▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – POLIVY (polatuzumab vedotin)

1 NAME OF THE MEDICINE

Polatuzumab vedotin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial is designed to deliver a total of 30 mg or 140 mg of polatuzumab vedotin.

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially binds with high affinity and selectivity to CD79b, a cell surface component of the B-cell receptor.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

POLIVY is a preservative-free white to grayish-white lyophilised powder supplied in single-dose vials that deliver 30 mg or 140 mg of polatuzumab vedotin. Upon reconstitution POLIVY concentrate contains 20 mg/mL of polatuzumab vedotin for intravenous infusion (refer to section *4.2 Dose and method of administration, Method of administration)*.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

POLIVY in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

POLIVY in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant.

4.2 DOSE AND METHOD OF 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 techniques 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 Dose and method of administration, Method of administration*). Do not administer as an IV push or bolus.

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

Dose

Diffuse large B-cell lymphoma

Previously untreated patients:

The recommended dose of POLIVY is 1.8 mg/kg given as an intravenous infusion every 21 days for 6 cycles in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP). POLIVY, rituximab, cyclophosphamide, and doxorubicin can be administered in any order on Day 1 after the administration of prednisone. Prednisone is administered on Days 1–5 of each cycle. Cycles 7 and 8 consist of rituximab as monotherapy.

Previously treated patients:

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. The recommended dose of bendamustine is 90 mg/m^2/day on Day 1 and 2 when administered with POLIVY and rituximab.

Previously untreated and previously treated patients:

An antihistamine and anti-pyretic should be administered 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, 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.

Duration of Treatment

The recommended duration of treatment is for 6 cycles.

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. Discontinue POLIVY immediately and permanently if the patient experiences a life-threatening reaction.

There are different potential dose modifications for POLIVY in patients with previously untreated and previously treated DLBCL. POLIVY dose modifications for events of peripheral neuropathy, infusion-related reactions and myelosuppression are different by indication (see Tables 1 – 3, below).

For dose modifications to manage peripheral neuropathy see Table 1.

Table 1 POLIVY dose modifications for peripheral neuropathy (PN)

Indication	**Severity of PN on Day 1 of any cycle**	**Dose modification**
Previously untreated DLBCL	Grade 2[a]	Sensory neuropathy: • Reduce POLIVY to 1.4 mg/kg. • If Grade 2 persists or recurs at Day 1 of a future cycle, reduce POLIVY to 1.0 mg/kg. • If already at 1.0 mg/kg and Grade 2 occurs at Day 1 of a future cycle, discontinue POLIVY. Motor neuropathy: • Withhold POLIVY dosing until improvement to Grade $\leqslant$1. • Restart POLIVY at the next cycle at 1.4 mg/kg. • If already at 1.4 mg/kg and Grade 2 occurs at Day 1 of a future cycle, withhold POLIVY dosing until improvement to Grade $\leqslant$ 1. Restart POLIVY at 1.0 mg/kg. • If already at 1.0 mg/kg and Grade 2 occurs at Day 1 of a future cycle, discontinue POLIVY. If concurrent sensory and motor neuropathy, follow the most severe restriction recommendation above.
	Grade 3[a]	Sensory neuropathy: • Withhold POLIVY dosing until improvement to Grade $\leqslant$ 2. • Reduce POLIVY to 1.4 mg/kg. • If already at 1.4 mg/kg, reduce POLIVY to 1.0 mg/kg. If already at 1.0 mg/kg, discontinue POLIVY. Motor neuropathy: • Withhold POLIVY dosing until improvement to Grade $\leqslant$ 1. • Restart POLIVY at the next cycle at 1.4 mg/kg. • If already at 1.4 mg/kg and Grade 2–3 occurs, withhold POLIVY dosing until improvement to Grade $\leqslant$ 1. Restart POLIVY at 1.0 mg/kg. • If already at 1.0 mg/kg and Grade 2–3 occurs, discontinue POLIVY If concurrent sensory and motor neuropathy, follow the most severe restriction recommendation above.

	Grade 4	Discontinue POLIVY.
Previously treated DLBCL	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.

[a] R-CHP may continue to be administered.

For dose modifications to manage myelosuppression see Table 2 below.

Table 2 POLIVY, chemotherapy and rituximab dose modifications to manage myelosuppression

Indication	Severity of myelosuppression on Day 1 of any cycle	Dose modification
Previously untreated DLBCL	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 dose reductions. If ANC recovers to > 1000/µL after Day 7: • resume all treatment; consider a dose reduction of cyclophosphamide and/or doxorubicin by 25-50%. • if cyclophosphamide and/or doxorubicin are already reduced by 25%, consider reducing one or both agents to 50%.
	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: • resume all treatment; consider a dose reduction of cyclophosphamide and/or doxorubicin by 25-50%. • if cyclophosphamide and/or doxorubicin are already reduced by 25%, consider reducing one or both agents to 50%.
Previously treated DLBCL	Grade 3–4 Neutropenia[1]	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[1]	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.

*ANC: absolute neutrophil count

For dose modifications to manage Infusion-related reactions see Table 3 below.

