PACK INSERT FOR MALAYSIA

Polivy® 140mg

Powder For Concentrate For Solution For Infusion
Polatuzumab Vedotin

1. NAME OF THE MEDICINAL PRODUCT

Polivy 140 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for concentrate for solution for infusion contains 140 mg of polatuzumab vedotin.

After reconstitution, each mL contains 20 mg of polatuzumab vedotin.

Polatuzumab vedotin is an antibody-drug conjugate composed of the anti-mitotic agent monomethyl auristatin E (MMAE) covalently conjugated to a CD79b-directed monoclonal antibody (recombinant humanized immunoglobulin G1 [IgG1], produced in Chinese Hamster Ovary cells by recombinant DNA technology).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to greyish-white lyophilized cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

This indication is approved under conditional registration which is based on complete response rate. Continued approval for this indication may be based on the outcome of clinical benefit in a confirmatory trial

4.2 Posology and method of administration

Polivy must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.

Posology

The recommended dose of Polivy is 1.8 mg/kg, given as an intravenous infusion every 21 days in combination with bendamustine and rituximab for 6 cycles. Polivy, bendamustine and rituximab can be administered in any order on Day 1 of each cycle. When administered with Polivy, the recommended dose of bendamustine is 90 mg/m^2/day on Day 1 and Day 2 of each cycle and the recommended dose of rituximab is 375 mg/m^2 on Day 1 of each cycle. Due to limited clinical

experience in patients treated with 1.8 mg/kg Polivy at a total dose >240 mg, it is recommended not to exceed the dose 240 mg/cycle.

If not already premedicated, premedication with an antihistamine and anti-pyretic should be administered to patients prior to Polivy.

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

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

For dose modifications for peripheral neuropathy (section 4.4) see Table 1 below.

Table 1 Polivy dose modifications for peripheral neuropathy (PN)

Severity of PN on Day 1 of any cycle	**Dose modification**
Grade 2-3	Withhold 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 rituximab dose modifications for myelosuppression

Severity of myelosuppression on Day 1 of any cycle	**Dose modification[1]**
Grade 3-4 Neutropenia	Withhold 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	Withhold 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 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.

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

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

Table 3: Polivy, bendamustine and rituximab dose modifications for infusion-related reactions (IRRs)

Severity of IRR on Day 1 of any cycle	Dose modification
Grade 1–3 IRR	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 IRR	Stop Polivy infusion immediately. Give supportive treatment. Permanently discontinue Polivy.

Special populations

Elderly
No dose adjustment of Polivy is required in patients ≥ 65 years of age (see section 5.2).

Renal impairment
No dose adjustment of Polivy is required in patients with creatinine clearance (CrCL) ≥ 30 mL/min. A recommended dose has not been determined for patients with CrCL < 30 mL/min due to limited data.

Hepatic impairment
The administration of Polivy in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × upper limit of normal [ULN]) should be avoided.

No adjustment in the starting dose is required when administering Polivy to patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 × ULN or aspartate transaminase [AST] greater than ULN).

Per studied population in mild hepatic impairment (defined as AST or ALT > 1.0 to 2.5 × ULN or total bilirubin > 1.0 to 1.5 × ULN), there was a 40% increase in unconjugated MMAE exposure, which was not deemed clinically significant.

Paediatric population
The safety and efficacy in children and adolescents less than 18 years have not been established. No data are available.

Method of administration

Polivy is for intravenous use.

The initial dose of Polivy should be administered as a 90-minute intravenous infusion. Patients should be monitored for IRRs/hypersensitivity reactions during the infusion and for at least 90 minutes following completion of the initial dose.

If the prior infusion was well tolerated, the 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.

Polivy must be reconstituted and diluted using aseptic technique under the supervision of a healthcare professional. It 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 micrometer pore size) and catheter. Polivy must not be administered as intravenous push or bolus.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Precaution to be taken before manipulating or administering the product
Polivy contains a cytotoxic component which is covalently attached to the monoclonal antibody. Follow applicable proper handling and disposal procedure (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

Myelosuppression

Serious and severe neutropenia and febrile neutropenia have been reported in patients treated with Polivy as early as the first cycle of treatment. Prophylactic granulocyte colony stimulating factor (G-CSF) administration was required in the clinical development and should be considered. Grade 3 or 4 thrombocytopenia or anaemia can also occur with Polivy. 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 for patients with Grade 3 or Grade 4 neutropenia and thrombocytopenia (see section 4.2).

