

TRANSPARENCY COMMITTEE SUMMARY 10 JUNE 2020

The legally binding text is the original French opinion version

polatuzumab vedotin
POLIVY 140 mg powder for concentrate for solution for infusion

First assessment

► Key points

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

► Role in the care pathway?

The treatment of patients with diffuse large B-cell lymphoma (DLBCL) involves, as first-line therapy, a combination of chemotherapy with an anti-CD20 monoclonal antibody, i.e., the R-CHOP regimen. In the event of primary resistance or relapse, the treatment of choice is salvage chemotherapy followed by consolidation by autologous transplant in the event of chemotherapy-sensitive disease.

In patients not eligible for transplant due to an inadequate response to salvage chemotherapy or to the patient's condition, treatment is based on immunochemotherapy with platinum and/or gemcitabine (in particular, the R-GemOx or R-DHAP regimens not followed by intensification and autologous transplant).

Relapsed or refractory patients following second-line salvage therapy may be able to have third-line chemotherapy. Treatment with CAR-T cells (axicabtagene ciloleucel or tisagenlecleucel) is recommended in patients whose life expectancy is compatible with the production timeframes. The following other options may be considered depending on the clinical situation:

- for relapsed patients (excluding refractory patients): additional intensive chemotherapy with the objective of performing allogeneic haematopoietic stem cell transplantation if the patient is eligible; where applicable an autologous transplant. An allogeneic transplant is generally considered in patients under the age of 70, in the absence of major comorbidities, in the presence

- of a donor (availability of a graft) and in the event of a complete response (or very good partial response) following the chemotherapy regimen;
- other chemotherapies,
- implementation of palliative care.

Role of the medicinal product in the care pathway

Considering:

- the methodological weakness of the clinical data obtained from a phase I/II multi-cohort trial including an exploratory randomised phase (with no superiority or non-inferiority hypothesis) performed with a liquid formulation of polatuzumab vedotin (without an MA) and in a limited number of patients who were heterogeneous in terms of their previous treatment line (min: 1; max: 7);
- the lack of clinical relevance of the comparator chosen for this randomised phase (rituximab + bendamustine - BR), little used in France, as well as that of the primary endpoint (complete response rate) in this clinical situation in which overall survival and quality of life data would have been more appropriate;
- the uncertainty with respect to this complete response rate, estimated to be 40% in patients treated with polatuzumab vedotin + BR compared to 17.5% in patients treated with BR, given the imbalances observed between these two groups, which may favour the polatuzumab vedotin + BR group (particularly with respect to the reasons for transplant ineligibility and disease prognostic factors);
- the lack of robust demonstration of an increase in overall survival compared to BR;
- the lack of quality of life data collected, which is regrettable since some of the adverse effects of polatuzumab vedotin could have an impact on this (in particular, peripheral neuropathy);
- uncertainties with the lyophilised form with the MA insofar as the data are very limited with this formulation (non-comparative cohort of 42 patients with efficacy results that appear to be inferior to those observed in the randomised phase with the liquid formulation);
- and the indirect comparisons (MAIC) submitted by the pharmaceutical company that do not enable quantification of the contribution of polatuzumab vedotin versus the reference treatments (R- GemOX-type polychemotherapy or CART-cells);

the Committee considers that POLIVY (polatuzumab vedotin) in combination with bendamustine and rituximab has no role in the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant, in view of the alternatives and pending potential data from future clinical development.

Reason for assessment	Inclusion in list
Indication concerned	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.
Clinical Benefit	<u>Insufficient</u> to justify its funding by the French national health insurance system.
Clinical Added Value	Not applicable.
Public health impact	POLIVY (polatuzumab vedotin) is unlikely to have an impact on public health.
Role in the care pathway	Considering: - the methodological weakness of the clinical data obtained from a phase I/II multi-cohort trial including an exploratory randomised phase (with no superiority or non-inferiority hypothesis) performed with a liquid formulation of polatuzumab vedotin (without an MA) and in a limited number of patients who were heterogeneous in terms of their previous treatment line (min: 1; max: 7); - the lack of clinical relevance of the comparator chosen for this randomised phase (rituximab + bendamustine - BR), little used in France; - the low clinical relevance of the primary endpoint chosen (complete response rate assessed by PET-CT, 6 to 8 weeks after D1 of cycle 6 or on administration of the last dose of treatment) in this clinical situation in which overall survival and quality of life data would have been more appropriate; - the uncertainty with respect to this complete response rate, estimated to be 40% in patients treated with polatuzumab vedotin + BR compared to 17.5% in patients treated with BR, given the imbalances observed between these two groups, which may favour the polatuzumab vedotin + BR group (particularly with respect to the reasons for transplant ineligibility and disease prognostic factors); - the lack of robust demonstration of an increase in overall survival compared to BR; - the lack of quality of life data collected, which is regrettable since some of the adverse effects of polatuzumab vedotin could have an impact on this (in particular, peripheral neuropathy); - uncertainties with the lyophilised form with the MA insofar as the data are very limited with this formulation (non-comparative cohort of 42 patients with efficacy results that appear to be inferior to those observed in the randomised phase with the liquid formulation); - and the indirect comparisons (MAIC) submitted by the pharmaceutical company that do not enable quantification of the contribution of polatuzumab vedotin versus the reference treatments (R- GemOX-type polychemotherapy or CART-cells); the Committee considers that POLIVY (polatuzumab vedotin) in combination with bendamustine and rituximab has no role in the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant, in view of the alternatives and pending potential data from future clinical development.
Target population	Not applicable.
Recommendations	The Committee highlights the fact that the results of the ongoing phase III POLARGO study assessing the safety and efficacy of polatuzumab vedotin in combination with rituximab, gemcitabine and oxaliplatin (R-GemOx) versus R-GemOx alone, are likely to answer the questions raised by the Committee with respect to the role of POLIVY (polatuzumab vedotin) in the treatment of patients with relapsed/refractory DLBCL who are not candidates for haematopoietic stem cell transplant.

01 BACKGROUND

This is an application for the inclusion of POLIVY (polatuzumab vedotin) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication “in combination with bendamustine and rituximab for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant”.

POLIVY was granted a conditional marketing authorisation in this indication on 16 January 2020 and has been used in a cohort compassionate use programme (ATU) since 20 January 2020 in the indication “in combination with bendamustine and rituximab for the treatment of adult patients with relapsed/refractory (R/R) DLBCL who are not candidates for haematopoietic stem cell transplant”.

Polatuzumab vedotin is an antibody-drug conjugate composed of the anti-mitotic agent monomethyl auristatin E (MMAE) covalently conjugated to a CD79b-directed monoclonal antibody present on the surface of B lymphocytes.

For information purposes, POLIVY was the subject of a joint assessment in this indication in the context of the European network for HTA agencies (EUnetHTA)¹.

02 THERAPEUTIC INDICATIONS

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

03 DOSAGE

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

Dosage

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.

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

¹ POLIVY. Final assessment report. 2020. Available online: <https://eunetha.eu/wp-content/uploads/2020/02/PTJA06-Final-Assessment-Report-V1.0.pdf>

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of diseases defined by abnormal proliferation of lymphoid cells, usually B lymphocytes (85% of cases²). NHL is differentiated into “aggressive” forms and “indolent” forms, characterised by different clinical behaviours and courses guiding the therapeutic approach. Aggressive lymphomas (with a high grade of malignancy) account for 50 to 60% of NHL cases².

■ **Diffuse large B-cell lymphoma (DLBCL)** is the most common type of aggressive NHL (approximately 60%²) and accounts for around 30-40% of all NHL (all types combined)². It is a heterogeneous entity. It may be primary or secondary to indolent B-cell lymphoma (transformed DLBCL). For example, B-cell follicular lymphoma, which accounts for around 80% of indolent forms of NHL, can be transformed into aggressive diffuse large B-cell lymphoma (DLBCL); this is then known as transformed follicular lymphoma (tFL). The clinical presentation of the latter is similar to that of DLBCL, with which it is therefore grouped together.

There were estimated to be more than 5,000 new cases of DLBCL, 55% of which in men, in France in 2018³. The median age at diagnosis is close to 70 years (69 in men and 74 in women). Two thirds of patients are aged 65 years or over at the time of their diagnosis.

This type of aggressive lymphoma is characterised by its symptomatic presentation and rapid onset (within a few weeks). Patients require immediate therapeutic management following their diagnosis since the prognosis is rapidly unfavourable in the absence of treatment. However, rapid treatment results in a cure in numerous cases.

Diagnosis is based on histological analysis of a biopsy of the site involved. DLBCL is characterised by diffuse proliferation of large cells destroying the normal lymph node architecture and a spontaneously aggressive course. A second reading of the biopsy by a pathologist specialised in lymphoma should be envisaged given the diagnostic problems posed by the diversity of histological subtypes that may have an impact on therapeutic management. A national reference network for the anatomical pathology of lymphomas, LYMPHOPATH, has been created for this purpose.

