AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

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

July 2019

ONE WALES INTERIM COMMISSIONING DECISION

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

Date of original advice: April 2017
Date of review: July 2019

The following Interim Pathways Commissioning Group (IPCG) 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.

Bendamustine in combination with rituximab is not a licensed regimen to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

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

Providers should consult the General Medical Council 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 Interim Commissioning decision.

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

One Wales advice promotes consistency of access across NHS Wales.

One Wales Interim Commissioning Process
Interim Pathways Commissioning Group (IPCG) summary of decision rationale

Medicine: **bendamustine in combination with rituximab**
Indication: **treatment of previously untreated and relapsed indolent lymphomas**
Meeting date: **29 May 2019**

Criteria	IPCG opinion
Final recommendation	IPCG recommends that the current One Wales decision should remain unchanged.
Summary of rationale	IPCG are content that there is no new significant information or evidence to warrant a full reassessment of bendamustine in combination with rituximab.

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

Background
Bendamustine with rituximab is available in NHS England through clinical commissioning for the first-line treatment of advanced, indolent non-Hodgkin's lymphoma[1]. 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[2]. 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[2].

A cohort of patients had been identified through data from individual patient funding request (IPFR) panels and clinicians in Wales considered 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 Waldenstrom'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.

Current One Wales Interim Commissioning Decision
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 (May 2018):

- 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.

Licence status
Bendamustine in combination with rituximab for the treatment of follicular lymphoma, marginal zone lymphoma and Waldenstrom's macroglobulinaemia is off-label.

Guidelines
The revised European Society for Medical Oncology (ESMO) clinical guidelines for diagnosis, treatment and follow-up of Waldenstrom's macroglobulinaemia recommend bendamustine plus rituximab as a first-line treatment option, and as a treatment option for late relapsed disease[3].

The ESMO consensus recommendations for the clinical management of elderly patients with malignant lymphoma were published in 2018[4]. Bendamustine plus rituximab is recommended as a first-line treatment option for follicular lymphoma[4].

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
There are no relevant new medicines or health technology appraisal advice.

Efficacy/Effectiveness
Five-year follow-up data of the BRIGHT study has been published as a report[5]. The associated conference abstract was described in the 2018 One Wales review report. Bendamustine plus rituximab demonstrated better long-term disease control than rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or rituximab plus cyclophosphamide, vincristine and prednisone (R-CVP) in patients with treatment-naïve non-Hodgkin's lymphoma or mantle cell lymphoma, as previously reported[5].

Three retrospective studies evaluating the efficacy of bendamustine plus rituximab in patients with treatment-naïve and/or relapsed/refractory Waldenstrom's macroglobulinemia have been published as articles and correspondence[6-8]. The associated conference abstracts were briefly described in

the 2018 One Wales review report. Two of the studies compared bendamustine plus rituximab to commonly used regimens for the treatment of Waldenstrom's macroglobulinemia (cyclophosphamide, dexamethasone and rituximab [CDR] and/or bortezomib, dexamethasone and rituximab [BDR])[6,7]. The third study was single arm[8]. Results were comparable across the studies, as shown in Table 1[6-8].

Table 1. Results from the retrospective studies[6-8]

	First-line						Relapsed/refractory	
	Castillo et al.			Paludo et al.		Laribi et al.	Paludo et al.	
Overall population	**BR (n = 57)**	**BDR (n = 87)**	**CDR (n = 38)**	**BR (n = 16)**	**CDR (n = 50)**	**BR (n = 69)**	**BR (n = 44)**	**CDR (n = 50)**
Median PFS (months) 95% CI	66	70	59	NR	34	87%*	58	31
	59–NR	53–89	34–84	NR–NR	23–NR	74–94	23–NR	15–50
	p = 0.1†			p = 0.07		NA	-	
OS (%) 95% CI	95§	96§	81§	-		97.1¶	-	
	81–99	85–99	60–92			81–99		
ORR (%)** p value	97	86	90	93	96	97	95	87
	-			p = 0.55		NA	p = 0.45	
MRR (%)†† p value	93	79	84	86	87	96	81	68
	-			p = 1.0		NA	p = 0.21	

BDR: bortezomib, dexamethasone and rituximab; BR: bendamustine plus rituximab; CDR: cyclophosphamide, dexamethasone and rituximab; CI: confidence interval; MRR: major response rate; NA: not applicable; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.
* PFS probability at two years
† Log rank p = 0.1 for BR versus BDR and for BR versus CDR
§ Estimated 5-year OS rate
¶ OS probability at two years
** minor response or better
†† partial response or better

An open-label, single-arm phase II study evaluating the efficacy of bendamustine plus rituximab for the first-line treatment of splenic marginal zone lymphoma has been published[9]. The overall response and complete response rates were 91% and 73%, respectively. Duration of response, progression-free survival and overall survival at three years were 93% (95% confidence interval [CI] 81 to 98), 90% (95% CI 77 to 96) and 96% (95% CI 84 to 98), respectively[9].

Safety
Safety results were published for the BRIGHT five-year follow-up study[5]. A statistically significantly (p = 0.022) higher incidence of secondary malignancy was observed in the bendamustine plus rituximab group compared with the R-CHOP/R-CVP group, most notably in the incidence of squamous and basal cell carcinomas of the skin. Other safety signals were in line with those previously reported[5].

Cost effectiveness
No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact
[Confidential data removed.]

Impact on health and social care services
The impact on the service remains minimal.

Patient outcome data
[Confidential data removed.]

References

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2. NHS England. National Cancer Drugs Fund list - version 1.133. Apr 2019. Available at: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Accessed Apr 2019.
3. Kastritis E, Leblond V, Dimopoulos M et al. Waldenstrom's macroglobulinaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2018;29(Suppl 4):iv41-iv50.
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5. Flinn I, van der Jagt R, Kahl B et al. First-line treatment of patients with indolent non-hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: results of the BRIGHT 5-year follow-up study. *Journal of Clinical Oncology.* 2019;37(12):984-991.
6. Castillo J, Gustine J, Meid K et al. Response and survival for primary therapy combination regimens and maintenance rituximab in Waldenstrom macroglobulinaemia. *British Journal of Haematology.* 2018;181(1):77-85.
7. Paludo J, Abeykoon J, Shreders A et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenstrom macroglobulinemia. *Annals of Haematology.* 2018;97(8):1417-1425.
8. Laribi K, Poulain S, Willems L et al. Bendamustine plus rituximab in newly-diagnosed Waldenstrom macroglobulinaemia patients. A study on behalf of the French Innovative Leukaemia Organization (FILO) [letter]. *British Journal of Haematology.* 2018. Available at: https://doi.org/10.1111/bjh.15718. Accessed Apr 2019.
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