Peripheral neuropathy (PN)

PN has been reported in patients treated with Polivy as early as the first cycle of treatment, and the risk increases with sequential doses. Patients with pre-existing PN may experience worsening of this condition. PN reported with treatment with Polivy is predominantly sensory PN. However, motor and sensorimotor PN have also been reported. Patients should be monitored for symptoms of PN such as hypoesthesia, hyperesthesia, paraesthesia, dysesthesia, neuropathic pain, burning sensation, muscle weakness, or gait disturbance. Patients experiencing new or worsening PN may require a delay, dose reduction, or discontinuation of Polivy (see section 4.2).

Infections

Serious, life threatening or fatal infections, including opportunistic infections, such as pneumonia (including *pneumocystis jirovecii* and other fungal pneumonia), bacteraemia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with Polivy (see section 4.8). Reactivation of latent infections has been reported. Patients should be closely monitored during treatment for signs of bacterial, fungal, or viral infections and seek medical advice if signs and symptoms appear. Anti-infective prophylaxis should be considered throughout treatment with Polivy. Polivy should not be administered in the presence of an active severe infection. Polivy and any concomitant chemotherapy should be discontinued in patients who develop serious infections.

Human Immunodeficiency Virus (HIV)

Polivy has not been evaluated in patients with HIV. With regard to co-administration of CYP3A-inhibitors see section 4.5.

Immunization

Live or live-attenuated vaccines should not be given concurrently with the treatment. Studies have not been conducted in patients who recently received live vaccines.

Progressive multifocal leukoencephalopathy (PML)

PML has been reported with Polivy treatment (see section 4.8). Patients should be monitored closely for new or worsening neurological, cognitive, or behavioural changes suggestive of PML. Polivy and any concomitant chemotherapy should be withheld if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Tumour lysis syndrome (TLS)

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

Infusion-related reactions

Polivy can cause IRRs, including severe cases. Delayed IRRs as late as 24 hours after receiving Polivy have occurred. An antihistamine and antipyretic should be administered prior to the administration of Polivy, and patients should be monitored closely throughout the infusion. If an IRR occurs, the infusion should be interrupted and appropriate medical management should be instituted (see section 4.2).

Embryo-foetal toxicity

Based on the mechanism of action and nonclinical studies, Polivy can be harmful to the foetus when administered to a pregnant woman (see section 5.3). Pregnant women should be advised regarding risk to the foetus.

Women of childbearing potential should be advised to use effective contraception during treatment with Polivy and for at least 9 months after the last dose (see section 4.6). Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with Polivy and for at least 6 months after the last dose (see section 4.6).

Fertility

In non-clinical studies, polatuzumab vedotin has resulted in testicular toxicity, and may impair male reproductive function and fertility (see section 5.3). Therefore, men being treated with Polivy are advised to have sperm samples preserved and stored before treatment (see section 4.6).

Elderly

Among 173 patients treated with Polivy in Study GO29365, 95 (55%) were ≥ 65 years of age. Patients aged ≥65 had a numerically higher incidence of serious adverse reactions (64%) than patients aged <65 (53%). Clinical studies of Polivy did not include sufficient numbers of patients aged ≥ 65 to determine whether they respond differently from younger patients.

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 (see section 4.8). Pre-existing liver disease, elevated baseline liver enzymes, and concomitant medicinal products may increase the risk. Liver enzymes and bilirubin level should be monitored.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drug interactions with concomitant medicines that are CYP3A4 inhibitors, substrates or inducers and co-medications that are P-gp inhibitors

Based on physiological-based pharmacokinetic (PBPK) model simulations of MMAE released from polatuzumab vedotin, strong CYP3A4 and P-gp inhibitors (e.g., ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE by 48%. Caution is advised in case of concomitant treatment with CYP3A4 inhibitor. Patients receiving concomitant strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities.

Unconjugated MMAE is not predicted to alter the AUC of concomitant medicines that are CYP3A4 substrates (e.g., midazolam).

Strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort [*Hypericum perforatum*]) may decrease the exposure of unconjugated MMAE.

Drug interactions of rituximab and bendamustine in combination with polatuzumab vedotin

The pharmacokinetics (PK) of rituximab and bendamustine are not affected by co-administration with polatuzumab vedotin. Concomitant rituximab 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women
Women of childbearing potential should be advised to use effective contraception during treatment with polatuzumab vedotin and for at least 9 months after the last dose.

Men
Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with polatuzumab vedotin and for at least 6 months after the last dose.