Table 3 POLIVY dose modifications for infusion-related reactions (IRRs)

Indication	Severity of IRR on Day 1 of any cycle	Dose modification
Previously untreated and previously treated DLBCL	Grade 1–3 IRR	Interrupt POLIVY infusion and give supportive treatment. For the first instance of Grade 3 wheezing, bronchospasm, or generalised 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

Paediatric populations

The safety and efficacy of POLIVY in children and adolescents (<18 years) has not been established (see section *5.2 Pharmacokinetics in special populations)*.

Elderly

No dose adjustment of POLIVY is required in patients ≥65 years of age (see section *5.2 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 section *5.2 Pharmacokinetics in special populations*).

Hepatic Impairment

The administration of POLIVY in patients with moderate or severe hepatic impairment (total 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 (total bilirubin greater than ULN and less than or equal to 1.5 x ULN or aspartate transaminase (AST) greater than ULN). (see sections *4.4 Special warnings and precautions for use* and *5.2 Pharmacokinetics in special populations*).

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 monomethyl auristatin E (MMAE) exposure, which was not deemed clinically significant.

Method of Administration

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 1.8 mL of sterile water for injection into the 30 mg POLIVY vial or 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 lyophilised 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.

To reduce microbiological hazard, the reconstituted solution should be used as soon as practicable after preparation. If storage is necessary, the reconstituted solution is stable for up to 72 hours at 2°C to 8°C and up to 20 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:

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

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

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

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

To reduce microbiological hazard, the prepared solution for infusion should be used as soon as practicable after preparation. If storage is necessary, the solution for infusion may be held for the storage times provided in Table 4. Discard if storage time exceeds these limits. *Do not freeze or expose to direct sunlight .*

Table 4 Maximum Allowable Storage Times of the Solution for Infusion Prior to Administration

Diluent used to prepare solution for infusion	Solution for infusion storage conditions[1]
0.9% Sodium Chloride	Up to 72 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 36 hours at 2°C to 8°C or up to 4 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 12 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. The total storage plus transportation times of the diluted product should not exceed the storage duration specified in Table 4.

The product is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 section *4.8 Adverse Effects (Undesirable effects)*). Prophylactic G-CSF administration should be considered. Grade 3 or 4 thrombocytopenia or anaemia can also occur with POLIVY (see section *4.8 Adverse Effects (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 section *4.2 Dose and method of 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 section *4.8 Adverse Effects (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 section *4.2 Dose and method of administration*).

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 Adverse Effects (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 section *4.8 Adverse Effects (Undesirable effects)*). Patients should be monitored closely for new or worsening neurological, cognitive, or behavioural changes suggestive of PML. POLIVY and any concomitant chemotherapy should be held if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Tumour Lysis Syndrome

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

Infusion Related Reactions (IRRs)

IRRs, including severe cases, have been observed with POLIVY. IRRs can occur as late as 24 hours after receiving POLIVY. Patients should be administered premedication with an antihistamine and anti-pyretic prior to administration of POLIVY. Patients should be monitored closely during administration for IRRs. Symptoms include fever, chills, flushing, dyspnoea, hypotension, or urticaria. If an IRR occurs, the infusion should be interrupted, and appropriate medical management should be instituted (section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Embryofoetal 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 *4.6 Fertility, Pregnancy and Lactation*). Advise a pregnant woman of the risk to the foetus.

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 section *4.6 Fertility, Pregnancy and Lactation*).

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 (see sections *4.2 Special populations* and *5.2 Pharmacokinetics in special populations*).

Use in 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 and these patients are likely to have increased exposure to MMAE with increased risk of adverse events. The administration of Polivy in patients with moderate or severe hepatic impairment (total bilirubin greater than 1.5 × ULN) should be avoided (see sections *4.2 Special populations* and *5.2 Pharmacokinetics in special populations*).

Use in renal impairment

The safety and efficacy of POLIVY in patients with CrCL <30 mL/min has not been formally studied (see sections *4.2 Special populations* and *5.2 Pharmacokinetics in special populations*).

Use in the elderly

In patients with DLBCL (previously untreated and previously treated) no overall differences in safety or efficacy were observed between patients ≥65 years of age and younger patients (see sections *4.2 Special populations* and *5.2 Pharmacokinetics in special populations*).

Paediatric use

The safety and efficacy of POLIVY in children and adolescents below 18 years of age has not been established (see sections *4.2 Special populations* and *5.2 Pharmacokinetics in special populations*).

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 physiologically-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., rifampicin) 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).

Co-administration with other CYP substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of MMAE-mediated inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. MMAE does not induce CYP1A2, CYP2B6 or CYP3A4/5 *in vitro*.

Co-administration with Drugs that are Substrates of Transporters

In vitro data indicate that MMAE is a P-gp substrate but does not inhibit P-gp at clinically relevant concentrations. MMAE was not an *in vitro* substrate or inhibitor for the BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3 or OCT2 transporters. MMAE was also not an *in vitro* inhibitor of BSEP or OAT1.

