Public Assessment Report

(Variation, Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL))

POLIVY

INFORMASI PRODUK

Nama obat	:	POLIVY
Bentuk sediaan	:	Serbuk untuk larutan infus
Zat aktif	:	Tiap vial mengandung: Polatuzumab vedotin 140 mg Polatuzumab vedotin 30 mg
Kemasan	:	Dus, 1 vial @ 140 mg Dus, 1 vial @ 30 mg
Pendaftar	:	PT. Menarini Indria Laboratories
Produsen	:	1. Polivy 140 mg: Diproduksi dan dikemas oleh BSP Pharmaceuticals S.P.A., Latina, Italy Dirilis oleh F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland 2. Polivy 30 mg: F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland
Kategori registrasi	:	Penambahan indikasi dan posologi baru
Indikasi yang diajukan	:	*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 adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.***
Posologi yang diajukan	:	*Polivy must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.* *Posology* ***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 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for 6 cycles. 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.* *Refer to the summary of product characteristics (SmPC) of chemotherapy agents given in combination with Polivy for patients with previously untreated DLBCL.* ***Relapsed or refractory 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. When administered with Polivy, the recommended dose of bendamustine is 90 mg/m2/day on Day 1 and Day 2 of each cycle and the recommended dose of rituximab is 375 mg/m2 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.*** ***Previously untreated and relapsed or refractory patients***

If not already premedicated, premedication with an antihistamine and antipyretic 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.
There are different potential dose modifications for Polivy in patients with previously untreated DLBCL.
For dose modifications to manage peripheral neuropathy (section 4.4) see Table 1 below.

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 ≤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 ≤ 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 ≤ 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 ≤ 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 ≤ 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.
R/R 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 (section 4.4) 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%.
R/R 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 (section 4.4) 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 DLBCL and R/R DLBCL	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 x 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 x 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 x ULN or total bilirubin > 1.0 to 1.5 x ULN), there was a not more than 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 handling 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).

PENGANTAR

Polivy mengandung zat aktif polatuzumab vedotin, yang merupakan antibodi monoklonal dan bekerja dengan cara berikatan dengan antigen CD79b pada permukaan sel B kanker, kemudian antibodi akan melepaskan senyawa vedotin yang merupakan konjugat dari antibodi yang berfungsi sebagai agen kemoterapi. Vedotin mengandung monomethyl auristatin E (MMAE) yang bekerja menghambat mikrotubulus dan menyebabkan kematian sel kanker.

Polivy telah mendapatkan izin edar di Indonesia sejak tahun 2023 dengan indikasi yang disetujui yaitu sebagai terapi kombinasi dengan rituximab, cyclophosphamide, doxorubicin, dan prednisone pada pasien dewasa dengan *Diffuse Large B-cell Lymphoma* (DLBCL) yang belum menerima terapi sebelumnya.

Saat ini pendaftar mengajukan penambahan indikasi sebagai terapi kombinasi dengan bendamustine dan rituximab untuk pengobatan *Diffuse Large B-cell Lymphoma* (DLBCL) yang relaps atau refrakter dan tidak dapat menerima transplantasi *haematopoietic stem cell*. Indikasi baru yang diajukan sudah disetujui di negara referensi (Uni Eropa, Amerika, Inggris, Kanada, dan Australia).

Berdasarkan data GLOBOCAN 2020, di Indonesia terdapat 16.125 kasus baru limfoma non-Hodgkin dan menempati peringkat ke-9 kasus kematian terbanyak akibat kanker, dengan angka 9.024 kematian (3,8%). Pilihan terapi yang tersedia di Indonesia untuk kasus DLBCL masih terbatas, yakni Rituximab (Mabthera).

ASPEK MUTU

Tidak ada perubahan.

ASPEK KHASIAT DAN KEAMANAN

Pendaftar menyerahkan studi klinik (GO29365, GO27834, GO29044, DCS4968g, GO29833, GO29834) dan dokumen pendukung mekanisme *reliance (EMA assessment report).*

Studi Nonklinik

Tidak ada studi nonklinik baru yang diserahkan, hal ini dapat diterima karena indikasi baru yang diajukan merupakan pengobatan untuk penyakit yang sama (DLBCL), tetapi berbeda pada populasi subjek yang menjadi target (belum pernah diobati vs relaps atau refrakter).