Pregnancy

There are no data in pregnant women using Polivy. Studies in animals have shown reproductive toxicity (see section 5.3). Based on the mechanism of action and nonclinical studies, polatuzumab vedotin can be harmful to the foetus when administered to a pregnant woman. In women of childbearing potential, the pregnancy status shall be checked prior to treatment. Polivy is not recommended during pregnancy and in women of childbearing potential not using contraception unless the potential benefit for the mother outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether polatuzumab vedotin or its metabolites are excreted in human breast milk. A risk for breast-feeding children cannot be excluded. Women should discontinue breast-feeding during treatment with Polivy.

Fertility

In nonclinical studies, polatuzumab vedotin has resulted in testicular toxicity, and may impair male reproductive function and fertility (see section 5.3).

Therefore, men being treated with this medicine are advised to have sperm samples preserved and stored before treatment. Men being treated with Polivy are advised not to father a child during treatment and for up to 6 months following the last dose.

4.7 Effects on ability to drive and use machines

Polivy has minor influence on the ability to drive and use machines. IRRs, PN, fatigue, and dizziness may occur during treatment with Polivy (see sections 4.4 and 4.8).

4.8 Undesirable effects

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 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 rituximab (BR) compared to randomized patients (n=39) who received BR alone. Randomized patients in the 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.

The most frequently-reported (≥ 30%) ADRs in patients treated with Polivy in combination with BR were anaemia (46.7%), thrombocytopenia (46.7%), neutropenia (46.7%), fatigue (40.0%), diarrhoea (37.8%), nausea (33.3%), and pyrexia (33.3%). Serious adverse reactions were reported in 27% of Polivy plus BR treated patients, which includes febrile neutropenia (6.7%), pyrexia (4.4%), and pneumonia (4.4%).

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

Tabulated list of ADRs from clinical trials

The ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100),

rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4 Summary of ADRs occurring in relapsed or refractory DLBCL patients treated with Polivy in combination with BR

Infections and infestations	
Very common	pneumonia[a], herpes virus infection[a], upper respiratory tract infection
Common	sepsis, cytomegalovirus infection
Blood and lymphatic system disorders	
Very common	febrile neutropenia, neutropenia, thrombocytopenia, anaemia, leukopenia, lymphopenia
Common	pancytopenia
Metabolism and nutrition disorders	
Very common	hypokalaemia, hypocalcaemia, hypoalbuminemia, decreased appetite
Nervous system disorders	
Very common	neuropathy peripheral, peripheral sensory neuropathy, dizziness
Common	gait disturbance, paraesthesia, hypoaesthesia
Eye disorders	
Common	vision blurred
Respiratory, thoracic and mediastinal disorders	
Very common	cough
Common	pneumonitis
Gastrointestinal disorders	
Very common	diarrhoea, nausea, constipation, vomiting, abdominal pain, upper abdominal pain
Skin and subcutaneous tissue disorders	
Very common	pruritis
Musculoskeletal disorders	
Common	arthralgia
General disorders and administration site conditions	
Very common	fatigue, pyrexia, asthenia, chills
Investigations	
Very common	weight decreased
Common	transaminase elevation, lipase increase, hypophosphataemia
Injury, poisoning and procedural complications	
Very common	infusion-related reactions[b]

[a] ADR associated with fatal outcome

[b] Defined as all adverse reactions reported as related to study treatment within 24 hours after treatment infusion

Uncommon, rare and very rare ADRs: none

Description of selected adverse drug reactions

In the Polivy plus BR arm, Grade 3 or higher neutropenia, thrombocytopenia, and anaemia were reported in 40%, 37.8%, and 24.4% of patients, respectively.

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 anaemia in either the Polivy plus BR arm or BR arm.

Peripheral neuropathy (PN)

In the Polivy plus BR arm, Grade 1 PN and Grade 2 PN 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.

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%) in the Polivy plus BR arm discontinued treatment due to infection compared to 5.1% of patients in the BR arm.

Progressive multifocal leukoencephalopathy (PML)
One case of PML, which was fatal, occurred in one patient treated with Polivy plus bendamustine and obinutuzumab. This patient had three prior lines of therapy that included anti-CD20 antibodies.

Hepatic toxicity
In another study, two cases of serious hepatic toxicity (hepatocellular injury and hepatic steatosis) were reported and were reversible.

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 diarrhoea and nausea.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.npra.gov.my/.

4.9 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; it was associated with a higher frequency and severity of PN events. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents; other antineoplastic agents; monoclonal antibodies
ATC code: L01XC37

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 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 diffuse large B-cell lymphoma. 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.

