%) and pruritis (12.8% vs 10.3%).

The incidence of Grade 3-4 events was higher in the pola-BR arm compared to the BR am (84.6% vs. 71.8%). Grade 3-4 AEs with a ≥10% higher incidence in the pola-BR arm compared to the BR arm were neutropaenia, thrombocytopaenia, anaemia, febrile neutropaenia, and lymphopaenia. Peripheral neuropathy events, were, as expected, more frequently reported in the pola-BR arm compared to the BR arm (43.6% vs.7.7%, all Grade 1 or 2).Grade 3-4 hepatic toxicity events (hypoalbuminaemia and transaminase elevation) were reported in 2 patients in the pola-BR arm and 1 patient in the BR arm (none indicative of drug related injury).

The overall incidence of serious AEs was comparable in the pola-BR and BR arms (64.1% vs. 61.5%), with no notable differences between the two arms and the most common SAEs were febrile neutropenia (n=4), pneumonia (n=4), and pyrexia (n=3).

Nine patients in the pola-BR and 11 patients in the BR arm had SAEs with fatal outcome (Grade 5). Treatment discontinuations due to AEs were more frequent in the pola- BR arm compared to the BR arm (33.3% vs. 15.4%) and the most frequent AEs leading to treatment discontinuations were cytopaenias (8/14 discontinuations; including Grade ≥3 neutropaenia in 2 patients and thrombocytopaenia in 4 patients). At the time of the clinical cut-off, 6/45 patients (13.3%) with R/R FL treated with pola-BR had died. The cause of death was disease progression in 2 patients, fatal AEs in 3 patients (reported as death, pneumonia, and sudden death), and complication of stem cell transplant in 1 patient. Of the 6 deaths, 2 (death and sudden death) occurred after study treatment was discontinued.

The most clinically important adverse events were neutropenia, peripheral neuropathy, infections, thrombocytopaenia, and anaemia. Neutropenia was mostly high grade in terms of severity, and febrile neutropaenia represented a minority of the neutropaenia events. Overall, neutropenia events were managed by with the prophylactic administration of G-CSF and by delay/interruption in study treatment. Similarly, thrombocytopenia was manageable with delay/interruption in study treatment. Anaemia events infrequently impacted study treatment dosing and a minority of the events were managed with blood transfusions.

Peripheral neuropathy was consistent with the mechanism of action of MMAE and the events were mostly Grade 1-2 in severity. Peripheral neuropathy events were managed with dose delay/interruption and dose reductions of polatuzumab if necessary, with few treatment discontinuations from refractory peripheral neuropathy observed. Infections were influenced by combination with chemotherapeutic agents and underlying lymphoma disease. Serious and opportunistic infections including those amenable to anti-infective prophylaxis were reported.

Hepatic toxicity events consisted primarily of low grade and transient transaminase elevations with no Hy's Law cases identified to date. These cases resolved uneventfully with study treatment discontinuation. Gastrointestinal toxicities were predominantly low grade in severity and infrequently impacted treatment dosing or patient outcome. Gastrointestinal toxicities were predominantly reported as diarrhoea, nausea, vomiting, or constipation.

In conclusion, the totality of safety evidence reflected a manageable AE profile for polatuzumab vedotin when used in combination with BR for the target patient population. Appropriate warnings and precautions have been put in place in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Patients with R/R DLBCL have poor outcomes, with limited therapeutic options. There is an unmet medical need in patients with R/R DLBCL with disease progression who are transplant ineligible. Most patients with R/R DLCBL are ineligible for haematopoietic stem cell transplant ASCT due to age, co-morbidities or chemotherapy-insensitive disease, and of the patients who proceed to transplant, only 30-40% will be cured. There are no universally established therapies for patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant. The most commonly used regimens are gemcitabine and/or platinum-based therapies or BR, however, with poor survival outcomes (median survival approximately 6 months).

Study GO29365 demonstrated that pola-BR combination significantly improved CR rates, PFS, and OS compared to BR alone. The primary efficacy endpoint of CR rate based on PET-CT,

as determined by the IRC, was higher in the pola-BR arm (40.0% [16/40]; 95% CI: 24.9%, 56.7%) than the BR arm (17.5% [7/40], 95% CI: 7.3%, 32.8%). PFS was prolonged by about 7.4 months. The sensitivity analysis and the consistent efficacy in the subgroups assured that the overall results were not driven by the imbalances favouring pola-BR arm. The relative risk of death was reduced by 58% in patients treated with pola–BR compared to BR (stratified HR 0.42; p=0.0023), however, OS was only exploratory in the study. DOR, PFS and EFS were also all longer in the pola- BR arm compared to the BR arm. Both IRC and investigator assessed DOR and PFS showed consistent and significant benefit favouring pola-BR. Despite the small sample size, the study demonstrated promising efficacy compared to the available therapies based on literature.

The most prominent and clinically impactful AEs were neutropaenia, peripheral neuropathy, infections, thrombocytopaenia, and anaemia. These AEs were manageable with interventions and were described in the package insert.

Overall, the benefit-risk profile of polatuzumab vedotin in combination with BR was considered positive for transplant ineligible patients with R/R DLBCL.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed refractory diffuse large B-cell lymphoma who are not eligible for haematopoietic cell transplant was deemed favourable and approval of the product registration was granted on 04 September 2020.

G APPROVED PACKAGE INSERT AT REGISTRATION

INF-POL-2020 08

Polivy®

Polatuzumab vedotin

---

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

ATC Code – L01XC37

1.2 TYPE OF DOSAGE FORM

Powder for concentrate for solution for infusion

1.3 ROUTE OF ADMINISTRATION

Intravenous (IV) Infusion

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Polatuzumab vedotin[1]

[1]Polatuzumab is produced by recombinant DNA technology.

Polivy is a preservative-free white to grayish-white lyophilized cake supplied in single-dose 20 ml vials that deliver 140 mg of polatuzumab vedotin. Upon reconstitution with 7.2ml of sterile water for injection, Polivy concentrate contains 20 mg/ml of polatuzumab vedotin for intravenous infusion.

Excipients

Succinic acid, sodium hydroxide, sucrose, polysorbate 20

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Polivy in combination with bendamustine and MabThera is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma who are not eligible for haematopoietic cell transplant.

