Polatuzumab vedotin (Polivy®) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of previously untreated diffuse large B-cell lymphoma (DLBCL)

General information

Drug description [1]	Indication [2]
Polatuzumab vedotin (Polivy®) is an antibody–drug conjugate targeting CD79b, which is ubiquitously expressed on the surface of malignant B cells.	Polatuzumab vedotin (Polivy®) in combination with R-CHP is indicated for the treatment of adult patients with previously untreated DLBCL.

Current treatment [3]

- In the UK, the most widely used treatment for front-line DLBCL presently is the combination known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).
- The R-CHOP regimen is usually given in 21-day cycles (once every 21 days) for an average of 6 cycles.
- However, the length and number of cycles given can vary based on the patient's individual disease and health status.
- In certain cases, 14-day cycles may be used, and for limited stage disease (Stage 2 or 3) 3-4 cycles may be used followed by radiation therapy.
- Steroids can also be given to enhance the effect of the chemotherapy.

Regulatory status

EMA [2]

Approval status for this indication: On 24 March 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Polivy®.

The CHMP adopted a new indication:

- Polivy® in combination with R-CHP is indicated for the treatment of adult patients with previously untreated DLBCL.

Other indications:

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

✓ **Orphan status**
✓ **Medicine under additional monitoring**
✓ **Medicine received a conditional marketing authorisation**[1]

FDA [4]

Approval status for this indication: not approved

Other indications:

- Polivy® is indicated in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, after at least two prior therapies (accelerated approval was granted for this indication based on complete response rate).

Costs [5]

Polivy® powder for solution for infusion 30 mg = **€ 2,100.00** (ex-factory price)
Polivy® powder for solution for infusion 140 mg = **€ 9,800.00** (ex-factory price)

Premedication [6]

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

Special warnings and precautions for use [6]

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

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- **Myelosuppression**
  - Serious and severe neutropenia and febrile neutropenia have been reported in patients treated with Polivy® as early as the first cycle of treatment.
  - Prophylactic granulocyte colony stimulating factor administration was required in the clinical development and should be considered. Grade 3 or 4 thrombocytopenia or anaemia can also occur with Polivy®. Complete blood counts should be monitored prior to each dose of Polivy®. More frequent lab monitoring and/or Polivy® delays or discontinuation should be considered for patients with Grade 3 or Grade 4 neutropenia and/or thrombocytopenia.
- **Peripheral neuropathy (PN)**
  - PN has been reported in patients treated with Polivy® as early as the first cycle of treatment, and the risk increases with sequential doses. Patients with pre-existing PN may experience worsening of this condition.
  - PN reported with treatment with Polivy® is predominantly sensory PN. However, motor and sensorimotor PN have also been reported. Patients should be monitored for symptoms of PN such as hypoesthesia, hyperesthesia, paraesthesia, dysesthesia, neuropathic pain, burning sensation, muscle weakness, or gait disturbance. Patients experiencing new or worsening PN may require a delay, dose reduction, or discontinuation of Polivy®.
- **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®.
  - Reactivation of latent infections has been reported. Patients should be closely monitored during treatment for signs of bacterial, fungal, or viral infections and seek medical advice if signs and symptoms appear. Anti-infective prophylaxis should be considered throughout treatment with Polivy®.
  - Polivy® should not be administered in the presence of an active severe infection. Polivy® and any concomitant chemotherapy should be discontinued in patients who develop serious infections.
- **Human Immunodeficiency Virus (HIV)**
  - Polivy® has not been evaluated in patients with HIV. With regard to co-administration of CYP3A-inhibitors.
- **Immunization**
  - Live or live-attenuated vaccines should not be given concurrently with the treatment. Studies have not been conducted in patients who recently received live vaccines.
- **Progressive multifocal leukoencephalopathy (PML)**
  - PML has been reported with Polivy® treatment. Patients should be monitored closely for new or worsening neurological, cognitive, or behavioural changes suggestive of PML. Polivy® and any concomitant chemotherapy should be withheld if PML is suspected and permanently discontinued if the diagnosis is confirmed.
- **Tumour lysis syndrome (TLS)**
  - Patients with high tumour burden and rapidly proliferative tumour may be at increased risk of TLS. Appropriate measures/prophylaxis in accordance with local guidelines should be taken prior to treatment with Polivy®. Patients should be monitored closely for TLS during treatment with Polivy®.
- **Infusion-related reactions**
  - Polivy® can cause IRRs, including severe cases. Delayed IRRs as late as 24 hours after receiving Polivy® have occurred. An antihistamine and antipyretic should be administered prior to the administration of Polivy®, and patients should be monitored closely throughout the infusion.
  - If an IRR occurs, the infusion should be interrupted and appropriate medical management should be instituted.
- **Embryo-foetal toxicity**
  - Based on the mechanism of action and nonclinical studies, Polivy® can be harmful to the foetus when administered to a pregnant woman. Pregnant women should be advised regarding risk to the foetus.
  - Women of childbearing potential should be advised to use effective contraception during treatment with Polivy® and for at least 9 months after the last dose. Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with Polivy® and for at least 6 months after the last dose.
- **Fertility**
  - In non-clinical studies, polatuzumab vedotin has resulted in testicular toxicity, and may impair male reproductive function and fertility. Therefore, men being treated with Polivy® are advised to have sperm samples preserved and stored before treatment.
- **Elderly**
  - Among 435 previously untreated DLBCL patients treated with Polivy® in combination with R-CHP in Study GO39942, 227 (52.2%) were ≥ 65 years of age. Patients aged ≥ 65 had an incidence of serious adverse reactions of 39.2% and 28.4% in patients aged < 65. A similar incidence of serious adverse reactions was seen in elderly patients in the R-CHOP treatment arm. Among 151 previously treated DLBCL patients treated with Polivy® in combination with bendamustine and rituximab (BR) in Study GO29365, 103 (68%) were ≥ 65 years of age. Patients aged ≥ 65 had a