Drug interactions of rituximab, bendamustine, cyclophosphamide, and doxorubicin in combination with polatuzumab vedotin

The pharmacokinetics (PK) of rituximab, bendamustine, cyclophosphamide, and doxorubicin are not affected by co-administration with POLIVY. 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. The plasma AUC of acMMAE and unconjugated MMAE for POLIVY plus R-CHP are in line with other studies of POLIVY. No dose adjustment is required.

Bendamustine does not affect acMMAE and unconjugated MMAE plasma AUC.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of POLIVY on human male and female fertility have not been studied. However, results from a repeat-dose toxicity study 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 IV 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 following a 6-week treatment-free period and correlated with decreased testes weight and gross findings of small and/or soft testes at recovery necropsy in males given doses $\geqslant$ 2 mg/kg. A no effect level was not established. Although there were no histological abnormalities in female reproductive organs from animal studies, dedicated fertility studies in female animals were not conducted. MMAE, the main active catabolite of polatuzumab vedotin, has been shown to have aneugenic properties in an *in vivo* rat bone marrow micronucleus study. These results were consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubule network) in cells.

Therefore, men being treated with POLIVY are advised to have sperm samples frozen and stored before treatment. Men being treated with POLIVY are advised to use effective contraception during treatment with POLIVY and not to father a child during treatment and for up to 6 months following the last dose. Effects on spermatogenesis cannot be excluded after a 6 month treatment-free period.

Use in pregnancy - Category D

There are no adequate or well-controlled studies with POLIVY in pregnant women. However, based on its mechanism of action and findings in animals, POLIVY can cause foetal harm when administered to a pregnant woman.

Embryofoetal lethality and toxicity were seen in a rat embryofoetal development study in which pregnant rats received two IV doses of 0.2 mg/kg MMAE, the main active metabolite of polatuzumab vedotin, during the period of organogenesis, and included an increased incidence of post-implantation loss, and an increase in the incidence of foetal malformations including protruding tongue, malrotated hindlimbs, gastroschisis and agnathia. These adverse embryofoetal development effects occurred at exposures less than that expected in patients receiving polatuzumab vedotin.

POLIVY should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated she should be clearly advised on the potential risk to the foetus.

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 the ‘Effects on fertility’ section above pertaining to advice for women whose male partners are being treated with POLIVY.

Use in lactation

It is not known whether polatuzumab vedotin or its metabolites are excreted in human breast milk. A risk to breast-fed children cannot be excluded. Women should discontinue breastfeeding during POLIVY treatment and for at least 3 months after the last dose.

Contraception

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.

4.7 EFFECTS ON 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 section *4.4 Special warnings and precautions for use* and *4.8 Adverse effects (Undesirable effects)*).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

The safety of POLIVY has been evaluated in 435 patients in Study GO39942 (POLARIX) and in 151 patients in Study GO29365. The adverse drug reactions (ADRs) described in this section were identified based on the following;

- during treatment and follow-up of previously untreated DLBCL patients from the pivotal clinical trial POLARIX (GO39942), who received POLIVY plus R-CHP (n=435) or R-CHOP (n=438). In the POLIVY plus R-CHP group, 91.7% of patients received 6 cycles of POLIVY versus 88.5% of patients who received 6 cycles of vincristine in the R-CHOP group
- during treatment and follow-up of previously treated diffuse large B-cell lymphoma (DLBCL) patients (n=151) from the pivotal clinical trial GO29365. This includes run-in phase patients (n=6) and randomised patients (n=39) and extension cohort patients (n=106) who received POLIVY in combination with bendamustine and rituximab (BR) compared to randomised patients (n=39) who received BR alone. Patients in the POLIVY treatment arm received a median of 5 cycles of treatment while randomised patients in the comparator arm received a median of 3 cycles of treatment.

Tabulated summary of Adverse Drug Reactions from clinical trials

Adverse Drug Reactions (ADRs) from the clinical trials are listed by MedDRA system organ class (SOC) in Table 5 (previously untreated DLBCL) and Table 6 (previously treated DLBCL).

The most frequently reported (⩾30%) ADRs (all grades) in patients treated with POLIVY in combination with R-CHP for previously untreated DLBCL were neuropathy peripheral, nausea, neutropenia, and diarrhoea. Serious adverse reactions were reported in 24.1% of POLIVY plus R-CHP treated patients which included the following that occurred in ⩾5% of patients: febrile neutropenia (10.6%) and pneumonia (5.3%).

The ADR leading to treatment regimen discontinuation in ≥1% of patients treated with POLIVY in combination with R-CHP for previously untreated DLBCL was pneumonia (1.1%).

The most frequently-reported (≥30%) ADRs (all grades) in patients treated with POLIVY in combination with BR for previously treated DLBCL were anaemia, thrombocytopenia, neutropenia, diarrhoea, nausea, and peripheral neuropathy. Serious adverse events were reported in 55.6% of POLIVY plus BR treated patients which included the following that occurred in ≥5% of patients: febrile neutropenia (9.3%), pyrexia (7.9%), pneumonia (6.6%), and sepsis (6.6%).

ADR leading to treatment regimen discontinuation in >5% of patients were thrombocytopenia (6.0%).

The following categories of frequency have been used: 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).