2.2 DOSAGE AND ADMINISTRATION

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Polivy.

Polivy therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients.

Polivy must be reconstituted and diluted using aseptic technique under the supervision of a healthcare professional. Polivy should be administered as an intravenous infusion through a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 μm pore size) and catheter (see *4.2 Special instructions for Use, Handling and Disposal*). Do not administer as an IV push or bolus.

For information on MabThera or bendamustine, refer to their respective full prescribing information. Refer to Table 2 for dose modification recommendations for neutropenia and thrombocytopenia.

Recommended Dosage

The recommended dose of Polivy is 1.8 mg/kg given as an intravenous infusion every 21 days in combination with bendamustine and MabThera for 6 cycles. Polivy, bendamustine, and MabThera 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 Polivy and MabThera.

If not already premedicated, administer premedication with an antihistamine and anti-pyretic to patients prior to administration of Polivy. The initial dose of Polivy should be administered as a 90-minute intravenous infusion. Patients should be monitored for infusion-related reactions during the infusion and for at least 90 minutes following completion of the initial dose. If the prior infusion was well tolerated, subsequent dose of Polivy may be administered as a 30-minute infusion and patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion.

Delayed or Missed Doses

If a planned dose of Polivy is missed, it should be administered as soon as possible and the schedule of administration should be adjusted to maintain a 21-day interval between doses.

Dose Modifications

Table 1, 2 and 3 provides management guidelines for Peripheral Neuropathy, myelosuppression and infusion-related reaction.

For dose modifications for peripheral neuropathy see Table 1.

Table 1 Polivy dose modifications for Peripheral Neuropathy

Severity on Day 1 of any cycle	Dose modification
Grade 2-3	Hold Polivy dosing until improvement to ≤ Grade 1. If recovered to Grade ≤1 on or before Day 14, restart Polivy at a permanently reduced dose of 1.4 mg/kg. If a prior dose reduction to 1.4 mg/kg has occurred, discontinue Polivy. If not recovered to Grade ≤1 on or before Day 14, discontinue Polivy.
Grade 4	Discontinue Polivy.

For dose modifications for myelosuppression see Table 2.

Table 2 Polivy, bendamustine, and MabThera dose modifications for myelosuppression

Severity on Day 1 of any cycle	Dose modification[a]
Grade 3-4 Neutropenia	Hold all treatment until ANC recovers to >1000 /μL. If ANC recovers to >1000 /μL on or before Day 7, resume all treatment without any additional dose reductions. If ANC recovers to >1000 /μL after Day 7: • restart all treatment, with a dose reduction of bendamustine from 90 mg/m^2 to 70 mg/m^2 or 70 mg/m^2 to 50 mg/m^2 • if a bendamustine dose reduction to 50 mg/m^2 has already occurred, discontinue all treatment
Grade 3-4 Thrombocytopenia	Hold all treatment until platelets recover to >75,000 /μL. If platelets recover to >75,000 /μL on or before Day 7, resume all treatment without any additional dose reductions. If platelets recover to >75,000 /μL after Day 7: • restart all treatment, with a dose reduction of bendamustine from 90 mg/m^2 to 70 mg/m^2 or 70 mg/m^2 to 50 mg/m^2 • if a bendamustine dose reduction to 50 mg/m^2 has already occurred, discontinue all treatment

[a]If primary cause is due to lymphoma, the dose of bendamustine may not need to be reduced.

For dose modifications for infusion-related reaction see Table 3.

Table 3 Polivy dose modifications for infusion-related reaction

Severity on Day 1 of an cycle	Dose modification
Grade 1–3 Infusion-Related Reaction	Interrupt Polivy infusion and give supportive treatment. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue Polivy. For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue Polivy. Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. For the next cycle, infuse Polivy over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
Grade 4 Infusion-Related Reaction	Stop Polivy infusion immediately. Give supportive treatment. Permanently discontinue Polivy.

The infusion rate of Polivy should be slowed or interrupted if the patient develops an infusion-related reaction. Discontinue Polivy immediately and permanently if the patient experiences a life-threatening reaction.

2.2.1 Special Dosage Instructions

Pediatric use

The safety and efficacy of Polivy in children and adolescents (<18 years) has not been established.

Geriatric use

No dose adjustment of Polivy is required in patients ≥ 65 years of age (see *2.5.5 Geriatric Use* and *3.2.5 Pharmacokinetics in special populations)*.

Renal Impairment

No dose adjustment of Polivy is required in patients with creatinine clearance (CrCL) ≥30ml/min. A recommended dose has not been determined for patients with CrCL <30ml/min (see *2.5.6 Renal Impairment* and *3.2.5 Pharmacokinetics in special populations*).

Hepatic Impairment

No dose adjustment of Polivy is required for patients with AST or ALT up to 2.5×ULN or total bilirubin up to 1.5×ULN. A recommended dose has not been determined for patients with AST>2.5×ULN or ALT>2.5×ULN, total bilirubin>1.5×ULN, or patients with a liver transplant (see *2.5.7 Hepatic Impairment* and *3.2.5 Pharmacokinetics in special populations*).

2.3 CONTRAINDICATIONS

Polivy is contraindicated in patients with a known hypersensitivity to polatuzumab vedotin or any of the excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Myelosuppression

Serious and severe neutropenia and febrile neutropenia have been reported in patients treated with Polivy as early as the first cycle of treatment (see *2.6 Undesirable Effects*). Prophylactic G-CSF administration should be considered. Grade 3 or 4 thrombocytopenia or anemia can also occur with Polivy (see *2.6 Undesirable Effects*). Complete blood counts should be monitored prior to each dose of Polivy. More frequent lab monitoring and/or Polivy delays or discontinuation should be considered in patients with Grade 3 or Grade 4 neutropenia and thrombocytopenia (see *2.2 Dosage and Administration)*.

