**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

# Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

**Consultee and commentator comments on the draft remit and draft scope**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Wording<br>*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* | Roche | None | Thank you for your comment. No further action required. |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of | Yes | Thank you for your comment. No further action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Radiologists (RCR) | | |
| Timing Issues<br>*What is the relative urgency of this appraisal to the NHS?* | Roche | Treatment for people with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) not suitable for hematopoietic stem cell transplant (HSCT) is an area of high unmet need. Polatuzumab vedotin is an innovative medicine that has therefore received EMA PRIME status and PIM designation by the MHRA. [redacted] | Thank you for your comment. No further action required. |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | Relapsed diffuse large B-cell lymphoma in patients who are unsuitable for stem cell transplantation is a rapidly fatal condition so this an urgent appraisal. Treatment options are limited so this is an area of unmet need. | Thank you for your comment. NICE aims, where possible, to produce timely guidance in line with marketing authorisation receipt. |
| Additional comments on the draft remit | Roche | None | Thank you for your comment. No further action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | | Thank you for your comment. No further action required. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information<br>*Consider the accuracy and completeness of this information* | Roche | None | Thank you for your comment. No further action required. |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), | No issues | Thank you for your comment. No further action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | | |
| The technology/ intervention<br>*Is the description of the technology or technologies accurate?* | Roche | None | Thank you for your comment. No further action required. |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | Yes | Thank you for your comment. No further action required. |
| Population<br>*Is the population defined* | Roche | The study population in GO29365 and the proposed licensed indication is aligned with patients seen in UK clinical practice. These are R/R DLBCL patients not suitable for HSCT because they were unsuitable for intensive | Thank you for your comment. No further action required. |

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| *appropriately? Are there groups within this population that should be considered separately?* | | salvage therapy and transplantation based on physician assessment; or had failed to respond to salvage therapy or relapsed after HSCT.<br><br>There is no evidence that any sub-groups in this population should be considered differently as the treatment effect of polatuzumab vedotin with bednamustine and rituximab (Pola-BR) versus bendamustine and rituximab (BR) in the randomised phase of GO29365 was consistent with the overall R/R DLBCL population for all sub-groups investigated, e.g., by prior lines of therapy or refractory status (1) | |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | The main issue here is how to define 'for whom haematopoietic stem cell transplant is not suitable'. This encompasses 3 main groups of patients:<br>1. Patient who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant.<br>2. Patients who have already had a stem cell transplant and have relapsed following it<br>3. Patients who are young and fit enough for a stem cell transplant but their disease is not in a good enough remission to proceed with this | Thank you for your comment.<br><br>Population was discussed during scoping workshop and it was agreed that group 3 would be a minority of patients in the current scope population, given that young and fit patients would receive intensive chemotherapy instead of polatuzumab vedotin in combination with bendamustine and rituximab. |
| Comparators | Roche | There are no universally established therapies for patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant, according to UK clinical experts consulted by Roche. The most commonly used regimens | Thank you for your comment. |

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| *Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?* | | are gemcitabine and/or platinum-based therapies or bendamustine combined with rituximab.<br><br>Experts confirmed that current clinical practice for this population is likely to vary across the country, with patients offered a chemotherapy regimen with rituximab (R), with the regimen depending on the expertise of the treatment centre and will also likely be informed by individual clinician and patient choice.<br>All the regimens mentioned in the draft scope in combination with R [DHAP (dexamethasone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), ICE (ifosfamide, carboplatin, etoposide), IVE (ifosfamide, etoposide, epirubicin)] are used as salvage regimens prior to HSCT and in particular DHAP, ICE or IVE would not be the appropriate comparators for patients that are not candidates for HSCT. Experts also confirmed that pixantrone is rarely used and therefore not a comparator in line with discussions in TA559 and TA567.<br>Best supportive care would not be a suitable comparator as chemotherapy would normally be offered for this group of patients. However, guidelines also recommend considering enrolment in clinical trials for some patients (2, 3).<br>There remains no evidence regarding the superiority of one salvage regimen over another in the limited number of randomised studies in the relapsed/refractory setting. For instance, the Phase III Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, which compared the efficacy of R-ICE or R-DHAP followed by ASCT with or without rituximab maintenance, demonstrated no difference in 2-year OS between salvage regimens and no difference in outcomes for other salvage regimens for patients receiving a 3rd line regimen rather than transplant (4).<br>The outcomes for transplant-ineligible patients (including patients who relapse after ASCT) remain poor, with median OS of approximately 6 months (5, 6). | Based on consultations comments and discussions during scoping workshop, comparators were amended to:<br>• R-GemOx (rituximab, gemcitabine oxaliplatin)<br>• R-Gem (rituximab gemcitabine)<br>• R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine)<br>• (R)- DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine)<br>• BR (bendamustine, rituximab) |