Table 5 Summary of adverse drug reactions occurring in patients with previously untreated DLBCL treated with POLIVY in combination with R-CHP (Study GO39942)

Adverse drug reactions	POLIVY + R-CHP n=435		R-CHOP n=438	
SOC	**All grades (%)**	**Grade 3 or Higher (%)**	**All grades (%)**	**Grade 3 or Higher (%)**
Infections and Infestations				
Upper respiratory tract infection	16.8	0.5	16	0.5
Pneumonia[a]	8.7		7.3	5.5
Urinary tract infection	8.3	1.8	7.1	1.1
Herpes virus infection	3.4	0.2	3.2	0.5
Sepsis[a]	2.1	2.1	3.4	3.4
Cytomegalovirus infection	0.7	0.5	0.2	0.2
Blood and Lymphatic System Disorders				
Neutropenia	38.4	34.5	39	36.5
Anaemia	28.7	12	26.9	8.7
Febrile Neutropenia	14.9	14.5	8.7	8.7
Leukopenia	14	9.7	13	9.8
Thrombocytopenia	13.3	5.3	13.2	5
Lymphopenia	6.9	4.6	8.7	5.7
Pancytopenia	0.2	0.2	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	16.6	1.1	14.2	0.7
Hypokalaemia	8.3	1.8	8.9	1.8
Hypoalbuminaemia	2.3	0.5	2.5	0
Hypocalcaemia	1.6	0.2	2.3	0.5
Nervous System Disorders				
Neuropathy Peripheral	52.9	1.6	53.9	1.1
Dizziness	8.7	0.2	7.8	0.2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	15.4	0	14.4	0
Dyspnoea	12.9	0.9	10	0.9

Pneumonitis	1.1	0.2	0.7	0
Gastrointestinal Disorders				
Nausea	41.6	1.1	37	0.5
Diarrhoea	30.8	3.9	20.1	1.8
Constipation	28.7	1.1	29	0.2
Abdominal Pain	15.6	1.1	13.9	1.6
Vomiting	15.2	1.1	14.4	0.7
Skin and Subcutaneous Tissue Disorders				
Alopecia	24.4	0	24	0.2
Rash	13.3	0.9	11.2	0
Pruritus	8.3	0	6.4	0.2
Skin infections	6.9	1.1	3	0.7
Dry skin	6	0	2.7	0
Musculoskeletal Disorders				
Myalgia	8.7	0.2	7.3	0.2
Arthralgia	6.2	0	8.4	0
General Disorders and Administration Site Conditions				
Fatigue	25.7	0.9	26.5	2.5
Mucositis	21.8	1.4	19.4	0.5
Pyrexia	15.6	1.4	12.6	0
Asthenia	12.2	1.6	12.1	0.5
Peripheral Oedema	11	0.2	9.1	0.2
Chills	4.6	0.2	5.3	0.5
Investigations				
Weight decreased	12.6	0.9	12.1	0.2
Transaminases increased	6.7	0.7	5.7	0.2
Hypophosphataemia	4.8	1.8	2.7	1.4
Injury, Poisoning, and Procedural				
Infusion related reaction[b]	13.3	1.1	16	1.6

[a]ADR associated with fatal outcome

[b]Infusion related reaction ADR is reflective of the combination regimen Pola + R-CHP due to same day administration.

Table 6 Summary of adverse drug reactions occurring in previously treated DLBCL patients treated with POLIVY in combination with BR (Study GO29365)

System Order Class/ ADR (MedDRA Preferred Term)	POLIVY + bendamustine + rituximab N = 151		Frequency (all grades)	Bendamustine + rituximab N=39		Frequency (all grades)
	All grades (%)	Grades 3-4 (%)		All grades (%)	Grades 3-4 (%)	
Infections and Infestations						
Pneumonia[a]	14.6	9.3	Very common	17.9	5.1	Very common
Sepsis	10.6	9.9	Very common	10.3	10.3	Very common
Upper respiratory tract infection	9.9	0.7	Common	7.7	0	Common
Herpes virus infection	5.3	0.7	Common	10.3	2.6	Very common
Cytomegalovirus infection	2.1	0.7	Common	2.6	2.6	Common
Blood and Lymphatic System Disorders						
Anaemia	31.8	12.6	Very common	28.2	17.9	Very common
Neutropenia	45.7	40.4	Very common	43.6	35.9	Very common
Thrombocytopenia	32.5	25.8	Very common	33.3	25.6	Very common
Febrile Neutropenia	11.3	10.6	Very common	17.9	17.9	Very common
Leukopenia	15.2	10.5	Very common	23.1	18.0	Very common
Lymphopenia	13.2	12.5	Very common	7.7	7.7	Common
Pancytopenia	3.3	2.0	Common	0	0	N/A
Metabolism and Nutrition Disorders						
Decreased appetite	25.8	2.6	Very common	20.5	0	Very common
Hypokalaemia	16.5	6.5	Very common	10.3	2.6	Very common
Hypoalbuminaemia	6.0	1.3	Very common	7.7	0	Common
Hypocalcaemia	5.3	0.7	Very common	5.2	0	Common
Nervous System Disorders						
Neuropathy Peripheral	30.5	0.7	Very common	7.7	0	Common
Dizziness	11.3	0	Very common	7.7	0	Common
Peripheral Sensory neuropathy	7.3	0	Common	0	0	N/A
Respiratory, Thoracic and Mediastinal Disorders						
Cough	15.9	0	Very common	25.6	0	Very common
Pneumonitis	1.3	0	Common	0	0	Very rare
Gastrointestinal Disorders						
Diarrhoea	35.8	4.0	Very common	28.2	5.1	Very common