■ **The choice of treatment** is based on a systematic assessment of the main prognostic criteria for these diseases. The IPI (International Prognostic Index) is used as a prognostic index for aggressive NHL. This takes into account the patient's age, the ECOG performance score, the lactate dehydrogenase (LDH) level, the disease stage and the extent of extranodal involvement.

The therapeutic options^{4,5} proposed for DLBCL are chemotherapy, monoclonal antibody immunotherapy, radiotherapy and haematopoietic stem cell transplant, primarily used at the time of relapse after salvage therapy. The first-line treatment of choice is based on R-CHOP induction immunochemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone). Almost 2/3 of patients achieve remission after this treatment⁴.

In patients not responding to this first-line treatment (primary refractory disease) or who relapse following this treatment, it is necessary to propose “salvage” therapy (second-line chemotherapy) (generally R-DHAP⁶, R-ICE⁷ or R-GDP⁸ for

² ALD 30 guide “Non-Hodgkin Lymphoma in adults”, HAS and INCa, March 2012

³ Sante publique France, National estimation of the incidence of cancers in France between 1990 and 2018, Study based on the Francim network cancer registries, Part 2 – Malignant blood diseases, July 2019

⁴ Tilly, H. et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26: 116-25

⁵ NCCN Guidelines Version 2019 Diffuse Large B-Cell Lymphoma

⁶ R-DHAP (rituximab, cisplatin, cytarabine and dexamethasone) or R-ICE (rituximab, ifosfamide, carboplatin and etoposide)

⁷ R-ICE (rituximab, ifosfamide, carboplatin and etoposide)

⁸ R-GDP (rituximab, gemcitabine, dexamethasone, platinum)

patients in whom high-dose chemotherapy can be envisaged thereafter) or, if applicable, due to age or comorbidities, a chemotherapy regimen adapted to patients who are not candidates for subsequent high-dose chemotherapy. If a response is achieved with the salvage therapy, the patients are considered to be chemosensitive and autologous haematopoietic stem cell transplantation, preceded by induction chemotherapy, may be proposed to eligible patients. The major eligibility criteria for high-dose chemotherapy (intensification) with autologous haematopoietic stem cell transplant are: chemosensitive disease, adequate performance status (no major organ dysfunction) and age < 65 to 70 ans (although there is no consensus concerning this threshold).

Patients who are not eligible for autologous SCT, in particular due to their age or an inadequate response to salvage chemotherapy, may receive platinum and/or gemcitabine-based immunochemotherapy (in particular R-GemOx or R-DHAP regimens) not followed by conditioning for transplant. None of the immunochemotherapies currently recommended have a marketing authorisation.

Relapsed or refractory patients following second-line salvage therapy may be able to have third-line chemotherapy. In patients in whom autologous SCT has failed or having relapsed following two previous treatment lines, treatment with CAR-T cells (axicabtagene ciloleucel or tisagenlecleucel) is recommended in patients whose life expectancy is compatible with the production timeframes. The following other options may be considered depending on the clinical situation:

- for relapsed patients (excluding refractory patients): additional intensive chemotherapy with the objective of performing allogeneic⁹ haematopoietic stem cell transplantation if the patient is eligible; where applicable an autologous transplant. An allogeneic transplant is generally considered in patients under the age of 70, in the absence of major comorbidities, in the presence of a donor (availability of a graft) and in the event of a complete response (or very good partial response) following the chemotherapy regimen;
- other chemotherapies,
- implementation of palliative care.

While rapid treatment leads to a cure in numerous cases, the prognosis is uncertain in the event of multiple relapses and poor in the event of refractory disease and in patients who are ineligible for SCT. **Consequently, the medical need in patients with relapsed or refractory diffuse large B-cell lymphoma ineligible for SCT is considered to be partially met by the available alternatives (platinum and/or gemcitabine-based chemotherapies, CAR-T cells in eligible patients). However, a medical need persists for access to effective, well tolerated alternatives capable of improving the survival and quality of life of patients.**

⁹ Very few patients are currently treated (< 100 allogeneic SCT patients/year in France). The SFGM-TC transplant registry recorded only 24 allogeneic SCTs in the treatment of DLBCL in 2016, predominantly in chemosensitive patients

05 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators (CRCs) for POLIVY (polatuzumab vedotin) are therapies used in the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant:

- Platinum and/or gemcitabine-based chemotherapies (and, in particular, the R-GemOX or R-DAHP regimens not followed by conditioning for transplant), which do not have an MA but are recommended
- CART cells in relapsed or refractory eligible patients, but only after the second line of treatment (and not from the first relapse)
- Pixantrone as monotherapy (however this remains a therapeutic option with a low clinical benefit).

5.1 Medicinal products

NAME (INN) Pharmaceutical company	PTG*	Indication	Date of opinion	Clinical Benefit	Clinical Added Value	Manag ement
PIXUVRI (pixantrone) <i>Servier</i>	No	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.	09/11/2016	Low	Considering that: - no new studies were supplied in the context of this reevaluation, - uncertainties persist with respect to the transposability of the data from the study initially assessed to clinical practice, with a non-optimal level of demonstration of efficacy, the Committee considers that PIXUVRI (pixantrone), as monotherapy, provides no clinical added value (CAV V) in the 3rd or 4th-line treatment of aggressive non-Hodgkin B-cell lymphoma.	Yes
YESCARTA (axicabtagene ciloleucel) <i>Gilead Sciences</i>	No	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) [...] after two or more lines of systemic therapy.	05/12/2018	Substantial	CAV III given: - relevant efficacy data obtained in the short term for the complete response rate (approximately 50% of the ITT population) and for overall survival in life-threatening clinical situations and for which the therapeutic options are limited and do not enable remission to be envisaged, - uncertainties with respect to the effect size in the absence of a direct comparison with the standard of care and the maintenance of clinical efficacy in the longer term,	Yes

					- the significant short-term toxicity and the absence of long-term safety data.	
KYMRIA (tisagenlecleucel) <i>Novartis Pharma</i>		Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	12/12/2018	Substantial	CAV IV given: - efficacy data obtained in the short term for the complete response rate (approximately 24% of the ITT population) and for overall survival with a median follow-up of around 7 months, in life-threatening clinical situations and for which the therapeutic options are limited and do not enable remission to be envisaged, - uncertainties with respect to the effect size in the absence of a direct comparison with the standard of care and the maintenance of clinical efficacy in the longer term, - the significant short-term toxicity and the absence of long-term safety data.	Yes

*pharmacotherapeutic group

5.2 Non-medicinal comparators

At an advanced stage of the disease and, in particular, in elderly patients and/or those with comorbidities, supportive care may be considered to be a clinically relevant comparator for POLIVY.

► Conclusion

On the date of performance of the study, the clinically relevant comparators for POLIVY (polatuzumab vedotin) were immunochemotherapy regimens not followed by conditioning for transplant and pixantrone.

Today, CART cells are also comparators in certain clinical situations covered by the MA for POLIVY (relapsed or refractory patients after 2 lines of treatment). However, given their concomitant development, we do not have comparative data between POLIVY and these medicinal products.

06 INFORMATION ON THE INDICATION ASSESSED INTERNATIONALLY

Country	MA		FUNDING	
	Yes / No / Ongoing If no, why	Indication identical to the one assessed or restricted	Yes / No / Ongoing If no, why	Population(s) MA or restricted
United Kingdom	Yes	Identical to the one	Ongoing	-
Germany			Yes	MA population
Netherlands			Ongoing	-
Belgium			Ongoing	-
Spain			Ongoing	-
Italy			Ongoing	-
USA	Yes	POLIVY (polatuzumab vedotin) in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who have received at least two prior	Yes	MA population

07 ANALYSIS OF AVAILABLE DATA

The application for inclusion of POLIVY (polatuzumab vedotin) in combination with bendamustine and rituximab (BR) is based on a clinical study conducted in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant:

- an open-label phase Ib/II study (study GO29365), including a randomised, controlled part versus the bendamustine plus rituximab combination, conducted in 80 patients (for the randomised phase II part). The polatuzumab vedotin plus BR combination was also assessed in this study in patients with R/R follicular lymphoma (R/R FL) (population not included in the MA, results not presented in this document). Finally, the polatuzumab vedotin plus bendamustine and obinutuzumab combination was also assessed in this study in patients with R/R DLBCL or R/R FL (population not included in the MA, results not presented in this document).
- a MAIC (*Matching Adjusted Indirect Comparison*) having compared polatuzumab vedotin in combination with BR with reference treatments (R- GEmOx, pixantrone, CART cells).

These data are presented in the paragraphs below. In addition, limited data from the compassionate use programme (named-patient and cohort ATU) are available and described in the “use data” section.