Peripheral Neuropathy

Peripheral neuropathy has been reported in patients treated with Polivy as early as the first cycle of treatment, and the risk increases with sequential doses (see *2.6 Undesirable effects*). Patients with pre-existing peripheral neuropathy may experience worsening of this condition. Peripheral neuropathy reported with Polivy treatment is predominantly sensory peripheral neuropathy; however, motor and sensorimotor peripheral neuropathy have also been reported. Patients should be monitored for symptoms of peripheral neuropathy such as hypoesthesia, hyperesthesia, paresthesia, dysesthesia, neuropathic pain, burning sensation, weakness, or gait disturbance. Patients experiencing new or worsening peripheral neuropathy may require a delay, dose reduction, or discontinuation of Polivy (see *2.2 Dosage and Administration*).

Infections

Serious, life threatening, or fatal infections, including opportunistic infections, such as pneumonia (including *pneumocystis jirovecii* and other fungal pneumonia), bacteremia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with Polivy (see *2.6 Undesirable Effects)*. Patients should be closely monitored during treatment for signs of bacterial, fungal, or viral infections. Anti-infective prophylaxis should be considered. Polivy and any concomitant chemotherapy should be discontinued in patients who develop serious infections.

Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported with Polivy treatment (see *2.6 Undesirable effects)*. Patients should be monitored closely for new or worsening neurological, cognitive, or behavioral changes suggestive of PML. Polivy and any concomitant chemotherapy should be held if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Tumor Lysis Syndrome

Patients with high tumor burden and rapidly proliferative tumor may be at increased risk of tumor lysis syndrome. Appropriate measures in accordance with local guidelines should be taken prior to treatment with Polivy. Patients should be monitored closely for tumor lysis syndrome during treatment with Polivy.

Embryo-Fetal Toxicity

Based on the mechanism of action and nonclinical studies, Polivy can be harmful to the fetus when administered to a pregnant woman. (see *2.5.2 Pregnancy, 3.1.1 Mechanism of Action, and 3.3.4 Reproductive toxicity*). Advise a pregnant woman of the risk to the fetus.

Females of reproductive potential should be advised to use effective contraception during treatment with Polivy and for at least 9 months after the last dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Polivy and for at least 6 months after the last dose (*see 2.5.1 Females and Males of Reproductive potential, 3.3.2 Genotoxicity* and *3.3.4 Reproductive toxicity*).

Hepatic Toxicity

Serious cases of hepatic toxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with Polivy. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Liver enzymes and bilirubin level should be monitored.

2.4.2 Drug Abuse and Dependence

Polivy does not have the potential for abuse and dependence.

2.4.3 Ability to Drive and Use Machines

Polivy may have a minor influence on the ability to drive and use machines.

Infusion related reactions, peripheral neuropathy, fatigue, and dizziness may occur during treatment with Polivy (see *2.4 Warnings and Precautions* and *2.6 Undesirable Effects*).

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Fertility

Based on animal studies, Polivy may impair male reproductive function and fertility (see *3.3.3 Impairment of Fertility*).

Contraception

Females

Females of reproductive potential should be advised to use effective contraception during treatment with Polivy and for at least 9 months after the last dose (see *3.3.2 Genotoxicity* and *3.3.4 Reproductive toxicity*).

Males

Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Polivy and for at least 6 months after the last dose (see *3.3.2 Genotoxicity* and *3.3.4 Reproductive toxicity*).

2.5.2 Pregnancy

Polivy is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Polivy can cause fetal harm based on the animal studies and the drug's mechanism of action (see *3.1.1 Mechanism of Action*).

Animal data

In animal studies, MMAE caused genotoxicity and embryo-fetal toxicity (see *3.3.2 Genotoxicity* and *3.3.4 Reproductive toxicity*).

Labor and Delivery

The safe use of Polivy during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether polatuzumab vedotin is excreted in human breast milk. No studies have been conducted to assess the impact of Polivy on milk production or its presence in breast milk. Since many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants due to Polivy, women should discontinue breastfeeding during Polivy treatment.

2.5.4 Pediatric Use

The safety and efficacy of Polivy in pediatric patients below the age of 18 years have not been established.

2.5.5 Geriatric Use

No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients (see *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*).

2.5.6 Renal Impairment

The safety and efficacy of Polivy in patients with CrCL <30 ml/min has not been formally studied (see *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations).*

2.5.7 Hepatic Impairment

The safety and efficacy of Polivy in patients with AST>2.5×ULN, ALT>2.5×ULN or total bilirubin>1.5×ULN has not been formally studied. Monitor these patients for adverse events after treatment (*see 2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetic in Special Populations).*

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

Summary of the safety profile

For the clinical development program of Polivy as a whole, an estimated total of 588 patients have received Polivy. The adverse drug reactions (ADRs) described in this section were identified during treatment and follow-up of previously treated diffuse large B-cell lymphoma (DLBCL) patients from the pivotal clinical trial GO29365. This includes run-in phase patients (n=6) and randomized patients (n=39) who received Polivy in combination with bendamustine and MabThera (BR) compared to randomized patients (n=39) who received BR alone. Randomized patients in the Polivy treatment arm received a median of 5 cycles of treatment while randomized patients in the comparator arm received a median of 3 cycles of treatment.

Tabulated summary of ADRs from clinical trials

Table 3 ADRs are listed by MedDRA system organ class (SOC).

The most frequently-reported (≥30%) ADRs in patients treated with Polivy in combination with BR were anemia, thrombocytopenia, neutropenia, fatigue, diarrhea, nausea, and pyrexia. Serious adverse events were reported in 64.4% of Polivy plus BR treated patients which included febrile neutropenia (11.1%), pyrexia (8.9%), pneumonia (8.9%), anemia (4.4%), duodenal ulcer hemorrhage (4.4%), sepsis (4.4%), and thrombocytopenia (4.4%).

ADRs leading to treatment regimen discontinuation in >5% of patients were thrombocytopenia (8.9%) and neutropenia (6.7%).