Studi Klinik

Studi klinik yang diserahkan meliputi 1 studi klinik pivotal (studi GO29365) dan 6 studi pendukung (DCS4968g, GO27834, GO29044, GO29833, GO29834, and BO29561) dan dokumen RMP.

Studi klinik pivotal GO29365 berisi data dengan cut-off 21 Oktober 2021. Pada studi ini, Polivy (polatuzumab vedotin) diberikan dalam kombinasi dengan bendamustine dan rituximab (Pola+BR) yang dibandingkan dengan bendamustin + rituximab (BR). Penggunaan bendamustine sebagai monoterapi maupun kombinasi bendamustine dengan rituximab untuk indikasi DLBCL belum disetujui di Indonesia maupun negara referensi lain.

a. Penilaian Efikasi

1. Berdasarkan penilaian *independent review committee* (IRC), efikasi kombinasi polatuzumab liquid + Bendamustine-Rituximab (Pola + BR, Arm C) lebih baik dibanding BR berdasarkan parameter:
   - *Complete response rate* (CR) 42,5% vs 17,5%; p=0,0128.
   - *Objective Response Rate* (OR) 42,5% vs 17,5%
   - *Best Objective Response* (BOR) 62,5% vs 25,0%
   - *Progression Free Survival* (PFS) 9,2 bulan vs 3,7 bulan
   - *Duration of Response* (DOR) 10,9 bulan vs 10,6 bulan
2. Parameter efikasi lainnya juga terlihat lebih baik pada kelompok Pola+BR, yaitu
   - *Event-free Survival/EFS (INV-assessed)* 6,2 bulan vs 2 bulan
   - *Overall survival* (OS) 12,4 bulan vs 4,5 bulan
3. Efikasi Pola+BR lyophilized cohort (Arm G dan H) menunjukkan hasil yang konsisten dengan Arm C, yaitu CR 39,6%, OR 43,4%, BOR 57,5%, DOR 13,4 bulan, PFS 7 bulan, EFS 5,1 bulan, dan OS 12,3 bulan.

b. Penilaian Keamanan

1. Secara umum, profil keamanan kombinasi polatuzumab vedotin dengan BR menunjukkan konsistensi dengan data cut-off sebelumnya.
2. Hasil imunogenisitas GO29365
   - Insiden munculnya anti-polatuzumab vedotin ADA terkait pengobatan adalah 5,2% (12 dari 233 pasien).
   - Dari 12 pasien yang memiliki ADA, 8 pasien menunjukkan ADA bersifat sementara, sementara 4 pasien menunjukkan ADA bersifat persisten.
3. AE yang sering dilaporkan neutropenia, trombositopenia, anemia, dan neuropati perifer (PN) pada formula liquid dan pyrexia, diare, mual, neutropenia, anemia, penurunan nafsu makan, dan kelelahan pada formula lyophilized.
4. AE grade 3-4 lebih tinggi di kelompok pola + BR dibandingkan BR saja (87,2% vs 71,8%). Efek samping grade 3-4 terjadi 78,3% pada arm G dan H.
5. Kematian akibat perkembangan penyakit lebih sedikit di kelompok pola + BR dibandingkan dengan BR (15 vs 20 pasien), sedangkan sebanyak 65 pasien meninggal pada arm G dan H (58 karena perkembangan penyakit, 1 sepsis neutropenik, 2 sepsis, 1 hidrosefalus, 1 syok septik, 1 pneumonia, dan 1 efek samping Grade 5 yang tidak terdefinisi setelah perkembangan penyakit).
6. Insiden AE serius (SAEs) lebih tinggi di pola + BR dibandingkan BR (69,2% vs 61,5%) dan 53,8%

pada arm G dan H.

7. Penghentian pengobatan lebih banyak terjadi pada pasien yang menerima pola + BR dibandingkan BR saja (33,3% vs 12,8%).