7.1 Efficacy

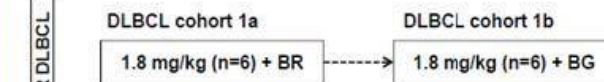
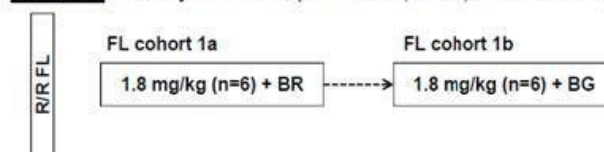
7.1.1 Study GO29365

7.1.1.1 Methods

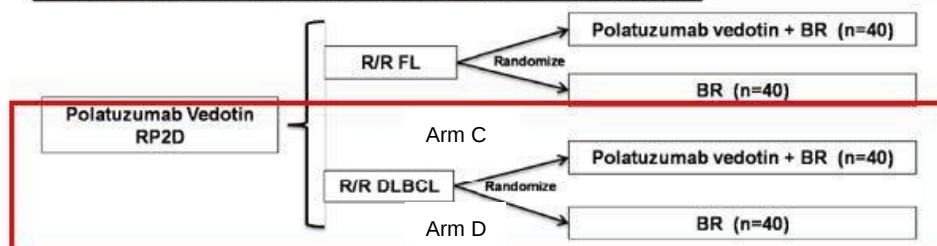
Reference	
Clinicaltrials.gov	Registration number: NCT02257567
Primary objective of the study	To evaluate the efficacy of polatuzumab vedotin in combination with bendamustine plus rituximab (BR) in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)
Type of study	Open-label, multicentre phase Ib/II study, with a randomised, controlled, comparative part, in parallel arms, versus BR alone.
Study date and duration	Start of enrolments (first patient included): 15 October 2014 Date of data extraction for the primary analysis: 30 April 2018 The study is still ongoing and will be complete when all patients enrolled in the study either have had at least two years of follow-up after the last visit or have discontinued the study. Study conducted in 54 centres in 13 countries (including 6 centres in France having
Main inclusion criteria	- Patients aged at least 18 years; - Histologically confirmed DLBCL; - Patients having received at least one prior therapy. Patients had to present DLBCL R/R to prior therapy as defined below: • patients ineligible for SCT in 2nd-line therapy, with progressive disease or no response (stable disease) within 6 months from the start of first-line therapy (primary refractory); • patients ineligible for SCT in 2nd-line therapy, with disease relapse $\geq$ six months from the start of first-line therapy (patients with first relapse); • patients ineligible for SCT in third-line therapy (or beyond), with progressive disease or no response (stable disease) within 6 months from the start of the previous treatment line (2 lines or plus refractory); • patients ineligible for SCT in third-line therapy (or beyond) with disease relapse $\geq$ 6 months from the start of the previous treatment line (patients with 2nd relapse or more); - If patients had received prior bendamustine, the response duration had to have been greater than one year (for patients having presented a relapse after a prior treatment); - Adequate haematological function unless inadequate function is due to bone marrow involvement or secondary hypersplenism due to the lymphoma in the investigator's opinion.
Main exclusion criteria	- History of severe allergic or anaphylactic reactions to humanised or murine monoclonal antibodies (or fusion proteins) or known sensitivity or allergy to murine products; - Contraindication to bendamustine, rituximab or obinutuzumab; - Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate within 5 half-lives or 4 weeks before D1 of cycle 1; - Treatment by radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy or any other investigational treatment in the context of lymphoma management within 2 weeks prior to cycle 1: • Any clinically significant acute toxicity linked to the prior therapy had to be grade $\leq$ 2 before D1 of cycle 1, with the exception of alopecia;

	- Ongoing corticosteroid treatment > 30 mg/day of prednisone or equivalent, for reasons other than to control lymphoma symptoms: • Patients receiving corticosteroid treatment ≤ 30 mg/day of prednisone or equivalent had to receive a stable dose before inclusion in the study and initiation of the study treatment (D1 of cycle 1); - Autologous SCT within 100 days prior to cycle 1; - Prior allogeneic SCT; - Eligibility for autologous SCT; - History of transformation of indolent disease to DLBCL; - Primary or secondary CNS lymphoma; - Grade > 1 peripheral neuropathy at the time of inclusion; - Bacterial, viral, fungal, mycobacterial or parasitic infection at inclusion or history of infection requiring treatment with IV antibiotics or hospitalisation within 4 weeks prior to cycle 1; - Chronic hepatitis B or C, patient with HIV seropositive status or infection with HTLV-1.
Main post-randomisation exclusion criteria.	Not applicable.
Study design	Only the results from patient cohorts with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) are described. The results from phase Ib (non-randomised) and those from arms concerning other combinations are not described in this document.

Phase Ib: Safety Run-in Separate FL (n=12) and DLBCL (n=12) cohorts



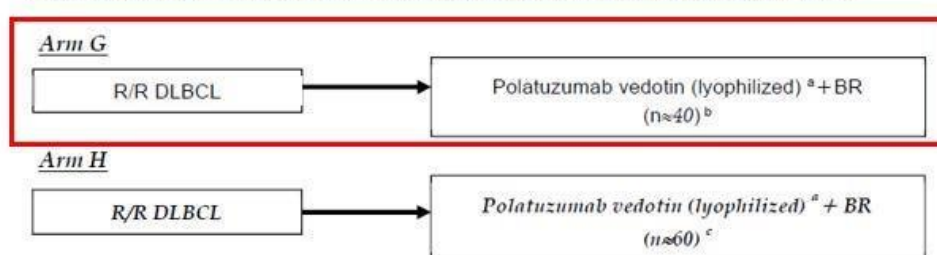
Phase II Randomization: Polatuzumab Vedotin plus BR vs BR



Phase II Expansion: Polatuzumab Vedotin plus BG



Phase II New Formulation Cohorts: Polatuzumab Vedotin (Lyophilized) + BR



Study treatments

In arms C and D, the patients were randomised (allocation ratio 1: 1) to receive:

Arm C:

- 6 cycles of polatuzumab vedotin (liquid formulation – without an MA) at a dose of 1.8 mg/kg IV infusion in combination with bendamustine (90 mg/m² IV infusion) and rituximab (375 mg/m² IV infusion). A cycle lasted 21 days.

Arm D:

- 6 cycles of bendamustine (90 mg/m² IV infusion) in combination with rituximab (375 mg/m² IV infusion). A cycle lasted 21 days.

In arm G (non-comparative cohort) patients received the lyophilised formulation of polatuzumab vedotin (formulation with an MA) in combination with rituximab and bendamustine with the same schedule and dosing requirements as patients in Arm C.

Dosage modifications or treatment interruptions were possible in the event of major toxicity.

Concomitant treatments: G-CSF for the treatment or prophylaxis of neutropenia was possible. In addition, premedication with paracetamol and diphenhydramine before administration of polatuzumab vedotin and rituximab (additional administration of corticosteroids was permitted at the discretion of the investigator). Finally, tumour lysis syndrome prophylaxis (hydration and allopurinol) was recommended in patients with high tumour burden and considered by the investigator to be at high risk.

Primary endpoint	Randomised Phase II stage (arms C and D): Complete response rate (CR) measured by positron emission tomography (PET) as determined by an Independent Review Committee (IRC), according to the modified Lugano response criteria of 2014¹⁰. Assessment of tumour response had to be performed 6 to 8 weeks after D1 of cycle 6 or at administration of the last dose of treatment (primary response assessment). Non-comparative arm (arm G): pharmacokinetic endpoints (not detailed in this opinion) and safety.
Secondary endpoints or exploratory endpoints	In this opinion, the following endpoints will be detailed: - CR rate measured by PET at the primary response assessment as determined by the investigator - Progression-free survival, assessed by PET, as determined by the investigator and the Independent Review Committee (IRC) - Overall survival - Patient-reported outcomes: TINAS (<i>Therapy-Induced Neuropathy Assessment Scale v1.0</i>)¹¹ score The protocol also scheduled analysis of the following efficacy criteria: - Overall response rate (complete + partial responses) at the primary tumour response assessment, measured by PET, as determined by the investigator and the IRC - CR rate assessed by conventional radiography, as determined by the investigator and the IRC - Overall response rate assessed by conventional imaging, as determined by the investigator and the IRC - Best overall response rate assessed by PET or conventional imaging, as determined by the investigator and the IRC - Duration of response assessed by PET, as determined by the IRC - Duration of response assessed by conventional imaging, as determined by the investigator and the IRC - Progression-free survival, assessed by conventional imaging, as determined by the Independent Review Committee (IRC) - Event-free survival, assessed by PET or conventional imaging, as determined by the investigator
Sample size	Randomised phase (arms C and D): No superiority or non-inferiority hypothesis was prespecified for this study. Consequently, calculation of the number of subjects required is not based on statistical hypotheses. The number of patients to be included had to be sufficient to calculate the CR rate in the two arms, as well as the difference in rates between the two arms. Hence the pharmaceutical company estimated that with 40 patients per arm: - the 95% exact Clopper-Pearson CIs for estimation of the CR rate would have a margin of error not exceeding $\pm 17\%$; - a true CR rate below 43% in arm C could be ruled out with 95% confidence if the observed CR rate is at least 60%; - in addition, assuming a 40% CR rate in arm D and a 65% CR rate in arm C, the 95% CI for the difference in CR rates would be 3.8%; 46.2%. Non-comparative cohort (arm G): the sample size was set at 20 patients to demonstrate pharmacokinetic equivalence between the two polatuzumab vedotin formulations.