Table 3 Summary of adverse drug reactions occurring in previously treated DLBCL patients treated with Polivy in combination with BR

Adverse drug reactions	**Polivy + bendamustine + MabThera N = 45**		**Bendamustine + MabThera N=39**	
SOC	**All grades (%)**	**Grades 3-4 (%)**	**All grades (%)**	**Grades 3-4 (%)**
Infections and Infestations				
Pneumonia[a]	15.6	6.7	10.3	0
Blood and Lymphatic System Disorders				

Anemia	46.7	24.4	25.6	17.9
Neutropenia	46.7	40.0	38.5	33.3
Thrombocytopenia	46.7	37.8	28.2	23.1
Febrile Neutropenia	11.1	11.1	12.8	12.8
Leukopenia	11.1	6.7	12.8	7.7
Lymphopenia	11.1	11.1	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	26.7	2.2	20.5	0
Hypokalemia	15.6	6.7	7.7	2.6
Hypoalbuminemia	13.3	2.2	5.1	0
Hypocalcemia	11.1	2.2	2.6	0
Nervous System Disorders				
Neuropathy Peripheral	20.0	0	2.6	0
Dizziness	13.3	0	7.7	0
Peripheral Sensory neuropathy	13.3	0	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	15.6	0	20.5	0
Gastrointestinal Disorders				
Diarrhea	37.8	4.4	28.2	5.1
Nausea	33.3	0	41.0	0
Constipation	17.8	0	20.5	2.6
Vomiting	17.8	2.2	12.8	0
Abdominal Pain	11.1	4.4	10.3	2.6

Abdominal Pain Upper	11.1	2.2	5.1	0
Skin and Subcutaneous Tissue Disorders				
Pruritis	13.3	0	10.3	2.6
General Disorders and Administration Site Conditions				
Fatigue	40.0	4.4	35.9	2.6
Pyrexia	33.3	2.2	23.1	0
Asthenia	11.1	0	15.4	0
Chills	11.1	0	7.7	0
Investigations				
Weight decreased	15.6	2.2	7.7	2.6
Injury, Poisoning, and Procedural				
Infusion-related reaction[b]	33.3	6.7	23.1	10.3

[a]ADR associated with fatal outcome
[b]Defined as all adverse events reported as related to study treatment within 24 hours after treatment infusion

Description of selected adverse drug reactions from clinical trials

Myelosuppression

8.9% of patients in the Polivy plus BR arm discontinued Polivy due to neutropenia compared to 2.6% of patients in the BR arm who discontinued treatment due to neutropenia. Thrombocytopenia events led to discontinuation of treatment in 11.1% of patients in the Polivy plus BR arm and 5.1% of patients in the BR arm. No patients discontinued treatment due to anemia in either the Polivy plus BR arm or BR arm.

Peripheral Neuropathy (PN)

In the Polivy plus BR arm, Grade 1 and 2 PN events were reported in 26.7% and 13.3% of patients, respectively. In the BR arm, Grade 1 and 2 PN events were reported in 2.6% and 5.1% of patients, respectively. No Grade 3-5 PN events were reported in either the Polivy plus BR arm or BR arm. 2.2% of patients discontinued Polivy treatment due to PN and 4.4% of patients had Polivy dose reduction due to PN. No patients in the BR arm discontinued treatment or had dose reductions due to PN. In the Polivy plus BR arm, the median onset to first event of PN was 1.8 months, and 61.1% of patients with PN events reported event resolution (see *2.4 Warnings and Precautions*).

Infections

Infections, including pneumonia and other types of infections, were reported in 53.3% of patients in the Polivy plus BR arm and 51.3% of patients in the BR arm. In the Polivy plus BR arm, serious infections were reported in 28.9% of patients and fatal infections were reported in 8.9% of patients. In the BR arm, serious infections were reported in 30.8% of patients and fatal infections were reported in 10.3% of patients. One patient (2.2%) discontinued treatment in the Polivy plus BR arm due to infection compared to 5.1% of patients in the BR arm (see *2.4 Warnings and Precautions*).

Progressive Multifocal Leukoencephalopathy (PML)

One case of PML, which was fatal, occurred in a patient treated with Polivy plus bendamustine and obinutuzumab. This patient had three prior lines of therapy that included anti-CD20 antibodies (*see 2.4 Warnings and Precautions).*

Hepatic toxicity

In another study, two cases of serious hepatic toxicity (hepatocellular injury and hepatic steatosis) were reported and were reversible (*see 2.4 Warnings and Precautions).*

Gastrointestinal Toxicity

Gastrointestinal toxicity events were reported in 80.0% of patients in the Polivy plus BR arm compared to 64.1% of patients in the BR arm. Most events were Grade 1-2, and Grade 3-4 events were reported in 22.2% of patients in the Polivy plus BR arm compared to 12.8% of patients in the BR arm. The most common gastrointestinal toxicity events were diarrhea and nausea.

2.6.2 Postmarketing Experience

Not applicable

2.7 OVERDOSE

There is no experience with overdose in human clinical trials. The highest dose tested to date is 2.4 mg/kg administered as an intravenous infusion. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No dedicated clinical drug-drug interaction studies with Polivy in humans have been conducted.

Drug interactions with co-medications that are CYP3A inhibitors, inducers or substrates

Based on physiological-based pharmacokinetic (PBPK) model simulations of MMAE released from polatuzumab vedotin, strong CYP3A inhibitors (e.g., ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE by 48%. Monitor patients receiving concomitant strong CYP3A inhibitors more closely for signs of toxicities. Strong CYP3A inducers (e.g., rifampin) may decrease the AUC of unconjugated MMAE by 49%.

Unconjugated MMAE is not predicted to alter the AUC of concomitant drugs that are CYP3A substrates (e.g., midazolam).

Drug interactions of MabThera and bendamustine in combination with polatuzumab vedotin

The pharmacokinetics (PK) of MabThera and bendamustine are not affected by co-administration with Polivy. Concomitant MabThera is associated with increased antibody conjugated MMAE (acMMAE) plasma AUC by 24% and decreased unconjugated MMAE plasma AUC by 37%, based on population PK analysis. No dose adjustment is required.