Pharmacodynamic effects

Cardiac electrophysiology

Polatuzumab vedotin did not prolong the mean QTc interval to any clinically relevant extent based on ECG data from two open-label studies in patients with previously treated B-cell malignancies at the recommended dosage.

Clinical efficacy and safety

The efficacy of Polivy was evaluated in an international, multicentre, 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 haematopoietic 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 indolent lymphoma, grade 3b FL, significant cardiovascular or pulmonary disease, active infections, AST or alanine transaminase (ALT) > 2.5× ULN or total bilirubin ≥ 1.5 x ULN, creatinine > 1.5 x ULN (or CrCl < 40 mL/min) unless due to underlying lymphoma.

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. rituximab was administered at 375 mg/m^2 on Day 1 of Cycles 1-6.

Among the 80 patients who were randomized to receive Polivy plus BR (n=40) or BR alone (n = 40) the majority were white (71%) and male (66%). The median age was 69 years (range: 30-86 years). Sixty-four out of 80 patients (80%) had ECOG performance score (PS) of 0-1 and 14 out of 80 patients (18%) had ECOG PS of 2. The majority of patients (98%) had DLBCL not otherwise specified (NOS). Overall, 48% of patients had activated B-cell (ABC) DLBCL and 40% 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. All except one patient in the pola+BR arm of the randomized Phase II were naïve to bendamustine treatment. 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 PET-CT by an Independent Review Committee (IRC).

Table 5 Summary of efficacy in patients with previously treated DLBCL from study GO29365

	Polivy + bendamustine + rituximab N = 40	**Bendamustine + rituximab 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 secondary and exploratory endpoints		
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; HR: Hazard Ratio; CI: Confidence Interval, NE: Not evaluable; CMH Cochran-Mantel-Haenszel

*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)

Overall survival (OS) was an exploratory endpoint which was not type 1 error controlled. The median OS in the Polivy+BR arm was 12.4 months (95% CI: 9.0, NE) vs 4.7 months (95% CI: 3.7, 8.3) in the control arm. The unadjusted estimate for OS HR was 0.42. When accounting for the influence of baseline covariates the OS HR was adjusted to 0.59. Covariates included primary refractory status, number of prior lines of therapy, IPI, and prior stem cell transplant.

Investigator-assessed progression free survival (PFS) was an exploratory endpoint which was not type 1 error controlled. The median PFS in the Polivy+BR arm was 7.6 months (95% CI: 6.0, 17.0) vs 2.0 months (95% CI: 1.5, 3.7) in the control arm. The unadjusted estimate for PFS HR was 0.34.

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 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.

5.2 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. Based on population PK analysis, the predicted acMMAE concentration at the end of cycle 6 is approximately 80% of the theoretical steady-state value. 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) after repeated every-three-week dosing.

Based on population pharmacokinetics simulations, a sensitivity analysis predicted exposure to unconjugated MMAE for patients with bodyweight over 100 kg to be increased by 27%.

Absorption

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

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 blood to plasma ratio is 0.79 to 0.98.

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

Biotransformation

Polatuzumab vedotin is expected to undergo catabolism in patients, resulting in the production of small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE related catabolites. The levels of MMAE metabolites have not been measured in human plasma.

In vitro studies indicate that MMAE is a substrate for CYP3A4/5 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.

Elimination

Based on a population PK 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 faeces and the minority of radioactivity is excreted in urine.

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of polatuzumab vedotin in the paediatric population (< 18 years old).

Elderly

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 PK 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.

Hepatic impairment

In patients with mild hepatic impairment [AST or ALT > 1.0 to 2.5 × ULN or total bilirubin > 1.0 to 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 PK 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.

5.3 Preclinical safety data

Systemic toxicity

In both rats and cynomolgus monkeys, the predominant systemic toxicities associated with administration of MMAE and polatuzumab vedotin included reversible bone marrow toxicity and associated peripheral blood cell effects.

Genotoxicity

No dedicated mutagenicity studies have been performed with polatuzumab vedotin. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

MMAE was genotoxic in the rat bone marrow micronucleus study probably through an aneugenic mechanism. This mechanism is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent.

Carcinogenicity

No dedicated carcinogenicity studies have been performed with polatuzumab vedotin and/or MMAE.

Impairment of fertility

No dedicated fertility studies in animals have been performed with polatuzumab vedotin. However, results of the 4-week rat toxicity study indicate the potential for polatuzumab vedotin to impair male reproductive function and fertility. Testicular seminiferous tubule degeneration did not reverse following a 6-week treatment-free period and correlated with decreased testes weight and gross findings at recovery necropsy of small and/or soft testes in males given ≥ 2 mg/kg.