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| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | We think the wrong comparators are being suggested here. The scope lists R-DHAP, R-GDP, R-IVE. However these are all multi-agent intensive chemotherapy regimens usually used in patients who are fit for stem cell transplant. So they could be used as comparators in population (3) listed above, when used as second line salvage regimens. It would not be justified to compare with data when these regimens are used as first line salvage regimens, as these regimens are adopted in people fit for stem cell transplant and at that time suitable for one (a group specifically excluded in the assessment).<br><br>For populations (2) and (3) we would suggest the following comparators which are used in patients failing stem cell transplant, or not suitable due to age and fitness:<br>- R-GemOx<br>- R-Gem<br>- R-P-MitCEBO<br>- Pixantrone (although this is not used much around the UK now, and tends to be used at later treatment lines)<br>- (R-)DECC<br>- PEP-C<br>- R-COCKLE<br><br>There is also the issue of CAR T-cells. These may be suitable for populations (2) and (3) above. However, access is currently limited and even in patients with a slot, bridging therapy is frequently needed, and it is more appropriate in our view to compare the benda+R+pola with the bridging therapy (as it maybe used for this) rather than comparing directly with the CAR T-cell therapy. In addition only patients PS 0-1 are eligible for CAR-T therapy. | Thank you for your comment.<br><br>Based on consultations comments and discussions during scoping workshop, comparators were amended to:<br>• R-GemOx (rituximab, gemcitabine oxaliplatin)<br>• R-Gem (rituximab gemcitabine)<br>• R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine)<br>• (R)- DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine) |

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| | | | • BR (bendamustine, rituximab) |
| Outcomes<br>*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* | Roche | None | Thank you for your comment. No further action required. |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | Yes | Thank you for your comment. No further action required. |
| Economic analysis<br>*Comments on aspects such as the appropriate time horizon.* | Roche | None | Thank you for your comment. No further action required. |
| | Joint response of Royal College of Physicians (RCP), National Cancer | We are not qualified to comment on this | Thank you for your comment. No further action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | | |
| Equality and Diversity<br>*NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:*<br>• *could exclude from full consideration any people protected by the* | Roche | No equality issues were identified. | Thank you for your comment. No further action required. |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | No issues with equality | Thank you for your comment. No further action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| *equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*<br>• *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*<br>• *could have any adverse impact on people with a particular disability or disabilities.*<br>*Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.* | | | |
| Other considerations | Roche | None | Thank you for your comment. No further action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| *Suggestions for additional issues to be covered by the appraisal are welcome.* | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | | Thank you for your comment. No further action required. |
| Innovation<br>*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*<br>*Do you consider that the use of the technology can result* | Roche | Antibody-drug conjugates (ADCs) are an innovative class of anticancer treatment agents that comprise a monoclonal antibody targeted to a tumour antigen, a chemical linker, and a potent cytotoxic agent, which is often too toxic to be given as conventional chemotherapy (7). Polatuzumab vedotin is the only ADC targeting CD79b, a signalling component of the B cell receptor expressed on the surface of B cells that is found in abundance in people with DLBCL. As such, CD79b expression is restricted to normal cells within the B cell lineage (with the exception of plasma cells) and malignant B-cells; therefore, targeted delivery of MMAE is expected to be restricted to these malignant cells<br>In the randomised phase of GO29365, pola+BR has clearly demonstrated a significant survival benefit in comparison to BR across all lines of therapy in the R/R DLBCL setting [OS HR 0.42; 95%CI: 0.24-0.75; p=0.0023]. A clinically meaningful benefit was also observed in terms of response rates, PFS by INV and IRC as well as DOR, with ongoing responses of at least 20 months observed in patients who have not received subsequent therapy (8). | Thank you for your comment. No further action required. |

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| *in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* | | The data from GO29365 also suggest that pola+BR has an acceptable safety and tolerability profile that is comparable to available chemotherapies, with the main adverse events being cytopenias.<br>Based on these data, pola+BR provides a major therapeutic innovation in a population with high unmet medical need. Polatuzumab vedotin has therefore received EMA PRIME status and PIM designation by the MHRA. | |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | Antibody-drug conjugates have been applied successfully to high grade B-cell lymphomas. The trial this evaluation is based on resulted in a significance overall survival difference. These 2 factors combined suggest this does have the potential to have a substantial impact on health-related benefits and is a step-change in the management of this condition.<br>It is innovative in it's potential in a population with a poor outcome and limited effective treatment options. | Thank you for your comment. No further action required. |
| Questions for consultation<br>*Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process* | Roche | Questions on the population, comparators and innovation were addressed in the sections above. The answers to the additional questions for consultation are below:<br>*Would you expect SCT to be feasible after treatment with polatuzumab vedotin in this population?*<br>The typical patient treated with Pola-BR in the proposed indication is highly unlikely to be a candidate for high intensity chemo and HSCT. The GO29365 study was not designed to investigate pola-BR as a salvage regimen for | Thank you for your comment.<br>Based on consultations comments and discussions during scoping workshop, comparators were amended to: R-GemOx (rituximab, gemcitabine |