similar incidence of serious adverse reactions (55%) to patients aged < 65 (56%). Clinical studies of Polivy® did not include sufficient numbers of patients aged ≥ 65 to determine whether they respond differently from younger patients.

- **Hepatic toxicity**
  - Serious cases of hepatic toxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with Polivy®.
  - Pre-existing liver disease, elevated baseline liver enzymes, and concomitant medicinal products may increase the risk. Liver enzymes and bilirubin level should be monitored.
- **Excipients**
  - This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Study characteristics [1, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
POLARIX, GO39942 NCT03274492	879 (440 vs. 439)	pola-R-CHP[2]	R-CHOP	PFS (investigator-assessed)	**ongoing**[3], randomised, double-blind, placebo-controlled, international phase 3 trial	-	F. Hoffmann–La Roche/ Genentech	[1]

Efficacy (I vs. C)[4], n=440 vs. n=439

PFS

Patients who died or had progression or relapse: 24.3% vs. 30.5; HR 0.73 (0.57–0.95), p=0.02

Death: n=19 vs. n=20

Progression or relapse: n=88 vs. n=114

Estimate at 1 year: 83.9% (95% CI, 80.4–87.4) vs. 79.8% (95% CI, 75.9–83.6)

Estimate at 2 years: 76.7% (95% CI, 72.7–80.8) vs. 70.2% (95% CI, 65.8–74.6)

Event-free survival

Patients who died, had progression or relapse, or had other events: 25.5% vs. 31.4%; HR 0.75 (95%CI, 0.58–0.96), p=0.02

Death: n=18 vs. n=20

Progression or relapse: n=86 vs. n=106

Other: n=8 vs. n=12

Estimate at 2 years: 75.6% (95%CI, 71.5–79.7) vs. 69.4% (95% CI, 65.0–73.8)

Response status at treatment completion (assessed by an independent central review committee)

Overall response: 85.5% vs. 83.8%

Complete response: 78.0% vs. 74.0%, p=0.16

Partial response: 7.5% vs. 9.8%

Stable disease: 1.8% vs. 1.4%

Progressive disease: 5.0% vs. 6.4%

Not evaluated or data missing: 7.7% vs. 8.4%

Overall survival

Safety (I vs. C)

SAEs: 34.0% vs. 30.6%

AEs of grade 5: n=13/435 (3.0%) vs. n=10/438 (2.3%)

AEs leading to discontinuation of at least one of the drugs in the trial regimen[5]**:** 6.2% vs. 6.6%

[2] Eight 21-day cycles of treatment were planned. During the first 6 cycles, patients received either pola-R-CHP or R-CHOP. On day 1 of each cycle, patients received either IV Polatuzumab vedotin at a dose of 1.8 mg per kg of body weight and a placebo matching IV vincristine (pola-R-CHP group) or a placebo matching polatuzumab vedotin and IV vincristine at a dose of 1.4 mg per m^2 of BSA (maximum of 2 mg) (R-CHOP group), plus IV doses of rituximab (375 mg per square meter), cyclophosphamide (750 mg per square meter), and doxorubicin (50 mg per square meter). All the patients also received oral prednisone at a dose of 100 mg once daily on days 1 through 5 of each of the first 6 cycles. During cycles 7 and 8, patients in both groups received rituximab monotherapy at a dose of 375 mg per m^2.