Bendamustine does not affect acMMAE and unconjugated MMAE plasma AUC.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E, or MMAE) to B-cells, which results in the killing of malignant B-cells. The polatuzumab vedotin molecule consists of MMAE covalently attached to a humanized immunoglobulin G1 (IgG1) monoclonal antibody via a cleavable linker. The monoclonal antibody binds with high affinity and selectivity to CD79b, a cell surface component of the B-cell receptor. CD79b expression is restricted to normal cells within the B-cell lineage (with the exception of plasma cells) and malignant B-cells; it is expressed in >95% of DLBCL. Upon binding CD79b, polatuzumab vedotin is rapidly internalized and the linker is cleaved by lysosomal proteases to enable intracellular delivery of MMAE. MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

3.1.2 Clinical / Efficacy Studies

The efficacy of Polivy was evaluated in an international, multicenter, open-label study (GO29365) which included a randomized cohort of 80 patients with previously treated DLBCL. Patients were randomized 1:1 to receive Polivy plus BR or BR alone for six 21-day cycles. Patients were stratified by duration of response to last prior treatment of ≤12 months or >12 months.

Eligible patients were not candidates for autologous hematopoietic stem cell transplant (HSCT) and had relapsed or refractory disease after receiving at least one prior systemic chemotherapy regimen. The study excluded patients with prior allogeneic HSCT, central nervous system lymphoma, transformed follicular lymphoma (FL), and grade 3b FL.

Polivy was given intravenously at 1.8 mg/kg administered on Day 2 of Cycle 1 and on Day 1 of Cycles 2-6. Bendamustine was administered at 90 mg/m^2 intravenously daily on Days 2 and 3 of Cycle 1 and on Days 1 and 2 of Cycles 2-6. MabThera was administered at 375 mg/m^2 intravenously on Day 1 of Cycles 1-6.

The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. The median age was 69 years (range 30 to 86 years) and 71% of patients were white and 66% were male. The majority of patients (98%) had DLBCL not otherwise specified (NOS). Overall, 48% of patients had activated B-cell (ABC) DLBCL and 40% of patients had germinal center B-cell like (GCB) DLBCL. Primary reasons patients were not candidates for HSCT included age (40%), insufficient response to salvage therapy (26%) and prior transplant failure (20%). The median number of prior therapies was 2 (range: 1-7) with 29% (n=23) receiving one prior therapy, 25% (n=20) receiving 2 prior therapies, and 46% (n=37) receiving 3 or more prior therapies. 80% of patients had refractory disease.

The primary endpoint of the study was complete response (CR) rate at end of treatment (6-8 weeks after day 1 of cycle 6 or last study treatment) as assessed by independent review committee (IRC). Efficacy results are summarized in Table 4 and in Figures 1-3.

Table 4 Summary of efficacy in patients with previously treated DLBCL from study GO29365

	Polivy + bendamustine + MabThera N= 40	**Bendamustine + MabThera N= 40**
	Median observation time 22 months	
Primary Endpoint		
Complete Response Rate* (IRC-assessed) at End of treatment**		
Responders (%)	16 (40.0)	7 (17.5)
Difference in response rate (%) [95% CI]	22.5 [2.6, 40.2]	
p-value (CMH chi-squared test***)	0.0261	
Key Endpoints		
Overall Survival		
Number (%) of patients with event	23 (57.5)	28 (70.0)
Median OS (95% CI), months	12.4 (9.0, NE)	4.7 (3.7, 8.3)
HR [95% CI]	0.42 [0.24, 0.75]	
p-value (Log-Rank test, stratified***)	0.0023¶	
Progression Free survival (INV-assessed)		
Number (%) of patients with event	27 (67.5)	35 (87.5)

Median PFS (95% CI), months	7.6 (6.0, 17.0)	2.0 (1.5, 3.7)
HR [95% CI]	0.34 [0.20, 0.57]	
p-value (Log-Rank test, stratified***)	<0.0001	
Duration of response (INV-assessed)		
Number of patients included in analysis	28	13
Number (%) of patients with event	17 (60.7)	11 (84.6)
Median DOR (95% CI), months	10.3 (5.6, NE)	4.1 (2.6, 12.7)
HR [95% CI]	0.44 [0.20, 0.95]	
p-value (Log-Rank test, stratified***)	0.0321	
Overall Response Rate* (INV-assessed) at End of Treatment**		
Responders (%) (CR, PR)	19 (47.5)	7 (17.5)
Difference in response rate (%) [95% CI]	30.0 [9.5, 47.4]	
p-value (CMH chi-squared test***)	0.0036	
Complete Response (%) (CR)	17 (42.5)	6 (15.0)
Difference in response rate (%) [95% CI]	27.5 [7.7, 44.7]	
p-value (CMH chi-squared test***)	0.0061	
Partial Response (%) (PR)	2 (5.0)	1 (2.5)
95% CI Clopper-Pearson	[0.6, 16.9]	[0.06, 13.2]
Best Overall Response Rate* (INV-assessed)		
Responders (%) [CR, PR]	28 (70.0)	13 (32.5)
Difference in response rate (%) [95% CI]	37.5 [15.6, 54.7]	
Complete Response (%) [CR]	23 (57.5)	8 (20.0)
95% CI Clopper-Pearson	[40.9, 73.0]	[9.1, 35.7]
Partial Response (%) [PR]	5 (12.5)	5 (12.5%)
95% CI Clopper-Pearson	[4.2, 26.8]	[4.2, 26.8]