System Order Class/ ADR (MedDRA Preferred Term)	POLIVY + bendamustine + rituximab N = 151		Frequency (all grades)	Bendamustine + rituximab N=39		Frequency (all grades)
	All grades (%)	Grades 3-4 (%)		All grades (%)	Grades 3-4 (%)	
Nausea	33.1	0.7	Very common	41.0	0	Very common
Constipation	18.5	0	Very common	20.5	2.6	Very common
Vomiting	17.2	2.6	Very common	12.8	0	Very common
Abdominal Pain	17.9	4.6	Very common	17.9	2.6	Very common
Abdominal Pain Upper	7.3	0.7	Common	5.1	0	Common
Skin and Subcutaneous Tissue Disorders						
Pruritis	9.3	0	Common	10.3	2.6	Very common
Musculoskeletal Disorders						
Arthralgia	4.0	0	Common	0	0	N/A
General Disorders and Administration Site Conditions						
Fatigue	26.5	2	Very common	35.9	2.6	Very common
Pyrexia	28.5	1.3	Very common	23.1	0	Very common
Asthenia	11.9	2.0	Very common	15.4	0	Very common
Chills	4.6	0	Common	7.7	0	Common
Investigations						
Weight decreased	13.9	0.7	Very common	7.7	2.6	Common
Transaminase elevation	7.3	0.7	Common	0	0	N/A
Hypophosphataemia	4.0	1.4	Common	2.6	2.6	Common
Lipase increased	4.0	1.4	Common	0	0	N/A
Injury, Poisoning, and Procedural						
Infusion-related reaction	11.9	2.0	Very common	5.1	0	Common

[a]ADR associated with fatal outcome

Description of selected adverse drug reactions from clinical trials

Myelosuppression

Study GO39942 (POLARIX)

0.5% of patients in the POLIVY plus R-CHP arm discontinued study treatment due to neutropenia compared to no patients in the R-CHOP arm. Thrombocytopenia events led to discontinuation of treatment in 0.2% of patients in the POLIVY plus R-CHP arm and none discontinued treatment in the R-CHOP arm. No patients discontinued treatment due to anaemia in either the POLIVY plus R-CHP arm or R-CHOP arm.

Study GO29365

4.0% of patients in the POLIVY plus BR arms 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 7.9% of patients in the POLIVY plus BR arms and 5.1% of patients in the BR arm. No patients discontinued treatment due to anaemia in either the POLIVY plus BR arms or BR arm.

Peripheral Neuropathy

Study GO39942 (POLARIX)

In the POLIVY plus R-CHP arm, Grade 1, 2, and 3 peripheral neuropathy were reported in 39.1%, 12.2%, and 1.6% of patients, respectively. In the R-CHOP arm, Grade 1, 2, and 3 peripheral neuropathy were reported in 37.2%, 15.5%, and 1.1% of patients, respectively. No Grade 4–5 peripheral neuropathy were reported in either the POLIVY plus R-CHP arm or R-CHOP arm. 0.7% of patients discontinued study treatment in the POLIVY plus R-CHP due to peripheral neuropathy compared to 2.3% in the R-CHOP arm. 4.6% of patients had study treatment dose reduction due to peripheral neuropathy compared to 8.2% in the R-CHOP arm. In the POLIVY plus R-CHP arm, the median time to onset of first event of peripheral neuropathy was 2.27 months compared to 1.87 months in the R-CHOP arm. 57.8% of patients with peripheral neuropathy reported event resolution as of the clinical cut-off date compared to 66.9% in the R-CHOP arm. The median time to peripheral neuropathy resolution was 4.04 months compared to 4.6 months in the R-CHOP arm.

Study GO29365

In the POLIVY plus BR arms, Grade 1 and 2 peripheral neuropathy events were reported in 15.9% and 12.6% of patients, respectively. In the BR arm, Grade 1 and 2 peripheral neuropathy events were reported in 2.6% and 5.1% of patients, respectively. One Grade 3 peripheral neuropathy event was reported in the POLIVY plus BR arms and no Grade 3 peripheral neuropathy events were reported in the BR arm. No Grade 4-5 peripheral neuropathy events were reported in either the POLIVY plus BR arm or BR arm. 2.6% of patients discontinued POLIVY treatment due to peripheral neuropathy and 2.0% of patients had POLIVY dose reduction due to peripheral neuropathy. No patients in the BR arm discontinued treatment or had dose reductions due to peripheral neuropathy. In the POLIVY plus BR arms, the median onset to first event of peripheral neuropathy was 1.6 months, and 39.1% of patients with peripheral neuropathy events reported event resolution.

