Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed indolent lymphomas (OW08)

December 2022

ONE WALES INTERIM DECISION

Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed indolent lymphomas

Date of original advice: Monday 27 March 2017
Date of review: December 2022

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Bendamustine in combination with rituximab can continue to be made available within NHS Wales for the treatment of previously untreated and relapsed follicular lymphoma, marginal zone lymphoma and Waldenstrom's macroglobulinaemia under the following circumstances:

- In the first-line setting, for use in fit patients with aggressive follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.

- In the relapsed setting, for use in patients with follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.

- For the treatment of Waldenstrom's macroglobulinaemia for first-line and relapsed disease in patients deemed unsuitable for anthracycline-based regimens and/or where other licensed and health technology appraisal-approved regimens are unsuitable.

The risks and benefits of the off-label use of bendamustine plus rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice assists consistency of access across NHS Wales.

This is a summary of new evidence available and patient outcome data collected, to inform the review.

Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed indolent lymphomas

This report was prepared by the All Wales Therapeutics and Toxicology Centre in September 2022. It summarises any new evidence available and patient outcome data collected since the last review in September 2021.

Background: Bendamustine with rituximab is available in NHS England through clinical commissioning for the first-line treatment of advanced, indolent non-Hodgkin's lymphoma. Bendamustine is available through NHS England's Cancer Drugs Fund for use in relapsed low-grade lymphoma, in people for whom standard treatment is unsuitable. According to the NHS England Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication.

A cohort of patients identified through data from individual patient funding request panels, and clinicians in Wales, have confirmed there to be an unmet need within the service. This cohort includes: young and fit people with aggressive, untreated and relapsed follicular lymphoma and marginal zone lymphoma, and Waldenström's macroglobulinaemia for whom standard therapy is unsuitable. Based on this unmet need, this medicine combination was considered suitable for assessment via the One Wales process. Clinical experts consulted for this review supported the ongoing need for the option for use in NHS Wales for this cohort of patients.

Current One Wales Decision: Supported with restrictions.

Licence status: Off-label use for this licensed medicine combination.

Guidelines: British Society of Haematology (BSH) (2022) guidelines for the diagnosis and management of patients with Waldenström macroglobulinemia. For patients without hyperviscosity and who are not considered frail, bendamustine plus rituximab is recommended as a treatment option for patients with marrow infiltration, lymphoma related symptoms or peripheral neuropathy; bulky disease, cryoglobulinaemia or another indication for rapid disease reduction; Bing Neel Syndrome alongside intrathecal chemotherapy; amyloid disease.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: In August 2022, tisagenlecleucel (Kymriah®) was licensed for the treatment of adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy with an orphan drug designation. This medicine is an advanced therapy medicinal product (ATMP). NICE is currently appraising tisagenlecleucel (Kymriah®) within its marketing authorisation for treating follicular lymphoma after two or more therapies, expected July 2023 (NICE ID3950).

In July 2022, axicabtagene ciloleucel (Yescarta®) was licensed for the treatment of adult patients with relapsed or refractory follicular lymphoma after three or more lines of systemic therapy. This medicine is an ATMP. NICE is currently appraising axicabtagene ciloleucel (Yescarta®) within its marketing authorisation for treating relapsed or refractory low-grade non-Hodgkin's lymphoma, expected November 2022 (NICE ID1685).

NICE TA833: Zanabrutinib is recommended as an option for treating Waldenström's macroglobulinaemia in adults who have had at least one treatment, only if bendamustine plus rituximab is also suitable, October 2022.

NICE TA795: Ibrutinib is not recommended, within its marketing authorisation, for treating Waldenström's macroglobulinaemia in adults who have had at least one previous therapy, June 2022.

Effectiveness: A systematic literature search identified one network meta-analysis (NMA) examining follicular lymphoma (FL), and three retrospective studies that included patients with marginal zone lymphoma (MZL) or FL (See Appendix 1). The authors of the NMA acknowledged the heterogeneity in design and reporting of the included randomised controlled trials (RCTs); they used sensitivity analyses to account for some of these differences and notable changes were not found. Additionally, most direct comparisons within the NMA were informed by a single RCT, included data was at study level, some RCT data (from subgroup or post hoc analysis) were not adequately powered and only one outcome (progression free survival [PFS]) could be explored. The study found that for treatment-naïve advanced FL, obinutuzumab-bendamustine-obinutuzumab (G-Benda-G) had the highest efficacy as measured by PFS. In addition, bendamustine was superior to cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) as a chemotherapy backbone, and rituximab maintenance following bendamustine plus rituximab improved PFS. One of the retrospective studies, examining bendamustine plus rituximab's activity in extranodal MZL, featured in last year's review as a conference abstract (Alderuccio et al. 2022). The updated study was an improvement on earlier results with most patients achieving complete or partial remission and enhanced five-year PFS and overall survival.