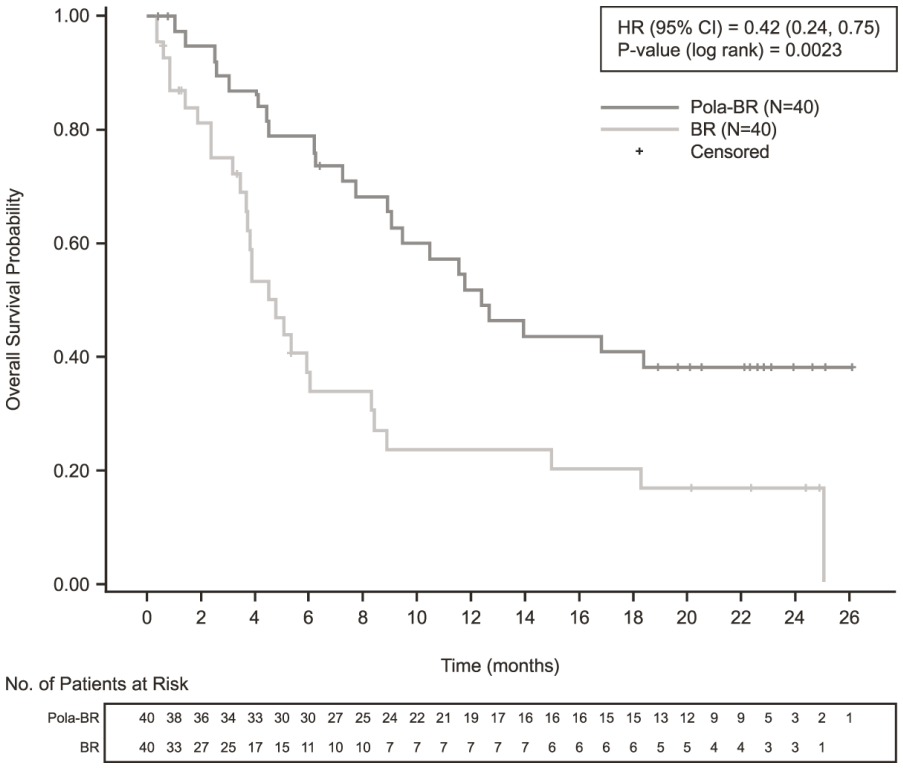
IRC: Independent Review Committee; INV: Investigator; CI: Confidence Interval, HR: Hazard Ratio; CMH Cochran-Mantel-Haenszel; OS: Overall survival; NE: Not evaluable; PFS: progression free survival; DOR: Duration of response

*Per modified Lugano 2014 criteria: Bone marrow confirmation of PET-CT CR required. PET-CT PR required meeting both PET-CT criteria and CT criteria.

**6-8 weeks after day 1 of cycle 6 or last study treatment

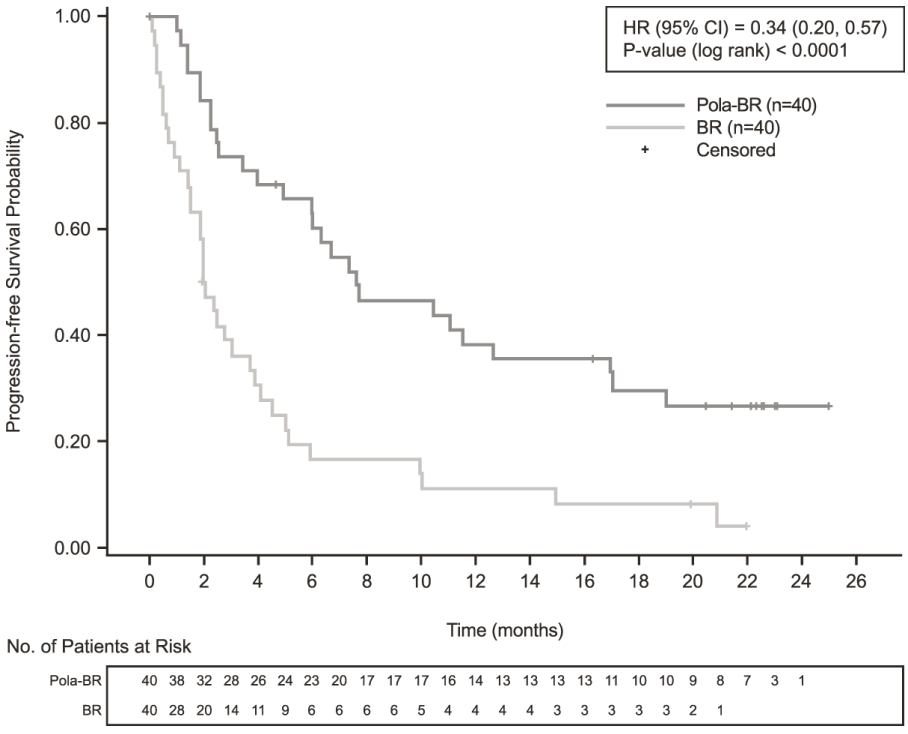
*** Stratification by duration of response to prior therapy (≤12 months vs >12 months)

Figure 1 Kaplan Meier curve of overall survival



No.: number; Pola: Polivy; BR: bendamustine and MabThera; HR: hazard ratio.

Figure 2 Kaplan-Meier curve of INV assessed progression-free survival



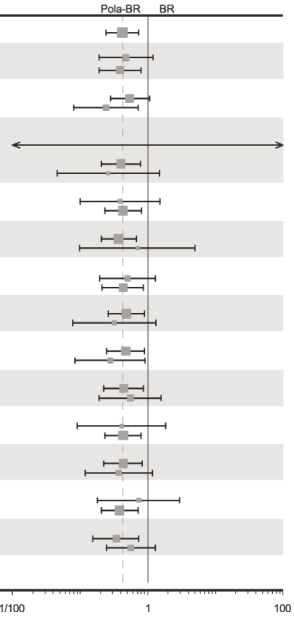
No.; number; Pola: Polivy; BR: bendamustine and MabThera; HR: hazard ratio.

Results of subgroup analyses

Results of subgroup analysis of overall survival were consistent with the results seen in the overall DLBCL population (see Figure 3 below).