¹⁰ The PET-CR as defined by conventional Lugano 2014 criteria also requires a negative bone marrow biopsy if the biopsy at inclusion was positive in order to define the PET-CR according to modified Lugano 2014 criteria. Otherwise, it will be considered to be a partial response (PR).

¹¹ The TINAS is a non-validated questionnaire assessing the severity of peripheral neuropathy associated with polatuzumab vedotin. It is composed of 11 items, each scored from 0 to 10 (0: no symptom, 10 worst imaginable manifestation of the symptom, as perceived by the patient).

Results analysis method	<u>Primary endpoint (randomised phase)</u>: the 95% CIs were estimated using the Clopper-Pearson method for each treatment arm. The difference in CR rates between arms C and D was estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution. An <u>exploratory</u> comparison of CR rates between the two arms was conducted using the Cochran Mantel Haenszel Chi² test adjusted for the stratification factors. Patients with no post-inclusion tumour assessments were considered to be non-responders. The primary analysis was performed after all the patients had completed a year of follow-up. Additional follow-up analyses were performed, without statistical adjustment for multiple analyses. <u>Secondary endpoints (PFS/OS)</u>: the distribution of durations for PFS and OS was described using the Kaplan-Meier method and 95% CIs were estimated using Greenwood's formula. <u>Analysis populations</u>: Primary efficacy analyses were based on the ITT population. No subgroup analyses were scheduled in the protocol. <u>Main protocol amendments</u>: - addition of a new non-comparative cohort (arm G) treated with the lyophilised formulation of polatuzumab vedotin (formulation intended for marketing with an MA). - addition of a second non-comparative cohort (arm H) also treated with the lyophilised formulation of polatuzumab vedotin. The results of this cohort are not currently available.
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The results described below correspond to patient data derived from:

- the randomised part: arm C (treated with polatuzumab vedotin liquid formulation – off-label + BR) versus arm D (treated with BR);
- the non-comparative arm G cohort (treated with polatuzumab vedotin lyophilised formulation + BR).

The results of the additional cohort H (also treated with polatuzumab vedotin lyophilised formulation + BR) are not yet available. The efficacy results from the randomised phase described in this opinion correspond to the analysis performed following extraction of the database on 30/04/2018. The pharmaceutical company submitted a follow-up analysis not described in this opinion since it was submitted in poster form only.

Insofar as no superiority or non-inferiority hypotheses were formulated in the protocol for this study, all the statistical analyses are considered to be exploratory.

7.1.1.2 Randomised Phase II (arms C and D) results

► Populations and analyses available

In total, 80 patients were randomised in phase II (40 patients in each arm). Among the patients treated with BR, a higher proportion (36/40 – 90% versus 29/40 – 72.5%) discontinued the study early, mainly due to death of the patient (see table 1).

Table 1: populations and early study discontinuations

	Randomised phase II	
	polatuzumab vedotin + BR (arm C) N=40	BR (arm D) N=40
Number of randomised patients (ITT population)	40	40
Patients having received the treatment (safety)	39 (97.5%)	39 (97.5%)
Patients having completed all treatments	18 (45.0%)	9 (22.5%)
Patients alive in follow-up	11 (27.5%)	4 (10.0%)
Study discontinuation:	29 (72.5%)	36 (90.0%)
• Death	23 (57.5%)	28 (70.0%)
• Adverse event	0	0
• Other*	6 (15.0%)	8 (20.0%)

* Includes withdrawal of consent, progressive disease, physician decision, loss of clinical benefit, lost-to-follow-up, and other

■ Main baseline characteristics of patients

The patients' characteristics are summarised in table 2 below.

Patients were mostly male (70% in the polatuzumab vedotin + BR group and 62.5% in the BR group), with a median age slightly higher in patients treated with BR (71 years vs. 67 years). Patients in each treatment arm had received a median of two prior lines of treatment (min: 1; max: 7). All the patients were ineligible for SCT. However the reasons for ineligibility varied between the two groups: age (47.5% in the BR arm vs. 32.5% in the polatuzumab vedotin + BR arm), relapse after prior SCT (15.0% vs. 25.0%) or insufficient response to salvage therapy (22.5% vs. 30.0%).

Patients in the BR group seemed to have more severe disease at baseline, with, in particular, a higher proportion of patients with bulky disease (37.5% vs. 25.0%), a higher IPI score (42.5% vs. 22.5%) as well as a higher number of patients with disease refractory to the last treatment line (85.0% vs. 75%). The median time between the last line of prior treatment was 131 days in the polatuzumab vedotin + BR group versus 82 days in the BR group.

Table 2: patient characteristics (study GO29365 - arms C and D)

Characteristics	Randomised phase II	
	polatuzumab vedotin + BR (arm C) N=40	BR (arm D) N=40
Age, years		
Median (Range)	67.0 (33-86)	71.0 (30-84)
≥ 65 years	23 (57.5%)	26 (65.0%)
Gender, n (%)		
Male	28 (70.0%)	25 (62.5%)
Race		
White	26 (65.0%)	31 (77.5%)
Asian	6 (15.0%)	4 (10.0%)
American Indian or Alaskan Native	0	1 (2.5%)
Black or African American	3 (7.5%)	0
Unknown	5 (12.5%)	4 (10.0%)
ECOG PS at baseline, n (%)		
0 or 1	33 (82.5%)	31 (77.5%)
2	6 (15.0%)	8 (20.0%)
Unknown	1 (2.5%)	1 (2.5%)
Primary reason for stem cell transplant ineligibility, n (%)		
Age	13 (32.5%)	19 (47.5%)
Comorbidities	1 (2.5%)	1 (2.5%)
Relapse following previous transplant	10 (25.0%)	6 (15.0%)
Insufficient response to salvage therapy	12 (30.0%)	9 (22.5%)

Other	2 (5.0%)	1 (2.5%)
Patient refused transplant	2 (5.0%)	2 (5.0%)
Performance status	0	2 (5.0%)
Baseline disease characteristics, n (%)		
Time in months since initial diagnosis and study entry: median (range)	20.4 (4 - 392)	14.0 (6 - 207)
DLBCL subtype – WHO 2016		
DLBCL, NOS: ABC	19 (47.5%)	19 (47.5%)
DLBCL, NOS: GCB	15 (37.5%)	17 (42.5%)
DLBCL, NOS	4 (10.0%)	4 (10.0%)
Follicular lymphoma	1 (2.5%)	0
Burkitt lymphoma	1 (2.5%)	0
Ann Arbor stage III or IV at study entry	34 (85.0%)	36 (90.0%)
Size of biggest mass ≥ 7.5 cm (<i>bulky disease</i>)	10 (25.0%)	15 (37.5%)
Extranodal involvement	27 (67.5%)	29 (72.5%)
Prognostic factors		
IPI score at enrolment		
0 -1 (Low)	9 (22.5%)	3 (7.5%)
2 (Low-Intermediate)	9 (22.5%)	8 (20.0%)
3 (High-Intermediate)	13 (32.5%)	12 (30.0%)
4-5 (High)	9 (22.5%)	17 (42.5%)
Number of prior chemotherapy lines received		
Median (range) 1 line	2.0 (1-7)	2.0 (1-5)
2 lines	11 (27.5%)	12 (30.0%)
≥ 3 lines	11 (27.5%)	9 (22.5%)
	18 (45.0%)	19 (47.5%)
Prior treatments		
Anti-CD20	39 (97.5%)	40 (100.0%)
Bendamustine	1 (2.5%)	0
High-dose chemotherapy with autologous stem cell transplant	10 (25.0%)	6 (15.0%)
Haematopoietic stem cell transplant	11 (27.5%)	10 (25.0%)
Refractory to anti-CD20		
Yes No	18 (45.0%)	18 (45.0%)
Unknown	10 (25.0%)	6 (15.0%)
	12 (30.0%)	16 (40.0%)
Refractory to last prior anti-lymphoma therapy^b		
n (%)	30 (75.0%)	34 (85.0%)
Time in days from last anti-lymphoma therapy^c:		
Median (min - max)	131.0 (17-11744)	82.0 (21-2948)
Duration of response to prior therapy^d		
≤ 12 months	32 (80.0%)	33 (82.5%)

^a Defined as no response or progression or relapse within six months of last anti-lymphoma therapy end date in patients whose last prior regimen contained an anti-CD20

^b Defined as no response or progression or relapse within six months of last anti-lymphoma therapy end date

^c Defined as time from end date of last anti-lymphoma therapy to first study treatment dose date

^d Duration of response to prior therapy based on IxRS (interactive voice or Web-based response system)

► **Primary endpoint: complete response rate assessed by an IRC** Analysis of the primary endpoint was performed at the primary tumour response assessment, 6 to 8 weeks after D1 of cycle 6, or at the last dose of study drug. In total, a complete response measured by PET was observed in 40% (n=16/40) of patients treated with polatuzumab vedotin + BR and in 17.5% (n=7/40) of patients treated with BR. Only one exploratory analysis was scheduled in the protocol to compare the two groups; this was in favour of the group treated with polatuzumab vedotin + BR.