Berdasarkan data GLOBOCAN 2020, di Indonesia terdapat 16.125 kasus baru limfoma non-Hodgkin dan menempati peringkat ke-9 kasus kematian terbanyak akibat kanker, dengan angka 9.024 kematian (3,8%). Pilihan terapi yang tersedia di Indonesia untuk kasus R/R DLBCL, khususnya yang tidak dapat menerima transplantasi haematopoietic stem cell masih terbatas.

Indikasi baru yang diajukan sudah disetujui di negara referensi (Uni Eropa, Amerika, Inggris, Canada, Australia).

EVALUASI

Penilaian Manfaat-Risiko

Polivy telah memiliki izin edar di Indonesia sejak tahun 2023. Saat ini pendaftar mengajukan indikasi dan posologi baru untuk Polivy yaitu sebagai terapi kombinasi dengan bendamustine dan rituximab untuk pengobatan *diffuse large B-cell lymphoma* (DLBCL) yang relaps atau refrakter dan tidak dapat menerima transplantasi *haematopoietic stem cell*.

Polatuzumab vedotin yang terkandung di dalam Polivy bekerja dengan cara berikatan dengan antigen CD79b pada permukaan sel B kanker, kemudian antibodi akan melepaskan senyawa vedotin yang merupakan konjugat dari antibodi yang berfungsi sebagai agen kemoterapi untuk memicu kematian sel kanker.

Berdasarkan data khasiat dan keamanan yang diperoleh dari hasil studi nonklinik dan klinik, Polivy sebagai terapi kombinasi dengan bendamustine dan rituximab untuk pengobatan *diffuse large B-cell lymphoma* (DLBCL) yang relaps atau refrakter dan tidak dapat menerima transplantasi *haematopoietic stem cell* memiliki efek yang menguntungkan, efek yang tidak menguntungkan, ketidakpastian dan keterbatasan sebagai berikut.

a. Efek yang menguntungkan:
   1) Efikasi kombinasi polatuzumab liquid + Bendamustine-Rituximab (Pola + BR, Arm C) menunjukkan hasil yang lebih baik dibanding BR berdasarkan parameter:
      - *Complete response rate* (CR) 42,5% vs 17,5%; p=0,0128.
      - *Objective Response Rate* (OR) 42,5% vs 17,5%
      - *Best Objective Response* (BOR) 62,5% vs 25,0%
      - *Progression Free Survival* (PFS) 9,2 bulan vs 3,7 bulan
      - *Duration of Response* (DOR) 10,9 bulan vs 10,6 bulan
   2) Parameter efikasi lainnya juga terlihat lebih baik pada kelompok Pola+BR, yaitu
      - *Event-free Survival/EFS (INV-assessed)* 6,2 bulan vs 2 bulan
      - *Overall survival* (OS) 12,4 bulan vs 4,5 bulan
   3) Efikasi Pola+BR lyophilized cohort (Arm G dan H) menunjukkan hasil yang konsisten dengan Arm C, yaitu CR 39,6%, OR 43,4%, BOR 57,5%, DOR 13,4 bulan, PFS 7 bulan, EFS 5,1 bulan, dan OS 12,3 bulan.
   4) Polivy dapat digunakan sebagai alternatif untuk pengobatan *diffuse large B-cell lymphoma* (DLBCL) yang relaps atau refrakter dan tidak dapat menerima transplantasi *haematopoietic stem cell,* mengingat di Indonesia pilihan terapi yang tersedia untuk kasus R/R DLBCL, khususnya yang tidak dapat menerima transplantasi *haematopoietic stem cell* masih terbatas, sementara di Indonesia terdapat 16.125 kasus baru limfoma non-Hodgkin berdasarkan data GLOBOCAN 2020.

b. Efek yang tidak menguntungkan:
   1) Pemberian Polivy dapat menyebabkan munculnya anti-polatuzumab vedotin ADA terkait pengobatan yaitu sebesar 5,2% (12 dari 233 pasien). Dari 12 pasien yang memiliki ADA, 8 pasien menunjukkan ADA bersifat sementara, sedangkan 4 pasien menunjukkan ADA bersifat persisten.
   2) AE yang sering dilaporkan berupa neutropenia, trombositopenia, anemia, dan neuropati perifer (PN)

pada formula liquid dan pyrexia, diare, mual, neutropenia, anemia, penurunan nafsu makan, dan kelelahan pada formula lyophilized.