Infections

Study GO39942 (POLARIX)

Infections, including pneumonia and other types of infections, were reported in 49.7% of patients in the POLIVY plus R-CHP arm and 42.7% of patients in the R-CHOP arm. Grade 3-4 infections occurred in 14.0% of patients in the POLIVY plus R-CHP arm and 11.2% of patients in the R-CHOP arm. In the POLIVY plus R-CHP arm, serious infections were reported in 14.0% of patients and fatal infections were reported in 1.1% of patients. In the R-CHOP arm, serious infections were reported in 10.3% of patients and fatal infections were reported in 1.4% of patients. 7 patients (1.6%) in the POLIVY plus R-CHP arm discontinued treatment due to infection compared to 10 patients (2.3%) in the R-CHOP arm.

Study GO29365

Infections, including pneumonia and other types of infections, were reported in 48.3% of patients in the POLIVY plus BR arms and 51.3% of patients in the BR arm. In the POLIVY plus BR arms, serious infections were reported in 27.2% of patients and fatal infections were reported in 6.6% 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. Four patients (2.6%) discontinued treatment in the POLIVY plus BR arms due to infection compared to two patients (5.1%) in the BR arm (see *4.4 Special warnings and precautions for use*).

Progressive Multifocal Leukoencephalopathy (PML)

Study GO39942 (POLARIX)

No cases of PML were reported with POLIVY plus R-CHP or in the R-CHOP arm.

Study GO29365

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 4.4 Special warnings and precautions for use).*

Hepatic toxicity

Study GO39942 (POLARIX)

Hepatic toxicity was reported in 10.6% of patients in the POLIVY plus R-CHP arm and 7.3% of patients in the R-CHOP arm. In the POLIVY plus R-CHP arm, most events were Grade 1–2 (8.7%); Grade 3 events were reported in 1.8% of patients. There were no Grade 4 or 5 events. Serious hepatic toxicity events were reported in 1 patient (0.2%) and were reversible.

Study GO29365

In another study, two cases of serious hepatic toxicity (hepatocellular injury and hepatic steatosis) were reported and were reversible (*see 4.4 Special warnings and precautions for use).*

Gastrointestinal Toxicity

Study GO39942 (POLARIX)

Gastrointestinal toxicity events were reported in 76.1% of patients in the POLIVY plus R-CHP arm compared to 71.9% of patients in the R-CHOP arm. Most events were Grade 1–2, and Grade ≥3 events were reported in 9.7% of patients in the POLIVY plus R-CHP arm compared to 8.2% of patients in the R-CHOP arm. The most common gastrointestinal toxicity events were nausea and diarrhoea.

Study GO29365

Gastrointestinal toxicity events were reported in 72.8% of patients in the POLIVY plus BR arms compared to 66.7% of patients in the BR arm. Most events were Grade 1-2, and Grade 3-4 events were reported in 16.5% of patients in the POLIVY plus BR arms compared to 12.9% of patients in the BR arm. The most common gastrointestinal toxicity events were diarrhoea and nausea.

Laboratory abnormalities
All identified laboratory abnormalities were reported as ADRs, refer to Table 5.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration 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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdose in human clinical trials. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers an 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 nanomolar 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 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.

Clinical trials
Previously untreated DLBCL:

The efficacy of POLIVY was evaluated in an international, multicentre, randomised double-blind, placebo-controlled study (POLARIX, GO39942) in 879 patients with previously untreated DLBCL.

Eligible patients were age 18–80 years, and had IPI score 2-5 and ECOG Performance Status 0–2. Histologies included DLBCL (NOS, ABC, GCB), high-grade B-cell lymphoma (HGBL; NOS, double-hit, triple-hit), and other large B-cell lymphoma subtypes (EBV positive, T-cell rich/histiocyte rich). Patients did not have known CNS lymphoma or peripheral neuropathy > Grade 1.

Patients were randomised 1:1 to receive POLIVY plus R-CHP or R-CHOP for six 21-day cycles followed by two additional cycles of rituximab alone in both arms. Patients were

stratified by IPI score (2 vs 3-5), presence or absence of bulky disease (lesion ⩾7.5 cm), and geographical region.

POLIVY was administered intravenously at 1.8 mg/kg on Day 1 of cycles 1–6. R-CHP or R CHOP were administered starting on Day 1 of Cycles 1–6 followed by rituximab alone on Day 1 of Cycles 7–8. Dosing in each treatment arm was administered according to the following:

- POLIVY + R-CHP arm: POLIVY 1.8 mg/kg, rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and prednisone 100 mg/day, on days 1-5 of every cycle, orally.
- R-CHOP arm: rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², and prednisone 100 mg/day, on days 1-5 of every cycle, orally.

The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. The median age was 65 years (range 19 to 80 years), 53.6% of patients were white and 53.8% were male. 43.8% had bulky disease, 38.0% had IPI score 2, 62.0% had IPI score 3–5, and 88.7% had Stage 3 or 4 disease. The majority of patients (84.2%) had DLBCL (including NOS, ABC, and GCB). 211 patients did not have a cell of origin (COO) result reported. Of the COO evaluable population (n=668), 33.1% of patients had ABC like DLBCL and 52.7% of patients had GCB like DLBCL, by gene expression profiling.