The complete response rates were also analysed by the investigator; these results are consistent with those of the IRC (42.5% vs. 15%).

Table 3: CR characteristics (study GO29365 - arms C and D)

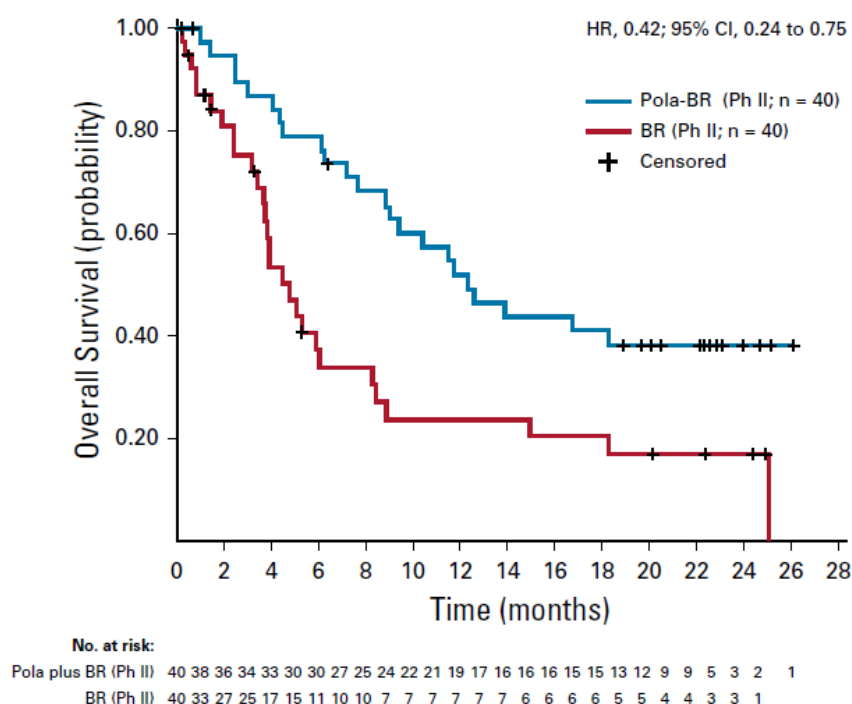
	<i>Randomised phase II</i>	
	polatuzumab vedotin + BR (arm C) N=40	BR (arm D) N=40
Patients with CR, n (%)	16 (40.0)	7 (17.5)
[95% CI] (Clopper-Pearson)	[24.86; 56.76]	[7.34; 32.78]
Difference [95% CI] (Wilson)	22.50 [2.62; 40.22]	

► **Secondary endpoints or exploratory endpoints**

- **Overall survival**

At the time of data analysis, a total of 51 patients had died: 28 (70%) in the group treated with BR and 23 (57.5%) in the group treated with polatuzumab vedotin + BR. The median overall survival was 12.4 months (95% CI = [9.0; NE]) in arm C and 4.7 months (95% CI = [3.7; 8.3]) in arm D, with a stratified HR = 0.42 (95% CI = [0.24; 0.75]).

Figure 1: Overall survival (study GO29365 - arms C and D)



- **Progression-free survival assessed by the IRC**

The majority of patients in both arms had a progression event during the study: 62.5% (n= 25/40) in the group treated with polatuzumab vedotin + BR and 80.0% (n= 32/ 40) in the group treated with BR. The median progression-free survival assessed by the IRC was 9.5 months in the polatuzumab vedotin + BR group (95% CI = [6.2; 13.9]) and 3.7 months (95% CI = [2.1; 4.5]) in the BR group, with a stratified HR = 0.36 (95% CI = [0.21; 0.63]). Progression-free survival was also analysed by the investigator; these results are consistent with those of the IRC.

- **TINAS score**

This was an exploratory endpoint aimed at analysing the severity of peripheral neuropathy (known adverse event with monoclonal antibodies conjugated with chemotherapy) assessed by patients using the TINAS questionnaire. These results will not be detailed insofar as:

- version V1.0 of the questionnaire was used and its assessment is based solely on an abstract that is not adequately detailed to demonstrate the validation and reproducibility of this scale¹²;
- patients were not included in the development of this scale, described as “provisional” by the authors¹³;
- the development of V3 highlighted the fact that the “pain” item was missing in previous versions¹⁴;
- following an amendment to the protocol during the study, data collection was changed from daily to weekly. Subsequent to this change, the programme for collection of baseline data by patients was inaccessible for several months, leading to a high number of missing data (approximately 30% of data at inclusion are missing);
- the questionnaire completion rate was low throughout the study (less than 25% of patients in the BR group could be assessed after 11 weeks);
- finally, the open-label nature of this study is liable to result in bias in the interpretation of this subjective endpoint.

7.1.1.3 Results from the additional non-randomised cohort (arm G)

► Populations and analyses available

The results for this cohort treated by polatuzumab vedotin (lyophilised formulation) in combination with BR are derived from an analysis performed following extraction of the database on 15/03/2019. At this date, the median patient follow-up was 8.4 months.

In total, 42 patients were included in this cohort. Half (21/42) of the patients discontinued the study early, mainly due to death of the patient (n=20/42).

► Patient characteristics

The patients were mostly men (59.5%), with a median age of 68 years. The percentage of patients aged 65 years or over was higher than in arm C (64.3% versus 57.3%). The main reasons for SCT ineligibility were as follows: age (40.5% versus 32.5% in arm C) and insufficient response to salvage therapy (35.7% versus 30.0%).

In comparison with the patients included in arm C, the patients in this cohort seemed to have less severe disease with an ECOG score equal to 2 in 7.1% (versus 15% in arm C), an Ann Arbor stage of III or IV in 73.8% (versus 85%), bulky disease in 26.2% (versus 25%) and extranodal disease in 57.1% (versus 67.5%).

The duration of response to the prior treatment line was less than or equal to 12 months in 92.9% of patients in arm G versus 80% in arm C.

Like the patients in arm C, the patients in arm G had received a median of 2 previous treatment lines (maximum: 7). However, the percentage of patients having received a single previous treatment line was higher in arm G (35.7%) than in arm C (27.5%).

► Efficacy results (exploratory endpoints)

The efficacy results are summarised in table 4 below. It should be highlighted that the median overall survival observed in this cohort (9.1 months) appears to be lower than that observed in arm C (12.4 months).

¹² Thomas SK et al. Validation of the chemotherapy-induced neuropathy assessment scale. J Clin Oncol 2012; 30: 15_suppl, 9140

¹³ Mendoza TR et al. Measuring Therapy-Induced Peripheral Neuropathy: Preliminary Development and Validation of the Treatment-Induced Neuropathy Assessment Scale. J Pain 2015; 16: 1032-43.

¹⁴ Williams LA et al. Concept domain validation and item generation for the Treatment-Induced Neuropathy Assessment Scale (TNAS). Support Care Cancer. 2019; 27: 1021-28

Table 4: CR rate, progression-free survival and overall survival (study GO29365 - arm G)

	Arm G
	Polatuzumab vedotin (lyophilised) + BR (N=42)
CR assessed by PET-CT (assessment by IRC)	
n (%)	14 (33.3)
[95% CI]	[19.6; 49.6]
PFS (assessment by IRC)	
Number of patients, n (%)	28 (66.7)
Median PFS, months, [95% CI]	5.5 [3.5; 7.0]
OS	
Number of patients, n (%)	20 (47.6)
Median OS, months, [95% CI]	9.1 [6.0; NE]

7.1.2 Indirect comparison

In addition to the phase I/II study including a randomised, comparative part versus BR, the pharmaceutical company submitted the results of an indirect comparison versus reference treatments at this stage of the disease.

The pharmaceutical company conducted a systematic literature review in order to identify pertinent publications for this indirect comparison. The comparators of interest selected for the literature review were: the BR combination, the R-GemOx combination, the gemcitabine, cisplatin and dexamethasone (GDP) combination, pixantrone and CAR-T cells (axicabtagene ciloleucel – axi-cel, tisagenlecleucel). The endpoint of interest selected for this MAIC was the complete response rate. Overall survival was considered where possible.