3) AE grade 3-4 lebih tinggi di kelompok pola + BR dibandingkan BR saja (87,2% vs 71,8%). Selain itu, insiden AE serius (SAEs) lebih tinggi di kelompok pola + BR dibandingkan BR (69,2% vs 61,5%). Namun demikian, kematian akibat perkembangan penyakit lebih sedikit di kelompok pola + BR dibandingkan dengan BR (15 vs 20 pasien), sedangkan sebanyak 65 pasien meninggal pada arm G dan H (58 karena perkembangan penyakit, 1 sepsis neutropenik, 2 sepsis, 1 hidrosefalus, 1 syok septik, 1 pneumonia, dan 1 efek samping Grade 5 yang tidak terdefinisi setelah perkembangan penyakit).

c. Ketidakpastian dan keterbatasan:
   1) Belum ada data keamanan jangka panjang.
   2) Belum ada data khasiat dan keamanan pada wanita hamil dan menyusui.
   3) Belum ada data khasiat dan keamanan pada orang dengan gangguan hati dan ginjal yang berat

Kesimpulan manfaat-risiko

Data khasiat dan keamanan menunjukkan adanya efek yang menguntungkan dan efek yang tidak menguntungkan, dimana Polivy sebagai terapi kombinasi dengan bendamustine dan rituximab untuk pengobatan *diffuse large B-cell lymphoma* (DLBCL) yang relaps atau refrakter dan tidak dapat menerima transplantasi *haematopoietic stem cell* memberikan efek menguntungkan yang lebih signifikan dibandingkan efek tidak menguntungkan. Data uji klinik menunjukan efikasi Polivy sebagai terapi kombinasi dengan bendamustine dan rituximab untuk pengobatan *diffuse large B-cell lymphoma* (DLBCL) yang relaps atau refrakter dan tidak dapat menerima transplantasi *haematopoietic stem cell,* dan dari data keamanan diketahui Polivy dapat menyebabkan *Adverse Event* (AE) *grade* 3-4 yang perlu diperhatikan dalam manajemen klinis dan dapat dimitigasi dengan modifikasi dosis sesuai dengan posologi serta tindakan kehati-hatian terkait AE *grade* 3-4 tersebut telah diinformasikan pada Informasi Produk bagian *special warnings and precautions for use*. Secara keseluruhan kajian risiko-manfaat menunjukkan hasil positif dan Polivy dapat diterima sesuai indikasi dan posologi yang diajukan.

KEPUTUSAN
Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi penambahan indikasi dan posologi Polivy serbuk untuk larutan infus dapat **diterima sesuai indikasi dan posologi yang diajukan.**

Indikasi yang disetujui:
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 adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

Posologi yang disetujui:
Polivy must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.
Posology
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 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for 6 cycles. 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.
Refer to the summary of product characteristics (SmPC) of chemotherapy agents given in combination with Polivy for patients with previously untreated DLBCL.

Relapsed or refractory 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. When administered with Polivy, the recommended dose of bendamustine is 90 mg/m2/day on Day 1 and Day 2 of each cycle and the recommended dose of rituximab is 375 mg/m2 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.

Previously untreated and relapsed or refractory patients
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.
There are different potential dose modifications for Polivy in patients with previously untreated DLBCL. For dose modifications to manage peripheral neuropathy (section 4.4) see Table 1 below.

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 ≤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 ≤ 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 ≤ 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 ≤ 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 ≤ 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.
R/R 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 (section 4.4) 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%.
R/R 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 (section 4.4) 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 DLBCL and R/R DLBCL	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 x 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 x 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 x ULN or total bilirubin > 1.0 to 1.5 x ULN), there was a not more than 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 handling 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).