The primary endpoint of the study was investigator-assessed progression-free survival. The median duration of follow up was 28.2 months. Efficacy results are summarised in Table 7 and in Figure 1.

Table 7 Summary of efficacy in patients with previously untreated DLBCL from study GO39942 (POLARIX)

	POLIVY + R-CHP N= 440	**R-CHOP N= 439**
Primary Endpoint		
Progression free survival[1)]*		
Number (%) of patients with events	107 (24.3%)	134 (30.5%)
HR (95% CI)	0.73 [0.57, 0.95]	
p-value[3)]**	0.0177	
2-year PFS estimate	76.7	70.2
[95% CI]	[72.65, 80.76]	[65.80, 74.61]
Key Endpoints		
Event-free survival (EFS_{eff})[1)]		
Number (%) of patients with event	112 (25.5%)	138 (31.4%)
HR [95% CI]	0.75 [0.58, 0.96]	
p-value[3)]**	0.0244	
Complete Response (%) (CR) Rate[2) 3)] *		

Responders (%)	343 (78.0%)	325 (74.0%)
Difference in response rate (%) [95% CI]	3.92 [-1.89, 9.70]	
p-value[4)]**	0.1557	

INV: Investigator; BICR: Blinded independent central review; CI: Confidence interval; HR: Hazard ratio; PFS: Progression free survival; EFS_{eff}: Event free survival efficacy: used to reflect EFS events that are due to efficacy and defined as time from date of randomisation to the earliest occurrence of any of the following: disease progression/relapse, death due to any cause, the primary efficacy reason determined by the investigator, other than disease progression/relapse, that led to initiation of any non-protocol specified anti-lymphoma treatment (NALT), if biopsy was obtained after treatment completion and was positive for residual disease regardless of whether NALT was initiated or not; CMH: Cochran-Mantel-Haenszel.

1) INV-assessed

2) BICR-assessed

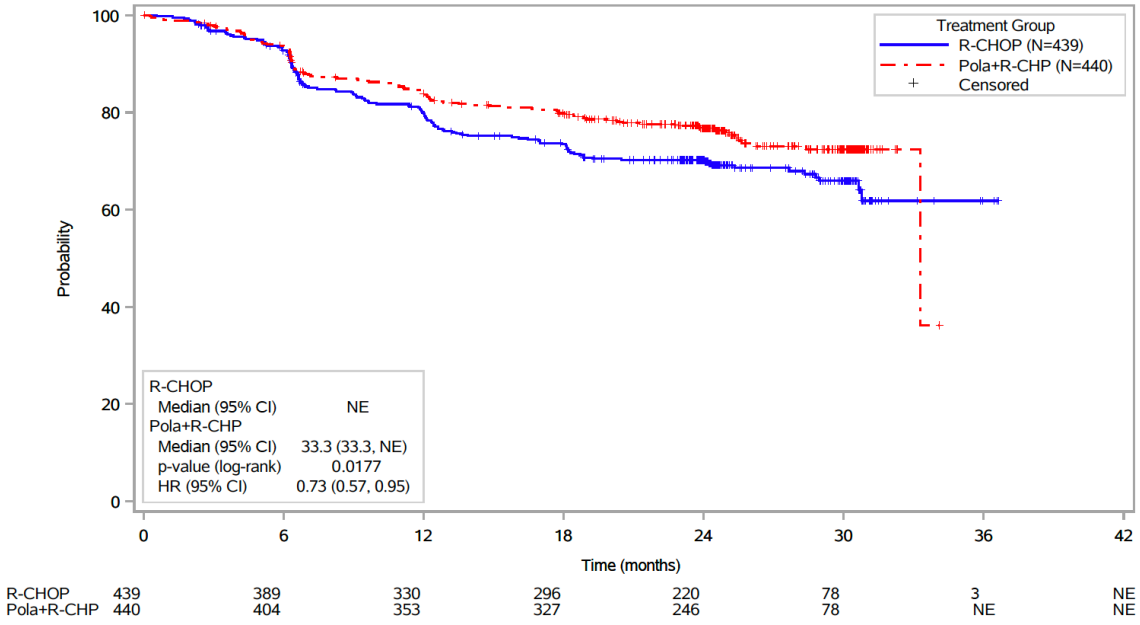
3) CR rate at end of treatment by fluorodeoxyglucosepositron emission tomography (FDG-PET) as determined by BICR

4) CMH chi-squared test

*Per Lugano 2014 Response Criteria

**Stratified by IPI (2 vs 3-5), presence or absence of bulky disease, geography

Figure 1 Kaplan Meier curve of INV-assessed progression free survival in Study GO39942 (POLARIX)



In the final analysis, Overall Survival between the POLIVY plus R-CHP and R-CHOP arms was similar, HR 0.94 (95% CI: 0.67, 1.33).

Previously treated DLBCL:

The efficacy of POLIVY was evaluated in Study GO29365, an open-label, multicenter clinical trial that included a cohort of 80 patients with relapsed or refractory DLBCL after at least one prior regimen. Patients were randomized 1:1 to receive either POLIVY in combination with bendamustine and a rituximab product (BR) or BR alone for six 21-day cycles. Randomisation was stratified by duration of response (DOR) to last therapy. Eligible patients were not candidates for autologous HSCT at study entry. The study excluded patients with Grade 2 or higher peripheral neuropathy, prior allogeneic HSCT, active central nervous system lymphoma, or transformed lymphoma.