Since no other randomised clinical trials having used BR treatment were identified in the literature, the performance of an indirect comparison network meta-analysis was not possible.

The data relative to polatuzumab vedotin + BR treatment are from study GO29315. Data from the two phases (I and II) as well as from additional cohort G were grouped together (n=88); consequently, this indirect comparison includes data for patients not treated at the dosage validated by the marketing authorisation for POLIVY.

The characteristics selected to adjust the MAIC were as follows (in order of importance):

- age at enrolment;
- ECOG score at enrolment;
- the percentage of refractory patients;
- the number of prior treatment lines received;
- and the SCT history.

The (aggregated) data relative to the reference treatments were extracted from the following studies:

- for axicabtagene ciloleucel (axi-cel), from the non-comparative ZUMA-1 clinical study (n=81) conducted in relapsed or refractory patients after at least two prior treatment lines or after transplant. The data were extracted from the report produced by the G-BA in 2018 after a median follow-up of approximately 20 months;
- for tisagenlecleucel, from the non-comparative JULIET clinical study (n=165) conducted in relapsed or refractory patients after at least two prior treatment lines or after transplant. The data were extracted from the EPAR and the report produced by the G-BA in 2018 after a median follow-up of 19 months;

- for pixantrone, from a randomised phase III comparative study versus salvage therapy (study PIX301, n=70)¹⁵ conducted in relapsed or refractory patients after at least two prior treatment lines;
- for R-GemOX, from a non comparative clinical study (study by Mounier et al¹⁶, n=49) conducted in patients presenting a first or second relapse having received prior treatment with anthracycline with or without rituximab.

► Results vs. R-GemOx

Only 65 patients in study GO29315 had characteristics comparable to the patients in the study by Mounier et al and were used for this MAIC. In total, the results suggest an overall response rate of 80.1% (95% CI = [63.9; 100]) in patients treated with polatuzumab vedotin + BR vs. 42.9% (95% CI = [28.8; 57.8]) in patients treated with R-GemOx, i.e., an adjusted difference of 37.2% (95% CI = [15.9; 76.1]) in favour of polatuzumab vedotin + BR.

Comparison of the overall survival or progression-free survival was not possible in the absence of a Kaplan Meier curve for the comparable subpopulation of patients in the publication by Mounier et al.

► Results vs. Pixantrone

Only 20 patients in study GO29315 had characteristics comparable to the patients in study PIX301. Due to this low population, the MAIC versus pixantrone could not be performed; only non-adjusted comparisons were submitted (not described in this report).

► Results vs. Tisagenlecleucel

Only 78 patients in study GO29315 had characteristics comparable to the patients in the JULIET study and were used for this MAIC. In total, the results suggest:

- a complete response rate of 54.7% (95% CI = [35.4; 67.0]) in patients treated with polatuzumab vedotin vs 24.2% (95% CI = [17.9; 31.5]) in patients included in the JULIET study (ITT population, including a high proportion of untreated patients), i.e., an adjusted difference of 30.0% (95% CI = [10.3; 45.2]) in favour of polatuzumab vedotin + BR.
- an overall survival median not reached (95% CI = [5.3; NE]) in patients treated with polatuzumab vedotin vs. 8.2 months (95% CI = [5.8; 11.7]) in patients treated with tisagenlecleucel (ITTm population), i.e., a non-significant HR of 0.54 (95% CI = [0.24; 1.18]).

► Results vs. Axi-cel

Only 66 patients in study GO29315 had characteristics comparable to the patients in the ZUMA-1 study and were used for this MAIC. In total the results suggest:

- a complete response rate of 39.3% (95% CI = [24.6; 56.1]) in patients treated with polatuzumab vedotin vs 45.7% (95% CI = [34.6; 57.1]) in patients included in the ZUMA-1 study (ITT population, including a high proportion of untreated patients), i.e., a non-significant adjusted difference of 6.5% (95% CI = [-25.5; 13.5]).
- an overall survival median of 9 months (95% CI = [4.4; NE]) in patients treated with polatuzumab vedotin + BR vs. 15.4 months (95% CI = [11.1; NE]) in patients treated with Axi-cel (ITTm population), i.e., a non-significant HR of 1.38 (95% CI = [0.57; 3.31]).

7.2 Quality of life

No quality of life assessment was scheduled in study GO29365, for which the efficacy and safety data are described in the present opinion.

¹⁵ Pettengel R et al. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. *Lancet Oncol.* 2012; 13: 696-706.

¹⁶ Mounier et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica.* 2013; 98: 1726-31

7.3 Safety

7.3.1 Data from clinical study GO29365

7.2.1.1 Randomised phase

In total, 100% of the patients treated with polatuzumab vedotin + BR and 97.4% of patients treated with BR had at least one adverse event (AE). However, the number of grade 3 and 4 AEs was higher among the patients treated with polatuzumab vedotin + BR (84.6%) than among the patients treated with BR (71.8%). AEs leading to treatment discontinuation were more common in patients treated with polatuzumab vedotin + BR (33.3% vs. 15.4%).

Of the 51 deaths occurring during the study, 20 were related to AEs (9 in patients treated with polatuzumab vedotin + BR and 11 in patients treated with BR).

The safety data from the randomised phase of study GO29315 are summarised in table 5 below.

Table 5: safety data (study GO29315 - arms C and D)

	Randomised phase II	
	Polatuzuma b vedotin + BR (arm C) N=39*	BR (arm D) N=39*
Number of patients having reported at least one AE, n (%)		
All grades	39 (100.0%)	38 (97.4%)
Grade 3-4	33 (84.6%)	28 (71.8%)
Grade 5	9 (23.1%)	11 (28.2%)
Serious AE	25 (64.1%)	24 (61.5%)
Number of AEs leading to treatment discontinuation		
Polatuzumab vedotin	12 (30.8%)	NA
All study treatments	13 (33.3%)	6 (15.4%)
Number of AEs leading to treatment interruption		
Polatuzumab vedotin	22 (56.4%)	NA
All study treatments	28 (71.8%)	19 (48.7%)

* one patient from each group left the study before receiving a treatment dose.

The most frequently observed AEs ($\geq 20\%$) were: neutropenia (53.8% in arm C vs. 38.5% in arm D), anaemia (53.8% vs. 25.6%) thrombocytopenia (48.7% vs. 28.2%), diarrhoea (38.5% vs. 28.2%), nausea (30.8% vs. 41.0%), constipation (17.9% vs. 20.5%), fatigue (35.9% in both arms), fever (33.3% vs. 23.1%), decreased appetite (25.6% vs. 20.5%), peripheral neuropathy (23.1% vs. 2.6%) and cough (15.4% vs. 20.5%).

7.2.1.2 Non-randomised cohort (arm G)

All the patients treated with polatuzumab vedotin (lyophilised form) + BR (n=42) had at least one AE. The percentage of serious AEs was 61.9%, for grade 3-4 AEs it was 78.6% and for AEs leading to treatment discontinuation it was 16.7%. Two patients died as a result of an AE in this cohort (sepsis). The most commonly observed AEs ($\geq 20\%$) were: nausea (42.9%), neutropenia (33.3%), diarrhoea (33.3%), fever (31.0%), decreased appetite (28.6%), constipation (23.8%), vomiting (23.8%) and anaemia (21.4%).

7.3.2 Data from the Risk Management Plan (RMP) – version 1.2

Important identified risks	None
Important potential risks	Carcinogenicity
Missing information	Long-term safety data

7.4 Use data

POLIVY (polatuzumab vedotin) has been available in France in the context of a named-patient compassionate use programme (ATU) since 12 July 2019 then as a cohort ATU compassionate use programme (ATU) since 24 December 2019 (effective since 20 January).

According to the data submitted by the pharmaceutical company, 88 patients had been treated with POLIVY at 14 February 2020 (51 patients in the context of a named-patient ATU and 37 patients in the context of the cohort ATU). The pharmaceutical company did not provide any clinical data concerning patients treated with POLIVY (polatuzumab vedotin) in the context of a compassionate use programme (ATU). The first cohort ATU report will be available in the second half of 2020.

7.5 Summary & discussion

Assessment of the efficacy and safety of polatuzumab vedotin in combination with rituximab and bendamustine (BR) in adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant is based primarily on:

- a phase I/II multi-cohort study (study GO29415) having evaluated polatuzumab vedotin in various combinations, various doses, different formulations and various diseases (although the MA only concerns the lyophilised formulation of polatuzumab vedotin in combination with BR in the treatment of relapsed/refractory DLBCL). The data of interest in this indication are based on:
 - o a randomised, exploratory, comparative phase versus BR (without a superiority or non-inferiority hypothesis) conducted with a liquid formulation not intended for marketing and not validated by the MA;
 - o an additional non-comparative cohort treated with the lyophilised formulation of polatuzumab vedotin, intended for marketing (with an MA).
- an adjusted indirect comparison (MAIC) versus the reference treatments at this stage of the disease (R-GemOx, CART-cells, pixantrone).