Reproductive toxicity

No dedicated teratogenicity studies in animals have been performed with polatuzumab vedotin. However, treatment of pregnant rats with MMAE at 0.2 mg/kg caused embryolethality and foetal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Succinic acid
Sodium hydroxide (for pH-adjustment)
Sucrose
Polysorbate 20 (E 432)

6.2 Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

24 months.

Reconstituted solution

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 refrigerated (2 °C – 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 refrigerated (2 °C – 8 °C) and up to 24 hours at room temperature (9 °C – 25 °C).

Diluted solution

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 refrigerated (2 °C – 8 °C), unless dilution has taken place in controlled and validated aseptic conditions. Chemical and physical stability of the

prepared solution for infusion has been demonstrated for the durations listed in Table 6. The diluted solution must be discarded if storage time exceeds the limits specified in Table 6.

Table 6 Durations for which 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]**
Sodium chloride 9 mg/mL (0.9%)	Up to 24 hours refrigerated (2 °C – 8 °C) or up to 4 hours at room temperature (9 °C – 25 °C)
Sodium chloride 4.5 mg/mL (0.45%)	Up to 72 hours refrigerated (2 °C – 8 °C) or up to 8 hours at room temperature (9 °C – 25 °C)
5% Glucose	Up to 72 hours refrigerated (2 °C – 8 °C) or up to 8 hours at room temperature (9 °C – 25 °C)

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

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

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 mL vial (colourless Type 1 glass) closed with a stopper (fluororesin laminate), with an aluminum seal with plastic flip-off cap containing 140 mg polatuzumab vedotin. Pack size of one vial.

6.6 Special precautions for disposal and other handling

General precautions

Polivy contains a cytotoxic component. To be administered under the supervision of a physician experienced in the use of cytotoxic agents. Procedures for proper handling and disposal of antineoplastic and cytotoxic medicines should be used.

The reconstituted product contains no preservative and is intended for single-dose only. Proper aseptic technique throughout the handling of this medicinal product should be followed.

Polivy must be reconstituted using sterile water for injection and diluted into an intravenous infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, or sodium chloride 4.5 mg/ml (0.45%) solution for injection, or 5% glucose prior to administration.

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

Instructions for 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 colourless to slightly brown, clear to slightly opalescent, and free of

visible particulates. Do not use if the reconstituted solution is discoloured, is cloudy, or contains visible particulates.

Instructions for dilution

1. Polivy must be diluted to a final concentration of 0.72-2.7 mg/mL in an intravenous infusion bag, with a minimum volume of 50 mL, containing 9 mg/mL sodium chloride solution for injection, or 4.5 mg/mL sodium chloride solution for injection, or 5% glucose.
2. Determine the volume of 20 mg/mL reconstituted solution needed based on the required dose (see below):

$$\text{Total Polivy dose (mL) to be further diluted} = \frac{\text{Polivy dose (mg/kg) X patient's weight (kg)}}{\text{Reconstituted vial concentration (20 mg/mL)}}$$

3. Withdraw the required volume of reconstituted solution from the Polivy vial using a sterile syringe and dilute into the intravenous infusion bag. Discard any unused portion left in the vial.
4. Gently mix the intravenous bag by slowly inverting the bag. Do not shake.
5. Inspect the intravenous bag for particulates and discard if present.

Avoid transportation of the prepared solution for infusion as agitation stress can result in aggregation. If the prepared infusion will be transported, remove air from the infusion bag and limit transportation to 30 minutes room temperature (9°C – 25°C) or 24 hours refrigerated (2°C – 8°C). If air is removed, an infusion set with a vented spike is required to ensure accurate dosing during the infusion. The total storage plus transportation times of the diluted product should not exceed the storage duration specified in Table 6 (see section 6.3).

Polivy must be administered using a dedicated infusion line equipped with sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 micrometer pore size) and catheter.

Polivy is compatible with intravenous infusion bags with product contacting materials of polyvinyl chloride (PVC) or polyolefins such as polyethylene (PE) and polypropylene. In addition, no incompatibilities have been observed with infusion sets or infusion aids with product contacting materials of PVC, PE, polyurethane, polybutadiene, acrylonitrile butadiene styrene, polycarbonate, polyetherurethane, fluorinated ethylene propylene, or polytetrafluorethylene and with filter membranes composed of polyether sulfone or polysulfone.

Disposal

Polivy is for single-use only.

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

Medicine: keep out of reach of children

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