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| *this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines).* | | patients suitable for high dose therapy and transplant, with eligibility criteria being patients not eligible for transplantation<br><br>*Where do you consider polatuzumab vedotin in combination with rituximab and bendamustine will fit into the existing NICE pathway, Blood and bone marrow cancers?*<br><br>The pola-BR regimen is expected to replace current R-chemo regimens for patients with R/R DLBC who are not candidates for HSCT. | oxaliplatin), R-Gem (rituximab gemcitabine), R-P-MitCEBO (rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine), (R)- DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine), BR (bendamustine, rituximab) |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | How do you define people for whom 'SCT is not suitable'? - *see answer above, 3 populations.*<br><br>Have all relevant comparators been included? – *also see above. No – most of the comparators listed are not relevant to all the populations. Additional comparators are suggested above.*<br><br>How should best supportive care be defined? – *involvement with palliative care, possible use of palliative radiotherapy for symptoms, possible use of steroids. Often patients remain under consultant haematology / oncology care as well as receiving active palliative care.*<br><br>Are the outcomes listed appropriate? – yes. PFS and OS are highly relevant outcomes in this field. HRQoL is relevant in all areas. | Thank you for your comment.<br><br>Based on consultations comments and discussions during scoping workshop, comparators were amended to: R-GemOx (rituximab, gemcitabine oxaliplatin), R-Gem (rituximab gemcitabine), R-P-MitCEBO (rituximab, prednisolone, |

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| | | Would you expect stem cell transplant to be feasible after treatment with polatuzumab? – *this depends on the population.*<br><br>*In population (1) above (i.e. elderly / co-morbid), no, patients would not progress to stem cell transplant*<br><br>*In population (2) above (i.e. relapsed after a stem cell transplant), yes – patients may become suitable for allogeneic stem cell transplant (usually a minority) or maybe bridged to CAR T-cell therapy.*<br><br>*In population (3) above, yes – may bridge to either allogeneic stem cell transplant (minority) or CAR T-cell therapy. A minority may progress to autologous haematopoietic stem cell transplant but usually only if achieved a complete metabolic response.*<br><br>Are there subgroups who maybe deemed more clinically or cost effective? *If the regimen can be used as part of a strategy to bridge to a potentially curative therapy such as allogeneic transplant or CAR T-cell therapy (populations (2) and (3) above) then is would be expected to be more cost effective. No subgroups would be predicted to be more clinically effective (although the drug targets CD79a, this is ubiquitous on B-cell lymphomas so would not act as an effective biomarker).*<br><br>How does it fit with the NICE pathway? *We could not see a relevant discussion in the link to the NICE pathway given so we cannot comment.*<br><br>Do you consider there will be any barriers to adoption of this technology? *No. Bendamustine and rituximab are commonly given across haematology units in the UK and polatuzumab is a straightforward drug to administer.*<br><br>Is it suitable to take this through the STA process? *The main issue we see is that bendamustine is not commissioned for the treatment of relapsed high* | mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine), (R)- DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine), BR (bendamustine, rituximab)<br><br>During scoping workshop, it was underlined that patients who tried a first-line treatment and who did not respond well would not be eligible to HSCT. |

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| | | *grade lymphoma. The lymphoma treating community has always been somewhat perplexed why there are such limitations on us using this agent since it became generic. But due to this, currently bendamustine is not a 'standard of care' drug for this indication in England. The other issue is there is currently a large global frontline study of R-CHOP compared with R-CHOP+polatuzumab in diffuse large B-cell lymphoma. If this is positive it may change the frontline treatment of this disorder which may affect use of polatuzumab at later stages. However the trial is still recruiting and we are someway from hearing the outcomes.* | |
| Additional comments on the draft scope | Roche | None | Thank you for your comment. No further action required. |
| | Joint response of Royal College of Physicians (RCP), National Cancer Research Institute (NCRI), Association of Cancer Physicians (ACP), Royal College of Radiologists (RCR) | | Thank you for your comment. No further action required. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

**Janssen**

## References

1. Sehn LH, Kamdar M, Herrera AF, McMillan A, Flowers C, Kim WS, et al. Adding Polatuzumab Vedotin (Pola) to Bendamustine and Rituximab (BR) Treatment improves Survival in Patients with Relapsed/ Refractory DLBCL: Results of a Phase 2 Clinical Trial. HemaSphere. 2018;2(S1):5802.

2. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26 Suppl 5:v116-25.

3. Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K, et al. Guidelines for the management of diffuse large B-cell lymphoma. British journal of haematology. 2016;174(1):43-56.

4. Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016;51(1):51-7.

5. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-8.

6. Mounier N, El Gnaoui T, Tilly H, Canioni D, Sebban C, Casasnovas RO, 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(11):1726-31.

7. Carter PJ, Senter PD. Antibody-drug conjugates for cancer therapy. Cancer journal (Sudbury, Mass). 2008;14(3):154-69.

8. Sehn LH, Herrera AF, Matasar M, Kamdar M, Assouline S, Hertzberg M, et al., editors. Polatuzumab Vedotin (Pola) Plus Bendamustine (B) with Rituximab (R) or Obinutuzumab (G) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Updated Results of a Phase (Ph) Ib/II Study. American Society of Hematology - 60th Annual Meeting; 2018.