■ Efficacy

- Study GO29315

In total, 80 patients were included in the randomised part of the study: 40 in each treatment arm. Imbalances were observed between the two arms, in particular as concerns the reason for transplant ineligibility: age (47.5% in the BR arm vs. 32.5% in the polatuzumab vedotin + BR arm), relapse after prior SCT (15.0% vs. 25.0%) or insufficient response to salvage therapy (22.5% vs. 30.0%). Furthermore, the patients in the BR group seemed to have more severe disease at baseline, with, in particular, a higher proportion of patients with bulky disease (37.5% vs. 25.0%), a higher IPI score (42.5% vs. 22.5%) as well as a higher number of patients with disease refractory to the last treatment line (85.0% vs. 75%).

A complete response assessed by PET-CT, 6 to 8 weeks after D1 of cycle 6 or on administration of the last dose of treatment (primary endpoint) was observed in 40% (n=16/40) of patients treated with polatuzumab vedotin + BR and in 17.5% (n=7/40) of patients treated with BR. Only one exploratory analysis was scheduled in the protocol to compare the two groups; this was in favour of the group treated with polatuzumab vedotin + BR.

The median progression-free survival assessed by the IRC was 9.5 months (95% CI = [6.2; 13.9]) in the group treated with polatuzumab vedotin + BR and 3.7 months (95% CI = [2.1; 4.5]) in the group treated with BR. The median overall survival was 12.4 months (CI 95% = [9.0; NE])

in the group treated with polatuzumab vedotin + BR and 4.7 months (95% CI = [3.7; 8.3]) the group treated with BR.

The additional non-comparative cohort included 42 patients whose characteristics differed from those of the patients in the randomised phase, in particular with respect to the main reasons for transplant ineligibility: age (40.5% versus 32.5% in the group treated with polatuzumab vedotin + BR in the randomised phase) and insufficient response to salvage therapy (35.7% versus 30.0%). The patients in this cohort seemed to have less severe disease with an ECOG score equal to 2 in 7.1% (versus 15% in the group treated with polatuzumab vedotin + BR in the randomised phase), an Ann Arbor stage of III or IV in 73.8% (versus 85%), bulky disease in 26.2% (versus 25%) and extranodal disease in 57.1% (versus 67.5%).

In this cohort, the complete response rate was 33.3% (n=14/42), the median progression-free survival was 5.5 months (95% CI = [3.7; 7.0]) and the median overall survival was 9.1 months (95% CI = [6.0; NE]).

Adjusted indirect comparison (MAIC)

These comparisons enable indirect comparison between the individual data (for POLIVY) and the published aggregated data. The level of evidence of these results is debatable, for the following reasons in particular:

- no argument was supplied concerning the prognostic factors considered. Yet the incorporation of all confounding factors is theoretically essential in order to obtain an unbiased result;
- the data from the phase I study were taken into account, despite this being conducted with a different polatuzumab vedotin dose to that in the MA;
- there are significant disparities between the studies, in particular with respect to:
 - median follow-up times;
 - patient and disease characteristics (age, proportion of relapsed and refractory patients, etc.);
 - treatment history and number of previous treatment lines;
- non-adjusted structural differences between the trials. The endpoint definitions: assessment of treatment response has been modified since the trials concerning second-line chemotherapies, with the use of PET-CT, whereas chest-abdomen-pelvis scans were primarily used in previous studies.

Consequently, this indirect comparison was presented for information purposes only. No reliable estimation of the difference in the effect of this medicinal product compared to the current standard of care can be performed based on these indirect comparisons.

► Safety

In the randomised phase, 100% of the patients treated with polatuzumab vedotin + BR and 97.4% of patients treated with BR had at least one adverse event (AE). However, the number of grade 3 and 4 AEs was higher among the patients treated with polatuzumab vedotin + BR (84.6%) than among the patients treated with BR (71.8%). AEs leading to treatment discontinuation were more common in patients treated with polatuzumab vedotin + BR (33.3% vs. 15.4%).

The most frequently observed AEs (≥ 20%) were: neutropenia (53.8% in arm C vs. 38.5% in arm D), anaemia (53.8% vs. 25.6%) thrombocytopenia (48.7% vs. 28.2%), diarrhoea (38.5% vs. 28.2%), nausea (30.8% vs. 41.0%), constipation (17.9% vs. 20.5%), fatigue (35.9% in both arms), fever (33.3% vs. 23.1%), decreased appetite (25.6% vs. 20.5%), peripheral neuropathy (23.1% vs. 2.6%) and cough (15.4% vs. 20.5%). Although the peripheral neuropathies were not considered to be severe in the study, the Committee highlights the fact that these can impact patients' quality of life.

In the additional cohort treated with polatuzumab vedotin (lyophilised form) + BR (n=42) all the patients had at least one AE. The percentage of serious AEs was 61.9%, for grade 3-4 AEs it was 78.6% and for AEs leading to treatment discontinuation it was 16.7%. Two patients died as a result of an AE in this cohort (sepsis).

► Discussion

The scope of the results is limited by the following points:

- Pivotal phase I/II study GO29365 is a set of very heterogeneous cohorts since it assessed polatuzumab vedotin in various combinations, various doses, different formulations and various diseases (although the MA only concerns the lyophilised formulation of polatuzumab vedotin in combination with BR in the treatment of relapsed/refractory DLBCL).
- The cohorts assessing polatuzumab vedotin in the MA indication were conducted on a limited number of patients, which the Committee considers to be very heterogeneous in terms of previous treatment lines received (minimum: 1; maximum: 7).
- The randomised, comparative phase versus BR of this study was performed without a pre-specified superiority or non-inferiority hypothesis for the efficacy analyses.
- The relevance of the comparator (BR) used is questionable. Although this combination is listed among the possible options in the American NCCN guidelines⁵, the European ESMO guidelines⁴ recommend the use of platinum and/or gemcitabine-based polychemotherapy regimens (in particular the R-Gemox regimen). The Committee also questions the reuse of rituximab in patients refractory to this medicinal product, as well as the bendamustine dose (90 mg/m²) use in the study,
- Imbalances were observed between the two randomised arms liable to favour the polatuzumab vedotin + BR arm, particularly with respect to the reasons for transplant ineligibility and disease prognostic factors.
- The primary endpoint for the study (complete response) is not the most relevant endpoint in this situation and the Committee expected robust results concerning quality of life and overall survival;
- The randomised phase was performed using the liquid formulation of polatuzumab vedotin, not intended for marketing and not validated by the MA for POLIVY. The lyophilised formulation, which has an MA, was analysed in an additional, non-comparative cohort of 42 patients in which the efficacy results, in terms of complete response, progression-free survival and overall survival, appear to be inferior to those observed in the randomised phase. A second non-comparative cohort using the lyophilised formulation was added following a protocol amendment. Enrolments in this cohort are still ongoing.
- No quality of life data was collected in this study, which is regrettable since some of the adverse effects of polatuzumab vedotin could have an impact on this (in particular, peripheral neuropathy).
- A comparative study versus R-Gemox in the same population is ongoing, at the request of the FDA (see paragraph 7.6.1).
- On the basis of the adjusted indirect comparison (MAIC), it is not possible to reach a conclusion with respect to the efficacy and safety of polatuzumab vedotin + BR versus the reference treatments at this stage of the disease.
- Finally, it should be emphasised that when polatuzumab vedotin was combined with obinutuzumab (another antiCD-20) and bendamustine, the complete response rate was 28.6% (95%CI = [11.3; 52.2]). This rate appears to be lower than that observed with the polatuzumab vedotin + BR combination, which is the subject of this assessment.

Given efficacy and safety data from a phase I/II study, for which the scope of the results is limited by the methodology and comparator chosen, the additional impact on morbidity and mortality has not currently been demonstrated. In the absence of data, no impact on quality of life is expected and the Transparency Committee regrets the absence of data, particularly with respect to the clinical situation and the safety profile of POLIVY.

Consequently, POLIVY does not provide a response to the identified partially met medical need.

7.6 Study programme

7.6.1 In the indication concerned by the present application

► POLARGO (ongoing)

- Methodology: Phase III open-label, randomised study to evaluate the safety and efficacy of Pola in combination with rituximab, gemcitabine and oxaliplatin (R-GemOx) versus R-GemOx alone in patients with relapsed or refractory DLBCL ineligible for SCT
- Primary endpoint: Overall survival
- Sponsor: Hoffmann-la-Roche
- Enrolment: 875 patients (30 in France)
- First results expected in Q2 2024

► Other strength/form/presentation to be marketed soon

Another strength is scheduled for polatuzumab vedotin: 30 mg powder for concentrate for solution for infusion (EMA authorisation scheduled in Q1 2021).