Safety: No new safety concerns or other relevant safety analyses were identified in the repeat literature search.

Cost-effectiveness: No relevant cost-effectiveness analyses have been identified.

Budget impact: No information on patient numbers has been provided.

Impact on health and social care services: Minimal.

Patient outcome data: No patient outcome data have been received.

Evaluation of evidence

The clinical evidence presented supports the current use of bendamustine with rituximab as a treatment option in line with the current One Wales advice. Bendamustine in combination with rituximab for the treatment of indolent lymphomas should only be used in circumstances where other licensed and health technology appraisal-approved regimens are unsuitable.

Next review date: 12 months

References: A full reference list is available on request.

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

Information presented in this document can be reproduced using the following citation: One Wales Interim Decision. Bendamustine in combination with rituximab for the treatment of indolent lymphomas (OW08). December 2022.

Appendix 1

Reference	Study details	Main results
Wang et al. 2022	NMA: of front-line regimens for FL. Identified seven RCTs employing 11 regimens, three of which utilised the bendamustine plus rituximab regimen under review (Stil NHL1, BRIGHT, Stil NHL7 [MAINTAIN]). All three have been considered either for the original ESR, or for subsequent reviews.	Three regimens were superior to bendamustine plus rituximab for PFS (G-Benda-G, R-Benda-R4, and R-Benda-R) while R-CHOP (HR 1.46; 95% CI: 1.12 – 1.87), R-CVP-R (HR 1.49; 95% CI: 1.00 – 2.34) and R-CVP (HR 1.73; 95% CI: 1.20 – 2.40) were inferior. R-CHOP-R (HR 0.96; 95% CI: 0.70 – 1.41) and R-Len-R (HR 0.97; 95% CI: 0.56 – 1.73) had very similar efficacy to bendamustine plus rituximab.
Clinical studies/Retrospective studies		
Alderuccio et al.2022 Alderuccio et al. 2020	Retrospective analysis Extranodal MZL (n = 237) Median six cycles (range 1 – 8); 20.3% received RM	The ORR was 93.2%, CR rate was 81% and PR rate was 12.2%, with no change from last year's results. Estimated five-year PFS was 80.5% (95% CI: 73.1 – 86) and OS was 89.6% (95% CI: 83.1 – 93.6), an improvement on last year's results.
Gogia et al. 2021	Retrospective analysis Treatment naïve FL (n = 51) Six cycles received by 88%; 29.4% received RM	The ORR was 88.23% and the CR rate was 64.7%. Nine deaths were recorded due to chemotoxicity (n = 1), disease (n = 6) and other causes (n = 2). Most reported toxicities were neutropenia (grade 3-4) (15.7%), skin rash (all grades) (33.7%) and infections (all grades) (15.7%).
Karadurmus et al. 2022	Retrospective analysis FL (n = 10); MZL (n = 9) Bendamustine 90 mg/m^2 received by 80% and 100 mg/m^2 received by 20% for FL; all MZL received bendamustine 90 mg/m^2 Median six cycles (range 2 – 9) for FL; median six cycles (range 2 – 8) for MZL	For FL patients, the ORR was 80% (95% CI: 44.4 – 97.5). Two-year PFS was 40% (95% CI: 12.3 – 67) and two-year OS was 76.2% (95% CI: 33.2 – 93.5). For MZL patients, the ORR was 88.9% (95% CI: 51.8 – 99.7). Two-year PFS was 71.4% (95% CI: 25.8 – 92) and two-year OS was 71.4% (95% CI: 25.8 – 92). The most common adverse events across the entire population were lymphopenia (74.7%), anaemia (64.6%) and neutropenia (61.6%).

CI: confidence interval; CR: complete response; ESR: evidence status report; FL: follicular lymphoma; G-Benda-G: obinutuzumab-bendamustine-obinutuzumab maintenance; HR: hazard ratio; MZL: marginal zone lymphoma; NMA: network meta-analysis; ORR: overall response rate; OS: overall survival; PFS: progression free survival; PR: partial response; R-Benda-R: rituximab-bendamustine-rituximab maintenance; R-Benda-R4: rituximab-bendamustine-four years of rituximab maintenance; R-CHOP: rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CHOP-R: rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone-rituximab maintenance; RCT: randomised controlled trial; R-CVP: rituximab-cyclophosphamide, vincristine, prednisolone; R-CVP-R: rituximab-cyclophosphamide, vincristine, prednisolone-rituximab maintenance; R-Len-R: rituximab-lenalidomide-rituximab maintenance; RM: rituximab maintenance