Figure 3 Forest plot of Overall survival

Baseline risk factors	Total n	Pola-BR (N=40) n	Pola-BR (N=40) Events	Pola-BR (N=40) Median (Months)	BR (N=40) n	BR (N=40) Events	BR (N=40) Median (Months)	Hazard Ratio	95%CI
All patients	80	40	23	12.4	40	28	4.7	0.42	(0.24, 0.74)
Age group (years)									
<65	31	17	10	10.6	14	9	3.8	0.47	(0.19, 1.19)
≥65	49	23	13	13.9	26	19	5.1	0.39	(0.19, 0.79)
Sex									
Male	53	28	18	12.1	25	18	4.5	0.54	(0.28, 1.06)
Female	27	12	5	-	15	10	4.7	0.24	(0.08, 0.72)
Race									
American Indian or Alaska Native	1	-	-	-	1	1	3.4	-	-
Asian	10	6	2	-	4	0	-	>999.99	(0.00, -)
Black or African American	3	3	2	4.4	-	-	-	-	-
White	57	26	15	12.6	31	23	4.7	0.40	(0.21, 0.77)
Unknown	9	5	4	9.0	4	4	4.1	0.26	(0.05, 1.49)
Baseline ECOG PS									
≥2	14	6	4	2.6	8	7	1.6	0.39	(0.10, 1.51)
0 or 1	64	33	19	13.9	31	21	5.3	0.43	(0.23, 0.80)
Ann Arbor Stage at study entry									
Stage III/IV	70	34	21	11.5	36	26	3.9	0.37	(0.21, 0.68)
Stage I/II	10	6	2	-	4	2	-	0.70	(0.10, 4.98)
Bulky disease									
Yes	25	10	7	11.8	15	12	3.7	0.50	(0.19, 1.31)
No	55	30	16	13.9	25	16	5.3	0.43	(0.21, 0.86)
Refractory to last prior anti-cancer therapy									
Yes	64	30	19	9.5	34	24	3.9	0.48	(0.26, 0.89)
No	16	10	4	-	6	4	8.3	0.32	(0.08, 1.33)
Lines of prior anti-lymphoma therapy									
≥2	57	29	18	11.5	28	20	3.8	0.47	(0.25, 0.89)
1	23	11	5	-	12	8	5.9	0.28	(0.08, 0.92)
IPI at study entry									
≥3	51	22	15	10.5	29	22	3.9	0.44	(0.22, 0.86)
<3	29	18	8	-	11	6	6.0	0.55	(0.19, 1.58)
Duration of response to prior anti-lymphoma therapy									
>12 months	14	8	3	-	6	4	13.3	0.41	(0.09, 1.83)
≤12 months	66	32	20	10.5	34	24	3.9	0.43	(0.23, 0.79)
Extranodal involvement at study entry									
Yes	56	27	18	11.5	29	21	3.9	0.43	(0.22, 0.82)
No	24	13	5	-	11	7	8.4	0.37	(0.12, 1.18)
Prior stem cell transplant									
Yes	16	10	6	13.9	6	3	5.3	0.73	(0.18, 2.95)
No	64	30	17	11.6	34	25	4.5	0.38	(0.20, 0.72)
Cell-of-origin (central review)									
ABC	38	19	12	12.8	19	15	4.7	0.34	(0.15, 0.74)
GCB	32	15	11	8.9	17	12	3.8	0.56	(0.24, 1.29)



ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; ABC: activated B-cell; GCB: germinal center B-cell like; Pola: Polivy; BR: bendamustine and MabThera; CI: confidence interval

3.1.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with polatuzumab vedotin. Across all arms of study GO29365, 8 out of 134 (6.0%) patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points. Across all seven clinical studies, 14 out of 536 (2.6%) patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points. Due to the limited number of anti-polatuzumab vedotin antibody positive patients, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to polatuzumab vedotin with the incidence of antibodies to other products may be misleading.

3.2 PHARMACOKINETIC PROPERTIES

Antibody-conjugated MMAE (acMMAE) plasma exposure increased dose-proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. After the first 1.8 mg/kg polatuzumab vedotin dose, the

acMMAE mean maximum concentration (C_{max}) was 803 (± 233) ng/ml and the area under the concentration-time curve from time zero to infinity (AUC_{inf}) was 1860 (± 966) day*ng/ml. Based on the population PK analysis, Cycle 3 acMMAE AUC increased by approximately 30% over cycle 1 AUC, and achieved more than 90% of the Cycle 6 AUC. The terminal half-life at cycle 6 was approximately 12 days (95% CI of 8.1-19.5 days) for acMMAE.

Exposures of unconjugated MMAE, the cytotoxic component of polatuzumab vedotin, increased dose proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. MMAE plasma concentrations followed formation rate limited kinetics. After the first 1.8 mg/kg polatuzumab vedotin dose, the C_{max} was 6.82 (± 4.73) ng/ml, the time to maximum plasma concentration is approximately 2.5 days, and the terminal half-life is approximately 4 days. Plasma exposures of unconjugated MMAE are <3% of acMMAE exposures. Based on the population PK analysis, there is a decrease of plasma unconjugated MMAE exposure (AUC and C_{max}) after repeated every-three-week dosing.

3.2.1 Absorption

Polivy is administered as an IV infusion. There have been no studies performed with other routes of administration.

3.2.2 Distribution

The population estimate of central volume of distribution for acMMAE was 3.15 L, which approximated plasma volume**.**

In vitro, MMAE is moderately bound (71% - 77%) to human plasma proteins. MMAE does not significantly partition into human red blood cells in vitro; the ratio of amount in blood to amount in plasma is 1.34 to 1.65.

In vitro data indicate that MMAE is a P-gp substrate but does not inhibit P-gp at clinically relevant concentrations.

3.2.3 Metabolism

Polatuzumab vedotin is expected undergo catabolism in patients, resulting in the production of small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE related catabolites.

In vitro studies indicate that MMAE is a substrate for CYP 3A4/5 but does not induce major CYP enzymes. MMAE is a weak time-dependent inhibitor of CYP3A4/5 but does not competitively inhibit CYP3A4/5 at clinically relevant concentrations.

MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

3.2.4 Elimination

Based on a population pharmacokinetic analysis, the conjugate (acMMAE) is primarily eliminated by non-specific linear clearance pathway with a value of 0.9 l/day.

In vivo studies in rats dosed with polatuzumab vedotin (radiolabel on MMAE) demonstrate that the majority of radioactivity is excreted in feces and the minority of radioactivity is excreted in urine.

3.2.5 Pharmacokinetics in Special Populations

Pediatric Population

No studies have been conducted to investigate the pharmacokinetics of Polivy in pediatric patients (<18 years old).

Geriatric Population

Age did not have an effect on the pharmacokinetics of acMMAE and unconjugated MMAE based on a population PK analysis with patients aged 20-89 years. No significant difference was observed in the pharmacokinetics of acMMAE and unconjugated MMAE among patients <65 years of age (n=187) and patients ≥65 years of age (n=273).

Renal impairment

In patients with mild (CrCL 60-89 ml/min, n=161) or moderate (CrCL 30-59 ml/min, n=109) renal impairment, acMMAE and unconjugated MMAE exposures are similar to patients with normal renal function (CrCL ≥ 90 ml/min, n=185), based on a population pharmacokinetic analysis. There are insufficient data to assess the impact of severe renal impairment (CrCL 15-29 ml/min, n=3) on PK. No data are available in patients with end-stage renal disease and/or who are on dialysis (see 2.2 Dosage and administration).