7.6.2 In other indications

Study name	Study design	Availability of data
Patients with previously untreated DLBCL		
POLARIX	The availability of the results of the POLARIX study is one of the conditions for the POLIVY MA. • Methodology: Phase III, randomised, double-blind study in patients with previously untreated DLBCL • Objective: To evaluate the efficacy, safety, pharmacokinetics and PRO in patients treated with polatuzumab vedotin + R-CHP compared to patients treated with R-CHOP • Primary endpoint: Progression-free survival assessed by the investigator • Sponsor: Hoffmann-la-Roche • Number of patients: 875 patients (186 in France)	Q2 2021
Patients with R/R DLBCL eligible for SCT		
POLARICE	• Methodology: Phase III multicentre, open-label, prospective study comparing Pola in combination with rituximab, ifosfamide, carboplatin and etoposide (R-ICE) versus R-ICE alone used as salvage therapy in patients with R/R DLBCL eligible for SCT. • Sponsor: GWT-TUD GmbH	Q4 2024
Elderly patients (age ≥ 80 years) with previously untreated DLBCL		
POLAR BEAR	• Methodology: Phase III randomised study, comparing Pola in combination with rituximab and mini-CHOP (endoxan, adriamycin, vincristine, prednisone) (R-mini-CHOP) versus R-mini-CHOP in elderly patients (age ≥ 80 years or frail patients ≥ 75 years) with previously untreated DLBCL • Sponsor: Nordic Lymphoma Group	Q4 2027

08 ROLE IN THE CARE PATHWAY

The treatment of patients with diffuse large B-cell lymphoma (DLBCL) involves, as first-line therapy, a combination of chemotherapy with an anti-CD20 monoclonal antibody, i.e., the R-CHOP regimen¹⁷. In the event of primary resistance or relapse, the treatment of choice is salvage chemotherapy followed by consolidation by autologous transplant in the event of chemotherapy-sensitive disease.

In patients not eligible for transplant due to an inadequate response to salvage chemotherapy or to the patient's condition, treatment is based on immunochemotherapy with platinum and/or gemcitabine (in particular, the R-GemOx or R-DHAP regimens not followed by intensification and autologous transplant).

Relapsed or refractory patients following second-line salvage therapy may be able to have third-line chemotherapy. Treatment with CAR-T cells (axicabtagene ciloleucel or tisagenlecleucel) is recommended in patients whose life expectancy is compatible with the production timeframes. The following other options may be considered depending on the clinical situation:

- for relapsed patients (excluding refractory patients): additional intensive chemotherapy with the objective of performing allogeneic¹⁸ haematopoietic stem cell transplantation if the patient is eligible; where applicable an autologous transplant. An allogeneic transplant is generally considered in patients under the age of 70, in the absence of major comorbidities, in the presence of a donor (availability of a graft) and in the event of a complete response (or very good partial response) following the chemotherapy regimen;
- other chemotherapies,
- implementation of palliative care.

Role of POLIVY in the care pathway:

Considering:

- **the methodological weakness of the clinical data obtained from a phase I/II multi-cohort trial including an exploratory randomised phase (with no superiority or non-inferiority hypothesis) performed with a liquid formulation of polatuzumab vedotin (without an MA) and in a limited number of patients who were heterogeneous in terms of their previous treatment line (min: 1; max: 7);**
- **the lack of clinical relevance of the comparator chosen for this randomised phase (rituximab + bendamustine - BR), little used in France;**
- **the low clinical relevance of the primary endpoint chosen (complete response rate assessed by PET-CT, 6 to 8 weeks after D1 of cycle 6 or on administration of the last dose of treatment) in this clinical situation in which overall survival and quality of life data would have been more appropriate;**
- **the uncertainty with respect to this complete response rate, estimated to be 40% of patients treated with polatuzumab vedotin + BR compared to 17.5% of patients treated with BR, given the imbalances observed between these two arms, which may favour the polatuzumab vedotin + BR arm (particularly with respect to the reasons for transplant ineligibility and disease prognostic factors);**
- **the lack of robust demonstration of an increase in overall survival compared to BR,**
- **the lack of quality of life data collected, which is regrettable since some of the adverse effects of polatuzumab vedotin could have an impact on this (in particular, peripheral neuropathy);**
- **uncertainties with the lyophilised form with the MA insofar as the data are very limited with this formulation (non-comparative cohort of 42 patients with**

¹⁷ R-CHOP: rituximab, cyclophosphamide, hydroxyadriamycin, oncovin and prednisone

¹⁸ Very few patients are currently treated (< 100 allogeneic SCT graft patients/year in France). The SFGM-TC transplant registry recorded only 24 allogeneic SCTs in the treatment of DLBCL in 2016, predominantly in chemosensitive patients

efficacy results that appear to be inferior to those observed in the randomised phase with the liquid formulation);

- and the indirect comparisons (MAIC) submitted by the pharmaceutical company that do not enable quantification of the contribution of polatuzumab vedotin versus the reference treatments (R- GemOX-type polychemotherapy or CART-cells);

the Committee considers that POLIVY (polatuzumab vedotin) in combination with bendamustine and rituximab has no role in the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant, in view of the alternatives and pending potential data from future clinical development.

09 COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

9.1 Clinical benefit

- Diffuse large B-cell lymphoma, particularly in relapsed/refractory patients who are not candidates for haematopoietic stem cell transplant, is a serious, life-threatening disease.
- This medicinal product is a curative treatment for diffuse large B-cell lymphoma.
- The efficacy/adverse effects ratio of POLIVY (polatuzumab vedotin) in combination with bendamustine and rituximab has not been adequately established in view of the numerous uncertainties associated with the available data (in particular, the choice of an endpoint and comparator of little relevance, the heterogeneity of the population included, the absence of a prespecified superiority or non-inferiority hypothesis, etc.). The Committee considers that the clinical development of this medicinal product should be continued (see Summary and Discussion).
- There are therapeutic alternatives.
- The Committee considers that POLIVY (polatuzumab vedotin) in combination with bendamustine and rituximab has no role in the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant (see 08. Role in the care pathway).

Public health impact

Considering:

- the seriousness of the disease, particularly in relapsed/refractory patients who are not candidates for haematopoietic stem cell transplant, which is life-threatening in the short-term,
- its prevalence,
- the partially met medical need at this stage of the disease,
- the lack of elements supporting the absence of a deterioration in the care and/or life pathway in the absence of quality of life data,
- the absence of any demonstrated impact on the organisation of care, in particular in terms of reduction of hospitalisations or AEs,
- the lack of response to the identified partially met medical need, POLIVY is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of POLIVY (polatuzumab vedotin) is insufficient to justify its funding by the French national health insurance system in the indication "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".

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication “in combination with bendamustine and rituximab for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant” and at the MA dosages.

9.2 Clinical Added Value

Not applicable.

9.3 Target population

Not applicable.

010 OTHER COMMITTEE RECOMMENDATIONS

The Committee highlights the fact that the results of the ongoing phase III POLARGO study assessing the safety and efficacy of polatuzumab vedotin in combination with rituximab, gemcitabine and oxaliplatin (R-GemOx) versus R- GemOx alone, are likely to answer the questions raised by the Committee with respect to the role of POLIVY (polatuzumab vedotin) in the treatment of patients with relapsed/refractory DLBCL who are not candidates for haematopoietic stem cell transplant.

Assessment schedule	Date of examination: 3 June 2020 Date of adoption: 10 June 2020
Stakeholders / external expertise	Yes (external expertise)
Presentations concerned	<u>POLIVY 140 mg powder for concentrate for solution for infusion</u> Pack of 1 vial (CIP: 34009 550 700 3 0)
Applicant	ROCHE
List concerned	Hospital (CSP L.5123-2)
MA	Initial date (centralised procedure): 16 January 2020 Conditional MA. As part of the undertakings for this conditional MA, the pharmaceutical company must submit to the EMA: - the final results of cohort H, treated by the lyophilised form of polatuzumab vedotin (as well as the grouped results with cohort G) (Q3 2020); - the results of the phase III, randomised, double-blind study, comparing polatuzumab vedotin + R-CHP versus R-CHOP in patients with previously untreated DLBCL (Q4 2021).
Prescribing and dispensing conditions / special status	List I Orphan medicine (16 April 2018), Named-patient compassionate use programmes (ATU) since 12 July 2019. Cohort compassionate use programme (ATU) granted on 24 December 2019 and which came into force on 20 January 2020 in the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant. Medicinal product for hospital use only (RH) Prescription medicinal product subject to prescription reserved for certain specialists (PRS)(haematology specialists or physicians with expertise in blood disorders) Medicinal product requiring special monitoring during treatment (SPT)
ATC code	L01XC37