[3] The POLARIX-trial is currently ongoing; the estimated study completion date is 06/2026.

[4] Primary (PFS, event-free survival, and complete response) and interim analysis data (OS).

[5] Among these patients, 19 (4.4%) in I discontinued polatuzumab vedotin because of AEs, and 22 (5.0%) in C discontinued vincristine because of AEs; both drugs were mainly associated with neurologic events.

Patients who died: 12.0% vs. 13.0%, HR 0.94 (95% CI, 0.65–1.37), p=0.75 Estimate at 2 years: 88.7% (95% CI, 85.7–91.6) vs. 88.6% (95%CI, 85.6–91.6) **Disease-free survival** Patients who died or had relapse: 16.3% vs. 21.8%, HR 0.70 (95%CI, 0.50–0.98) **Disease progression or relapse with CNS involvement** 3.0% vs. 2.7% **Subsequent treatment for lymphoma** Patients who had received at least one subsequent course of therapy for lymphoma that was not specified in the protocol: 22.5% vs. 30.3% Patients receiving radiotherapy (preplanned or unplanned): 9.3% vs. 13.0% Patients receiving systemic therapy: 17.0% vs. 23.5%, including stem-cell transplantation (3.9% vs. 7.1%) and chimeric antigen receptor (CAR) T-cell therapy (2.0% vs. 3.6%) 8 patients (all in the R-CHOP group) received polatuzumab vedotin as part of a subsequent therapy (after disease progression, unblinding was permitted for individual patients).	

Risk of bias (RCT) [10]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[6]	yes[7]	unclear
					First published: 04/2022 **Last updated**: 07/2022

Abbreviations: AE=adverse event, AJ=adjustment, BSA= body-surface area, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DLBCL=diffuse large B-cell lymphoma, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HIV=Human Immunodeficiency Virus, HR=hazard ratio, I=intervention, Int.=intention, IRRs=infusion-related reactions, MG=median gain, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PML=progressive multifocal leukoencephalopathy, PN=peripheral neuropathy, QoL=quality of life, R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R-CHP=rituximab, cyclophosphamide, doxorubicin, and prednisone, SAE=serious adverse event, ST=standard treatment, TLS=tumour lysis syndrome

References:

1. Tilly H, Morschhauser F, Sehn LH, Friedberg JW, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med 2022;386:351-63. [Available from: https://www.nejm.org/doi/10.1056/NEJMoa2115304].
2. European Medicines Agency (EMA). Medicines. Polivy. 2022-03-28.
3. National Institute for Health Research (NIHR). Polatuzumab vedotin in addition to R-CHP for diffuse large B-cell lymphoma – first line [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/17287-TSID_10382-Polatuzumab-Vedotin-for-Diffuse-Large-B-Cell-Lymphoma-v1.0-NOV2020-NON-CONF.pdf].
4. U.S. Food and Drug Administration (FDA). Polivy. Label Information [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761121Orig1s003lbl.pdf].
5. Österreichischer Apotheker-Verlag. Warenverzeichnis Online [Available from: https://warenverzeichnis.apoverlag.at/].
6. European Medicines Agency (EMA). Polivy: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/polivy-epar-product-information_en.pdf].
7. Protocol for: Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med 2022;386:351-63.

[6] Currently, only primary and interim analysis data is available; the POLARIX trial is ongoing until 06/2016. Results are currently not available for all prespecified endpoints.

[7] The trial was sponsored by F. Hoffmann–La Roche/Genentech and was designed by the sponsor in collaboration with the Lymphoma Study Association. The first draft of the manuscript was written primarily by one academic author and one author employed by the sponsor; medical writing assistance was funded by the sponsor.

8. Supplement to: Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med 2022;386:351-63.
9. U. S. National Library of Medicine, ClinicalTrials.gov. A Study Comparing the Efficacy and Safety of Polatuzumab Vedotin With Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone (R-CHP) Versus Rituximab-Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Participants With Diffuse Large B-Cell Lymphoma (POLARIX) [Available from: https://clinicaltrials.gov/ct2/show/NCT03274492].
10. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015) [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].