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EVIDENCE BRIEFING
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Polatuzumab vedotin in combination with rituximab and bendamustine for the treatment of diffuse large B-cell lymphoma

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Developer/Company	Roche Products Ltd	**UKPS ID**	645060

SUMMARY

Polatuzumab vedotin in combination with rituximab and bendamustine is in clinical development for previously treated adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who are not candidates for hematopoietic stem cell transplant. DLBCL is a cancer affecting a type of white blood cells called lymphocytes or B-cells. It is the most common form of non-Hodgkin lymphoma among adults, though it can also occur in children and young adults in rare cases. DLBCL is an aggressive cancer and although it can be cured in more than half of people affected, it remains a serious and life threatening disease, particularly when it relapses or does not respond to treatment.

Polatuzumab vedotin is a first-in-class antibody drug specifically developed for the treatment of cancers that affect the blood and lymph system. It is a monoclonal antibody that acts by selectively binding to CD79b, a protein which is abundantly expressed on the surface of B-cells. It is administered as an intravenous infusion, absorbed by the cancer cells and the chemotherapy agent linked to the antibody releases inside the cancer cells and destroys them. Adding polatuzumab vedotin to bendamustine with rituximab may improve effectiveness in patients whose disease had come back or in whom other treatment had not worked well enough.

PROPOSED INDICATION

Previously treated adult patients with relapsed or refractory diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant (HSCT).[a]

TECHNOLOGY

DESCRIPTION

Polatuzumab vedotin (RG7596) in combination with rituximab and bendamustine is in clinical development for previously treated adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who are not candidates for HSCT. Polatuzumab vedotin is a first-in-class anti-CD79b antibody drug conjugate (ADC).[1] It is made up of a monoclonal antibody combined with a cytotoxic (cell-killing) agent called monomethyl auristatin E (MMAE). CD79b is a cell surface antigen expressed on the surface of normal and malignant B-cells, and the anti-CD79b monoclonal antibody is designed to attach specifically to CD79b expressed on the malignant B-cells. When the antibody attaches to CD79b, the B-cells rapidly internalise the medicine and MMAE is released inside them. MMAE stops microtubules in the B-cells from working. Microtubules are structures that cells need to survive and divide. By targeting the malignant B cells and causing them to die, the medicine is expected to reduce symptoms of the disease.[2] The CD79b protein is highly specific and expressed in the majority of types of B-cell Non-Hodgkin's Lymphoma (NHL), making it a promising target for the development of new therapies.[1]

In the phase II clinical trial (NCT02257567) polatuzumab vedotin is administered intravenously (IV) at 1.8 milligrams per kilogram (mg/kg) on Day 2 of Cycle 1, then on Day 1 of each subsequent cycle for up to 6 cycles, rituximab is administered IV at 375mg/m^2 on day 1 of each cycle for up to 6 cycles and bendamustine is administered IV at 90 mg/m^2 per day on days 2 and 3 of cycle 1, then on days 1 and 2 of each subsequent cycle for up to 6 cycles (each cycle is 21 days).[3]

INNOVATION AND/OR ADVANTAGES

Early results suggest that adding polatuzumab vedotin to existing treatment improved their effectiveness in patients with DLBCL whose disease had returned or in whom other treatment had not worked well enough. Therefore this product might be of significant benefit in such patients. [2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Polatuzumab vedotin does not currently have Marketing Authorisation in the EU/UK for any indication.

- Polatuzumab vedotin is a designated orphan drug in the EU in 2018 for DLBCL.[2]
- Polatuzumab vedotin was awarded PRIME status for R/R DLBCL by EMA in June 2017.[4]
- Polatuzumab vedotin was designated Breakthrough Therapy for R/R DLBCL by the FDA in 2017.[5]

Polatuzumab vedotin is also in phase II clinical development for B-cell non-Hodgkin lymphoma[3, 6-11] and phase III for the first line treatment of DLBCL.[12]

Rituximab is licensed in the UK for the treatment of the following:[13]

- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukaemia
- Rheumatoid arthritis

[a] Information provided by Roche Products Ltd on UK PharmaScan

- Granulomatosis with polyangiitis and microscopic polyangiitis

Bendamustine is licensed in the UK for the treatment of the following:[14]

- Chronic lymphocytic leukaemia
- Indolent non-Hodgkin's lymphomas
- Multiple myeloma

PATIENT GROUP

DISEASE BACKGROUND

Non-Hodgkin's lymphoma (NHL) is a type of cancer of the lymphatic system, and diffuse large B-cell lymphoma (DLBCL) is the most common high grade variant.[15] DLBCL develops from abnormal mature B-cells. As the abnormal cells are larger than normal, healthy B-cells, and the abnormal cells are spread diffusely throughout the tumour, wiping out the normal structure of the lymph node. The causes of lymphoma are not known, but most people diagnosed with DLBCL are aged 65 years and over, and the disease affects slightly more men than women.[16]

The first symptoms of DLBCL are usually painless lumps, often in the neck, armpit or groin, which are enlarged lymph nodes. DLBCL can also develop in lymph nodes deep inside the body which cannot be felt from the outside. DLBCL can be hard to diagnose as people have different symptoms depending what organs and tissues are affected, but diagnosis can be confirmed by a biopsy. Most people have advanced-stage DLBCL when they are diagnosed.[16]

A relapse is when the lymphoma comes back after successful treatment and refractory means the lymphoma did not respond to the first course of treatment. Relapse is more likely to happen within the first 2 years after treatment. As time goes on, relapse generally becomes less likely.[17]

CLINICAL NEED AND BURDEN OF DISEASE

The latest available statistics in the Cancer Registration Statistics, England, 2016 showed 6,310 new registrations of diffuse NHL (ICD-10 code C83) in the 20 years and over age group (due to the age group splits it is not possible to define 18 year and over).[18] It is estimated that about a third of people with NHL have DLBCL,[15] which would equate to 2,103 registrations per year in this age group.

Although most patients are cured with 6-8 cycles of first-line R-CHOP chemotherapy, about 10-15% have primary refractory disease and a further 20-30% relapse.[19] This would equate to around 210 – 315 patients having primary refractory disease, and 420 – 630 having relapsed disease, per year. Nearly 40% of patients with DLBCL will eventually die of relapsed disease or disease that is refractory to first-line therapy.[20] The latest five-year survival for NHL was reported as 66.9% (age-standardised persons, patients diagnosed between 2011 and 2015).[21]

For patients who are not cured with first-line therapy, high-dose chemotherapy followed by autologous stem cell transplantation (SCT) offers a second chance for cure. Less than half of patients who are eligible for transplant will be cured;[22] however, not all patients are eligible for transplant and the outcome in these patients is dismal with generally no chance of prolonged periods of disease control.[23] In addition, patients who progress through front-line therapy do very poorly even after receipt of salvage treatment followed by autologous transplant with a 3-year progression-free survival (PFS) rate of 17% .[24]

For hospital activity, in 2016/17 there were 35,255 admissions with primary diagnosis (ICD-10 code C83.3) Diffuse large B-cell lymphoma, of which 27,933 were day cases.[25]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Most types of high grade NHL, of which DLBCL is a variant, are usually treated with radiotherapy or immunochemotherapy with the aim of curing the lymphoma. Some people don't respond well to their first treatment (refractory lymphoma). Without therapy, patients with DLBCL have survival times measured in months. Standard treatment with combination chemotherapy plus rituximab can cure a percentage of patients resulting in survival rates of approximately 70, 60, and 45 percent at 3, 5, and 10 years respectively after diagnosis.[26-30]

Generally, the same treatment options are used for relapsed and refractory lymphoma. Most people who relapse can have more treatment. Treatment can still be very successful. NICE guidelines recommend salvage therapy with multi-agent immunochemotherapy to those fit enough to tolerate intensive therapy consolidated with a stem cell transplant who are fit enough for transplantation.[17, 31]

CURRENT TREATMENT OPTIONS

According to NICE guidelines, treatment options for relapsed or refractory DLBCL patients who are not candidates for stem cell transplant include:

- Salvage regimens with rituximab and chemotherapy.[17, 31]
- Pixantrone monotherapy as an option for treating patients with multiple relapsed or refractory aggressive DLBCL only if the person has previously been treated with rituximab and the person is receiving third- or fourth-line treatment and the manufacturer provides pixantrone with the discount agreed in the patient access scheme.[32]

PLACE OF TECHNOLOGY

If licenced, polatuzumab vedotin in combination with rituximab and bendamustine may replace other therapy options for the treatment of previously treated adult patients with DLBCL who are not candidates for HSCT.

CLINICAL TRIAL INFORMATION

Trial	NCT02257567, 2014-001361-28; 18 years and older; polatuzumab vedotin in combination with rituximab or obinutuzumab plus bendamustine; phase II
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU (incl UK), USA, Canada, Australia and Republic of Korea
Design	Randomised
Participants	N=250 (planned); 18 years and older; relapsed or refractory FL (Grades 1, 2, or 3a) or relapsed or refractory DLBCL
Schedule	Randomised to: • Arm C (Phase II Randomization): Polatuzumab+BR in DLBCL • Arm D (Phase II Randomization): BR in DLBCL • Arm F (Phase II Expansion): Polatuzumab+BG in DLBCL • Cohort 1A (Phase Ib Safety Run-In): Polatuzumab+BR in DLBCL

	• Arm G (Phase II NF Cohort): Polatuzumab+BR in DLBCL • Drug: Bendamustine (B) Bendamustine 90 milligrams per meter-squared (mg/m^2) per day administered IV on Days 2 and 3 of Cycle 1, then on Days 1 and 2 of each subsequent cycle for up to 6 cycles (each cycle is 21 days) • Drug: Obinutuzumab (G) Obinutuzumab 1000 milligrams (mg) IV on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent cycle for up to 6 cycles (each cycle is 21 days) • Drug: Polatuzumab vedotin (Liquid) Polatuzumab vedotin 1.8 milligrams per kilogram (mg/kg) administered IV on Day 2 of Cycle 1, then on Day 1 of each subsequent cycle for up to 6 cycles (each cycle is 21 days) • Drug: Rituximab (R) Rituximab standard dose, 375 mg/m^2 IV on Day 1 of each cycle for up to 6 cycles (each cycle is 21 days) • Drug: Polatuzumab vedotin (Lyophilized) Participants in the New Formulation (NF) Cohort (Arm G) will follow the same schedule and dosing requirements as participants in the other Phase II cohorts (Arms A-F).
Follow-up	Active treatment for 6 cycles (21 days), follow-up 2 years.
Primary Outcomes	Phase I: Percentage of Participants with Adverse Events [Time Frame: From Baseline until up to 90 days after last dose (up to 36 weeks overall)] Phase II: Percentage of Participants with Complete Response (CR) According to Modified Lugano Criteria as Measured by Positron Emission Tomography (PET) Scan and Determined by Independent Review Committee (IRC) [Time Frame: 6 to 8 weeks after Cycle 6 Day 1 (cycle length 21 or 28 days) or last dose of study drug (up to 28 weeks overall)
Secondary Outcomes	Efficacy, pharmacokinetics and safety
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion July 2021

ESTIMATED COST

The cost of polatuzumab vedotin is not yet known.

The NHS indicative price of 2 vials of rituximab (10mg/ml) at 100m/10ml concentrate costs £349,25.[33]

The NHS indicative price of a bendamustine 25mg vial costs £6.85.[34]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for treatment relapsed or refractory diffuse large B-cell lymphoma [ID986] (GID-TA10140). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma ID1166 (GID-TA10269). Expected publication date: 23 January 2019.
- NICE technology appraisal in development. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115] (GID-TA10214). Expected publication date: 19 December 2018.
- NICE quality standard. Haematological cancers (QS150). June 2017.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- Chaganti S, Illidge T, Barrington S, Mckay P, Linton K, Cwynarski K et al. Guidelines for the management of diffuse large B-cell lymphoma. 2016.[19]
- Vitolo U, Seymour JF, Martelli M, Illerhaus G, Illidge T, Zucca E et al. Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[35]
- 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. 2015.[36]

REFERENCES

1 Dornan D, Bennett F, Chen Y, Dennis M, Eaton D, Elkins K, et al. Therapeutic potential of an anti-CD79b antibody–drug conjugate, anti–CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. *Blood*. 2009;114(13):2721-9. Available from: https://doi.org/10.1182/blood-2009-02-205500

2 European Medicines Agency. *Polatuzumab vedotin for the treatment of diffuse large B-cell lymphoma*. 2018. Available from: https://www.ema.europa.eu/medicines/human/orphan-designations/eu3182013#about-section [Accessed 2 October 2018]

3 ClinicalTrials.gov. *A Study of Polatuzumab Vedotin (DCDS4501A) in Combination With Rituximab or Obinutuzumab Plus Bendamustine in Participants With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma*. 2018. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02257567 [Accessed 2 October 2018]

4 European Medicines Agency. *Recommendations on eligibility to PRIME scheme*. 2017. Available from: https://www.ema.europa.eu/documents/chmp-annex/recommendations-eligibility-prime-scheme-adopted-chmp-meeting-19-22-june-2017_en.pdf [Accessed 5 October 2018]

5 Hoffmann-La Roche Ltd. *Media Release*. 2017. Available from: https://www.roche.com/media/releases/med-cor-2017-12-10.htm [Accessed 2 October 2018]

6 ClinicalTrials.gov. *A Study Evaluating Safety and Efficacy of Obinutuzumab, Polatuzumab Vedotin (Pola), and Atezolizumab (Atezo) in Participants With Relapsed or Refractory Follicular Lymphoma (FL) and Rituximab, Atezo, and Pola in Participants With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02729896 [Accessed 5 October 2018]

7 ClinicalTrials.gov. *A Study of Polatuzumab Vedotin in Combination With Rituximab or Obinutuzumab, Cyclophosphamide, Doxorubicin, and Prednisone in Participants With B-Cell Non-Hodgkin's Lymphoma*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01992653 [Accessed 5 October 2018]

8 ClinicalTrials.gov. *A Phase Ib/II Study Investigating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Mosunetuzumab (BTCT4465A) in Combination With CHOP or CHP-Polatuzumab Vedotin in Participants With B-Cell Non-Hodgkin Lymphoma*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03677141 [Accessed 5 October 2018]

9 ClinicalTrials.gov. *A Study of Pinatuzumab Vedotin (DCDT2980S) Combined With Rituximab or Polatuzumab Vedotin (DCDS4501A) Combined With Rituximab or Obinutuzumab in Participants With Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma (NHL) (ROMULUS)*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01691898 [Accessed 5 October 2018]

10 ClinicalTrials.gov. *A Study of Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory Follicular Lymphoma (FL) and Rituximab in Combination With Polatuzumab Vedotin and Lenalidomide in Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02600897 [Accessed 29 October 2018]

11 ClinicalTrials.gov. *A Study of Obinutuzumab, Rituximab, Polatuzumab Vedotin, and Venetoclax in Relapsed or Refractory Follicular Lymphoma (FL) or Diffuse Large B-Cell Lymphoma (DLBCL)*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02611323 [Accessed 29 October 2018]

12 ClinicalTrials.gov. *A Study Comparing the Efficacy and Safety of Polatuzumab Vedotin With Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone (R-CHP) Versus Rituximab-Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Participants With Diffuse Large B-Cell Lymphoma (POLARIX)*. 2018. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03274492 [Accessed 29 October 2018]

13 EMC. *Mabthera 100mg Concentrate for Solution for Infusion: 4.1 Therapeutic indications*. 2018. Available from: https://www.medicines.org.uk/emc/product/3801/smpc#INDICATIONS [Accessed 10 October 2018]

14 EMC. *Bendamustine hydrochloride 2.5mg/ml Powder: 4.1 Therapeutic indications*. 2018. Available from: https://www.medicines.org.uk/emc/product/7302/smpc#INDICATIONS [Accessed 10 October 2018]

15 Cancer Research UK. *Non-Hodgkin lymphoma* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/high-grade [Accessed 2 October 2018]

16 Lymphoma action. *Diffuse large B-cell lymphoma*. 2018. Available from: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma [Accessed 2 October 2018]

17 Lymphoma action. *What happens if lymphoma relapses?* 2018. Available from: https://lymphoma-action.org.uk/about-lymphoma-living-lymphoma/what-happens-if-lymphoma-relapses [Accessed 2 October 2018]
18 Office for National Statistics. *Cancer registration statistics, England*. 2018. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 2 October 2018]
19 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. Available from: https://doi.org/10.1111/bjh.14136
20 Vaidya R, Witzig TE. Prognostic factors for diffuse large B-cell lymphoma in the R (X) CHOP era. *Annals of oncology*. 2014;25(11):2124-33. Available from: https://doi.org/10.1093/annonc/mdu109
21 Office for National Statistics. *Cancer survival in England - adults diagnosed*. 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 2 October 2018]
22 Gisselbrecht C, Glass B, Mounier N, Gill DS, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *Journal of Clinical Oncology*. 2010;28(27):4184. Available from: http://doi.org/10.1200/JCO.2010.28.1618
23 Thieblemont C, Coiffier B. Lymphoma in older patients. *Journal of Clinical Oncology*. 2007;25(14):1916-23. Available from: http://doi.org/10.1200/JCO.2006.10.5957
24 Vardhana SA, Sauter CS, Matasar MJ, Zelenetz AD, Galasso N, Woo KM, et al. Outcomes of primary refractory diffuse large B-cell lymphoma (DLBCL) treated with salvage chemotherapy and intention to transplant in the rituximab era. *British journal of haematology*. 2017;176(4):591-9. Available from: http://doi.org/10.1111/bjh.14453
25 NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17*. 2017. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2016-17 [Accessed 2 October 2018]
26 Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New England Journal of Medicine*. 2002;346(4):235-42. Available from: http://doi.org/10.1056/NEJMoa011795
27 Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010:blood-2010-03-276246. Available from: http://doi.org/10.1182/blood-2010-03-276246
28 Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23(18):4117-26. Available from: http://doi.org/10.1200/JCO.2005.09.131
29 Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *Journal of Clinical Oncology*. 2006;24(19):3121-7. Available from: http://doi.org/10.1200/JCO.2005.05.1003
30 Pfreundschuh M, Schubert J, Ziepert M, Schmits R, Mohren M, Lengfelder E, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *The Lancet Oncology*. 2008;9(2):105-16. Available from: https://doi.org/10.1016/S1470-2045(08)70002-0

31 NICE. *Non-Hodgkin's lymphoma: diagnosis and management*. 2016. Available from: https://www.nice.org.uk/guidance/NG52/chapter/Recommendations#management-of-diffuse-large-bcell-lymphoma [Accessed 10 October 2018]

32 NICE. *Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B -cell lymphoma*. 2014. Available from: https://www.nice.org.uk/guidance/ta306 [Accessed 2 October 2018]

33 BNF. *Rituximab: Solution for infusion*. 2018. Available from: https://bnf.nice.org.uk/medicinal-forms/rituximab.html [Accessed 8 October 2018]

34 BNF. *Bendamustine Hydrochloride: Powder for solution for infusion*. 2018. Available from: https://bnf.nice.org.uk/medicinal-forms/bendamustine-hydrochloride.html [Accessed 8 October 2018]

35 Vitolo U, Seymour JF, Martelli M, Illerhaus G, Illidge T, Zucca E, et al. Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology*. 2016;27(suppl_5):v91-v102. Available from: https://doi.org/10.1093/annonc/mdw175

36 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*. 2015;26(suppl_5):v116-v25. Available from: https://doi.org/10.1093/annonc/mdv304

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