Following premedication with an antihistamine and antipyretic, POLIVY was given by intravenous infusion at 1.8 mg/kg 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. A rituximab product was administered at a dose of 375 mg/m^2 intravenously on Day 1 of Cycles 1–6. The cycle length was 21 days.

Of the 80 patients randomised to receive POLIVY plus BR (n = 40) or BR alone (n = 40), the median age was 69 years (range: 30–86 years), 66% were male, and 71% were white. Most patients (98%) had DLBCL not otherwise specified. The 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% receiving one prior therapy, 25% receiving 2 prior therapies, and 46% receiving 3 or more prior therapies. Eighty percent of patients had refractory disease to last therapy.

In the POLIVY plus BR arm, patients received a median of 5 cycles, with 49% receiving 6 cycles. In the BR arm, patients received a median of 3 cycles, with 23% receiving 6 cycles.

Efficacy was based on complete response (CR) rate at the end of treatment and DOR, as determined by an independent review committee (IRC). Other efficacy measures included IRC-assessed best overall response.

Response rates are summarised in Table 8

Table 8 Response Rates in Patients with Relapsed or Refractory DLBCL

Response per IRC, n (%)[a]	**POLIVY + BR n = 40**	**BR n = 40**
Objective Response at End of Treatment[b]	18 (45)	7 (18)
(95% CI)	(29, 62)	(7, 33)
CR	16 (40)	7 (18)
(95% CI)	(25, 57)	(7, 33)
Difference in CR rates, % (95% CI)[c]	22 (3, 41)	
Best Overall Response of CR or PR[d]	25 (63)	10 (25)
(95% CI)	(46, 77)	(13, 41)
Best Response of CR	20 (50)	9 (23)
(95% CI)	(34, 66)	(11, 38)

PR = partial remission.
[a] PET-CT based response per modified Lugano 2014 criteria. Bone marrow confirmation of PET-CT CR was required. PET-CT PR required meeting both PET criteria and CT criteria for PR.
[b] End of treatment was defined as 6–8 weeks after Day 1 of Cycle 6 or last study treatment.
[c] Miettinen-Nurminen method.
[d] PET-CT results were prioritized over CT results.

In the POLIVY plus BR arm, of the 25 patients who achieved a partial or complete response, 16 (64%) had a DOR of at least 6 months, and 12 (48%) had a DOR of at least 12 months. In the BR arm, of the 10 patients who achieved a partial or complete response, 3 (30%) had a DOR lasting at least 6 months, and 2 (20%) had a DOR lasting at least 12 months.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with polatuzumab vedotin. In Studies GO39442 (POLARIX) and GO29365, 1.4% (6/427) and

5.2% (12/233) of patients tested positive for antibodies against polatuzumab vedotin, respectively, of which none were positive for neutralising antibodies. 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.

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.

Absorption

POLIVY is administered as an IV 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 concentration 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.

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.

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

Excretion

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 (95%) of radioactivity is excreted in faeces and the minority (5%) of radioactivity is excreted in urine.

Pharmacokinetics in Special Populations

Elderly

Age did not have an effect on the pharmacokinetics of acMMAE and unconjugated MMAE based on population PK analyses with patients aged 19-89 years. No significant difference was observed in the pharmacokinetics of acMMAE and unconjugated MMAE among patients <65 years of age (n=394) and patients ≥65 years of age (n=495).

Children

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

Renal Impairment

In patients with mild (CrCL 60-89 mL/min, n=361) or moderate (CrCL 30-59 mL/min, n=163) renal impairment, acMMAE and unconjugated MMAE exposures are similar to patients with normal renal function (CrCL ≥ 90 mL/min, n=356), based on population pharmacokinetic analyses. There are insufficient data to assess the impact of severe renal impairment (CrCL 15-29 mL/min, n=4) on PK. No data are available in patients with end-stage renal disease and/or who are on dialysis (see section *4.2 Dose and method of 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=133], acMMAE exposures are similar whereas unconjugated MMAE AUC are not more than 40% higher compared to patients with normal hepatic function (n=737), 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=11) on PK. Limited data are available in patients with severe hepatic impairment or liver transplantation (see section *4.2 Dose and method of administration)*.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No dedicated mutagenicity studies in animals have been performed with polatuzumab vedotin. 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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Succinic acid, sodium hydroxide, sucrose, polysorbate 20.

6.2 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) or polytetrafluorethylene (PTFE) and with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

The reconstituted solution should be used immediately. If the solution is not used immediately, it can be stored no longer than 72 hours at 2°C to 8°C, or 20 hours at ambient temperature.

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

POLIVY is available in a single-use glass vial in a pack size of 1 vial.

The POLIVY vial stoppers are not derived from natural rubber latex.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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). Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number: 1313206-42-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

21 October 2019

10 DATE OF REVISION OF THE TEXT

14 February 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Inclusion of Infusion-Related Reactions