SPECIALISED COMMISSIONING – RESPONSE TO AMENDMENTS REQUESTED TO EVIDENCE REVIEW DURING ENGAGEMENT OR CONSULTATION

URN	1828
POLICY TITLE	Bendamustine for relapsed/refractory classical Hodgkin lymphoma
CRG:	Chemotherapy
NPOC:	Cancer Programme of Care

Description of comments during consultation	NHS England was asked to consider the findings and relevance to the policy of the following studies: • *Corazzelli G, Angrilli F, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. British Journal of Haematology. 2013; 160: 207–15.* • *Ghesquières H, Stamatoullas A, et al. Clinical experience of bendamustine in relapsed or refractory Hodgkin lymphoma: a retrospective analysis of the French compassionate use program in 28 patients. Leukemia & Lymphoma. 2013; 54: 2399–2404.* • *Moskowitz AJ, Hamlin PA Jr, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2013; 31(4): 456-60.* • *Zinzani P, Vitolo U, et al. Safety and efficacy of single-agent bendamustine after the failure of brentuximab vedotin in patients with relapsed or refractory Hodgkin's lymphoma: experience on 27 patients. Clinical Lymphoma Myeloma and Leukemia. 2015; 15: 404–8.* • *Eyre TA, Phillips EH, et al. Results of a multicentre UK-wide retrospective study*

	evaluating the efficacy of brentuximab vedotin in relapsed, refractory classical Hodgkin lymphoma in the transplant naive setting. Br J Haematol. 2017;179(3):471-479. • *Howell M, Gibb A, et al. Bendamustine can be a bridge to allogeneic transplantation in relapsed Hodgkin lymphoma refractory to brentuximab vedotin. Br J Haematol. 2017;179(5):841-843.* • *LaCasce AS, Bociek RG, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood. 2018; 132(1): 40-48.*
Action taken by Public Health lead	The PPP was reviewed to define the appropriate patient groups relevant for the development of the policy and the intervention. There are two groups of patients with relapsed / refractory classical Hodgkin Lymphoma that need to be considered: • those who have relapsed following autologous stem cell transplant and who have also failed treatment with or are not suitable for brentuximab vedotin; • those who have failed at least 3 lines of prior treatment, which must also include brentuximab vedotin unless not suitable, and who are not suitable for a stem cell transplant. The intervention was treatment with bendamustine. The studies were then reviewed against these criteria. The following studies did not meet these criteria: • *Corazzelli G, Angrilli F, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. British Journal of Haematology. 2013; 160: 207–15.* Did not meet the patient group criteria – prior treatment with brentuximab vedotin not specified.

	• *Ghesquières H, Stamatoullas A, et al. Clinical experience of bendamustine in relapsed or refractory Hodgkin lymphoma: a retrospective analysis of the French compassionate use program in 28 patients. Leukemia & Lymphoma. 2013; 54: 2399–2404.* Did not meet the patient group criteria – prior treatment with brentuximab vedotin not specified. • *Moskowitz AJ, Hamlin PA Jr, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2013; 31(4): 456-60.* Did not meet the patient group criteria – prior treatment with brentuximab vedotin not specified. • *Eyre TA, Phillips EH, et al. Results of a multicentre UK-wide retrospective study evaluating the efficacy of brentuximab vedotin in relapsed, refractory classical Hodgkin lymphoma in the transplant naive setting. Br J Haematol. 2017;179(3):471-479.* Did not meet the intervention criteria – study assessed only brentuximab. • *Howell M, Gibb A, et al. Bendamustine can be a bridge to allogeneic transplantation in relapsed Hodgkin lymphoma refractory to brentuximab vedotin. Br J Haematol. 2017;179(5):841-843.* This study has already been included as it was submitted as part of the PPP. • *LaCasce AS, Bociek RG, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood. 2018; 132(1): 40-48.* Did not meet the intervention criteria – study examined bendamustine in combination with brentuximab.

	The following study met the criteria: • Zinzani P, Vitolo U, et al. Safety and efficacy of single-agent bendamustine after the failure of brentuximab vedotin in patients with relapsed or refractory Hodgkin's lymphoma: experience on 27 patients. *Clinical Lymphoma Myeloma and Leukemia*. 2015; 15: 404–8. **ABSTRACT** Background: The optimal treatment of patients with heavily pretreated Hodgkin's lymphoma is controversial. Brentuximab vedotin is an active single agent in this context. Also, bendamustine can be regarded as a safe and effective alternative for patients with relapse after autologous transplantation and as an interesting cytoreductive strategy before allogeneic transplantation. Patients and methods: An observational, multicenter, retrospective study is reported of single-agent bendamustine in 27 heavily pretreated patients with relapsed or refractory Hodgkin's lymphoma, who had all received brentuximab vedotin as their last treatment and who showed disease progression, refractory disease, or early relapse. The primary study endpoint was the objective response rate, and the secondary endpoint was the safety of the bendamustine regimen. Results: The overall response rate was 55.5%, with 10 of 27 patients (37.0%) obtaining a complete response. In comparison, the overall response rate previously observed with brentuximab vedotin in the same subset of patients was much lower (18.5%). Among the 10 patients with a complete response after bendamustine, only 1 had had a complete response to brentuximab, with 2 having a partial response and 7 stable or progressive disease. With a median duration of response of 8 months, all these patients had maintained a continuous response at the last follow-up examination. The treatment was well tolerated, with rather infrequent adverse events and transient and manageable toxicities.

	Conclusion: Albeit with the limits of an observational retrospective study, these data indicate that bendamustine shows its efficacy in patients already treated with brentuximab vedotin, regardless of their previously obtained response and without any significant toxicity. This is a small retrospective study. All patients received bendamustine and there is no comparator. It is therefore only weak evidence of clinical effectiveness.
Outcome	Low grade evidence identified by stakeholders that does not materially affect the conclusions of the existing evidence reviews