Hepatic impairment

In patients with mild hepatic impairment [AST >1.0 - 2.5×ULN or ALT >1.0 - 2.5×ULN or total bilirubin >1.0 - 1.5×ULN, n=54], acMMAE exposures are similar whereas unconjugated MMAE AUC are 40% higher compared to patients with normal hepatic function (n=399), based on a population pharmacokinetic analysis.

There are insufficient data to assess the impact of moderate hepatic impairment (total bilirubin >1.5 - 3×ULN, n=2) on PK. No data are available in patients with severe hepatic impairment or liver transplantation (see *2.2 Dosage and administration).*

3.3 NONCLINICAL SAFETY

3.3.1 Carcinogenicity

No dedicated carcinogenicity studies in animals have been performed with Polivy and/or MMAE.

3.3.2 Genotoxicity

No dedicated mutagenicity studies in animals have been performed with Polivy. MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This mechanism is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

3.3.3 Impairment of Fertility

No dedicated fertility studies in animals have been performed with Polivy. However, results of repeat-dose toxicity in rats indicate the potential for polatuzumab vedotin to impair male reproductive function and fertility. In the 4-week repeat-dose toxicity study in rats with weekly dosing of 2, 6, and 10 mg/kg, dose-dependent testicular seminiferous tubule degeneration with abnormal lumen contents in the epididymis was observed. Findings in the testes and epididymis did not reverse and correlated with decreased testes weight and gross findings of small and/or soft testes at recovery necropsy in males given doses $\geq$ 2 mg/kg.

3.3.4 Reproductive toxicity

No dedicated teratogenicity studies in animals have been performed with Polivy. However, MMAE was evaluated in rats in a GLP embryo-fetal developmental and toxicokinetic study, in which pregnant rats received 2 intravenous doses of 0.2 mg/kg MMAE during the period of organogenesis on gestational day 6 and 13. Treatment with MMAE at 0.2 mg/kg caused fetal external malformations including protruding tongue, malrotated limbs, gastroschisis, and agnathia. Systemic exposure (AUC) in rats at a dose of 0.2 mg/kg MMAE is approximately 50% of the AUC in patients who received the recommended dose of 1.8 mg/kg Polivy every 21-days.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Vials

Store unopened vials at 2°C to 8°C.

Keep vial in the outer carton in order to protect from light.

Do not freeze. Do not shake.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Shelf life of reconstituted product and solution for infusion

See *4.2 Special Instructions for use, Handling and disposal* below.

The reconstituted solution and solution for infusion should not be frozen or exposed to direct sunlight.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Polivy must be reconstituted using sterile water for injection and diluted into an IV infusion bag containing 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose by a healthcare professional prior to administration.

Use aseptic technique for reconstitution and dilution of Polivy. Appropriate procedures for the preparation of antineoplastic products should be used.

The reconstituted product contains no preservative and is intended for single-dose usage only. Discard any unused portion.

A dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 μm pore size) and catheter must be used to administer diluted Polivy.

Reconstitution

1. Using a sterile syringe, slowly inject 7.2 ml of sterile water for injection into the 140 mg Polivy vial to yield a single-dose solution containing 20 mg/ml polatuzumab vedotin. Direct the stream toward the wall of the vial and not directly on the lyophilized cake.

2. Swirl the vial gently until completely dissolved. *Do not shake*

3. Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Do not use if the reconstituted solution is discolored, cloudy, or contains visible particulates.

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would

normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 72 hours at 2°C to 8°C and up to 24 hours at room temperature (9°C to 25°C).

Dilution

1. Polatuzumab vedotin must be diluted to a final concentration of 0.72 – 2.7 mg/ml in an IV infusion bag with a minimum volume of 50ml containing 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose.

2. Determine the volume of 20 mg/ml reconstituted solution needed based on the required dose:

$$\text{Volume} = \frac{\text{Polivy dose (1.8 or 1.4 mg/kg) X patient's weight (kg)}}{\text{Reconstituted vial concentration (20 mg/ml)}}$$

3. Using a sterile syringe, withdraw and discard a volume of diluent equivalent to the required volume of reconstituted solution from the IV infusion bag.

4. Withdraw the required volume of reconstituted solution from the Polivy vial using a sterile syringe and dilute into the IV infusion bag. Discard any unused portion left in the vial.

5. Gently mix the IV bag by slowly inverting the bag. *Do not shake*.

6. Inspect the IV bag for particulates and discard if present.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Acceptable chemical and physical stability of the prepared solution for infusion has been demonstrated for the durations listed in Table 6. Discard if storage time exceeds these limits. *Do not freeze or expose to direct sunlight.*

Table 6 Durations for which acceptable chemical and physical stability of the prepared solution for infusion have been demonstrated

Diluent used to prepare solution for infusion	Solution for infusion storage conditions[1]
0.9% Sodium Chloride	Up to 24 hours at 2°C to 8°C or up to 4 hours at room temperature (9°C to 25°C)
0.45% Sodium Chloride	Up to 72 hours at 2°C to 8°C or up to 8 hours at room temperature (9°C to 25°C)
5% Dextrose	Up to 72 hours at 2°C to 8°C or up to 8 hours at room temperature (9°C to 25°C)

[1]To ensure product stability, do not exceed specified storage durations.

Avoid transportation of the prepared solution for infusion as agitation stress can result in aggregation. If the prepared solution for infusion will be transported, remove air from the infusion bag and limit transportation to 30 minutes at 9°C to 25°C or 24 hours at 2°C to 8°C. If air is removed, an infusion set with a vented spike is required to ensure accurate dosing during the infusion.

Incompatibilities

- Do not mix Polivy with, or administer through the same infusion line, as other medicinal products.
- No incompatibilities have been observed between Polivy and IV infusion bags with product contacting materials of polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). In addition, no incompatibilities have been observed with infusion sets or infusion aids with product contacting materials of PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), or fluorinated ethylene propylene (FEP) and with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

4.3 PACKS

Vials 140 mg 1

Medicine: keep out of reach of children

Current at Aug 2020

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland