CPAG Summary Report for Clinical Panel – URN: 1607 Bendamustine with Rituximab for relapsed low-grade Non-Hodgkin's Lymphoma (NHL)

The Benefits of the Proposition (Grade of Evidence to be left blank)			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Choose an item.	Overall survival (OS) was not defined in the paper by Rummel et al 2016; however it is usually defined as the time from random assignment until death as a result of any cause (Cheson et al 2007). At median 96 months follow-up, patients with low-grade relapsed and/or refractory NHL treated with bendamustine plus rituximab (B-R) had longer median OS than those receiving fludarabine plus rituximab (109.7 months [95% CI 50.2 to not reached] vs 49.1 months [36.2 to 59.0], HR 0.64 (95% CI 0.45 to 0.91), p=0.012). There were 55 deaths in the B-R group and 71 deaths in the fludarabine plus rituximab (F-R) group, out of 230 patients recruited to the study. The results suggest that patients with low-grade relapsed and/or refractory NHL treated with B-R have a significantly longer median OS compared to those who treated with F-R. These results need to be interpreted with caution due to methodological uncertainty and bias as well as a number of confounders. Study bias included the fact that this was an open-label study; patients, physicians, and individuals assessing outcomes and analysing data were not masked to treatment allocation. The outcomes were investigator-assessed and evaluations were completed locally at participating centres and were not centrally reviewed. In addition, it is not clear to what extent the inclusion of 27 patients who were not bendamustine naïve, as well as the inclusion of 44 patients who also received rituximab as maintenance therapy may have affected the comparative outcomes and the effect size. These results are not generalisable to the use of B-R compared to any other comparator treatment.
2.	Progression	Choose an item.	Progression free survival (PFS) was defined

	free survival		by Rummel et al 2016 as the time between first treatment and one of the following events: progressive disease, relapse after response, or death from any cause. At 96 months median follow up, the median PFS for patients with low-grade relapsed and/or refractory NHL treated with bendamustine plus rituximab (B-R) was 34.2 months (95% CI 23.5 to 52.7) vs. 11.7 months (8.0 to 16.1) in the fludarabine with rituximab (F-R) group (HR 0.54 [95% CI 0.38 to 0.72], p<0.0001). At one-year, the disease had not progressed in 76% of patients in the B-R arm and 48% of those in the F-R arm (B-R vs F-R: 0.76 (95% CI 0.68 to 0.84) vs 0.48 (0.39 to 0.58), non-inferiority[1] p<0.0001). The results suggest that B-R was at least as effective as F-R in improving PFS in patients with relapsed low-grade NHL who are refractory to treatment at one year but more effective than F-R at 96 months follow-up in these patients. It appears that patients with low-grade FL who also received rituximab maintenance therapy have a longer PFS than those who did not and this happened irrespective of whether they were treated with B-R or F-R. These results need to be interpreted with caution due to methodological uncertainty and bias as well as a number of confounders. Study bias included the fact that this was an open-label study where patients, physicians, and individuals assessing outcomes and analysing data were not masked to treatment allocation. The outcomes were investigator-assessed and evaluations were completed locally at participating centres and were not centrally reviewed. In addition, it is not clear to what extent the inclusion of 27 patients who were not bendamustine naïve, as well as the inclusion of 44 patients who also received rituximab as maintenance therapy may have affected the comparative outcomes and the effect size. These results are not generalisable to the use of B-R compared to any other comparator treatment.
3.	Mobility	Choose an item.	
4.	Self-care	Choose an item.	
5.	Usual	Choose an item.	

[1] Non-inferiority trials test whether a new experimental treatment (B-R in this case) is not unacceptably less efficacious than an active control treatment (F-R) already in use.

	activities		
6.	Pain	Choose an item.	
7.	Anxiety / Depression	Choose an item.	
8.	Replacement of more toxic treatment	Choose an item.	
9.	Dependency on care giver / supporting independence	Choose an item.	
10.	Safety	Choose an item.	
11.	Delivery of intervention	Choose an item.	

Other health outcome measures determined by the evidence review (Grade of Evidence to be left blank)			
No	Outcome measure	*Grade of evidence*	Summary from evidence review
1.	Overall response	Choose an item.	Overall response (OR) refers to patients who respond to treatment. The criteria for meeting this outcome were not defined by Rummel et al 2016. There was a superior OR rate in patients treated with B-R compared with those treated with F-R: 82% vs 51%, p<0.0001. The results suggest that patients with low-grade relapsed and/or refractory NHL treated with B-R had a better OR rate than those treated with F-R. It is difficult to interpret these results because the outcome was not defined and was subject to inter-assessor differences and individual interpretation. This is particularly noteworthy as the evaluations were carried out locally (55 centres) rather than centrally. It is not clear to what extent the inclusion of 27 patients who were not bendamustine naïve, as well as the inclusion of 44 patients who also received rituximab as maintenance therapy may have affected the comparative outcomes and the effect size. These results are not generalisable to the use of B-R compared to any other

			comparator treatment.
2.	Complete response	Choose an item.	Complete response (CR) was not defined by Rummel et al 2016. However a patient with lymphoma is usually considered to have complete response when there is complete disappearance of all measurable and non-measurable disease (Cheson et al 2007). There was a superior CR rate in patients with low-grade relapsed and/or refractory NHL treated with B-R compared with those treated with F-R: 40% vs 17%, p=0.0002. The results suggest that more patients with low-grade relapsed and/or refractory NHL had CR with B-R therapy than F-R therapy. However it is unknown how B-R compares with current standard treatments such as fludarabine, cyclophosphamide and rituximab (FCR). It is difficult to interpret these results because the outcome was not defined and was subject to inter-assessor differences and individual interpretation. This is particularly noteworthy as the evaluations were carried out locally (55 centres) rather than centrally. It is not clear to what extent the inclusion of 27 patients who were not bendamustine naïve, as well as the inclusion of 44 patients who also received rituximab as maintenance therapy may have affected the comparative outcomes and the effect size. These results are not generalisable to the use of B-R compared to any other comparator treatment.
3.	Partial response	Choose an item.	Partial response (PR) was not defined by Rummel et al 2016. However, a patient with lymphoma is usually considered to have partial response when there is at least one lesion that does not qualify for a CR and/or measurable disease ≥ 50% decrease in the sum of the product of the diameters of up to six dominant lesions identified at baseline (Cheson et al 2007) There was no difference in the PR rate between patients with low-grade relapsed and/or refractory NHL treated with B-R or F-R: 42% vs 34%, p=0.2345. The results suggest no difference in PR between B-R and F-R therapy in patients with low-grade relapsed and/or refractory NHL.

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4.	Stable disease	Choose an item.	Stable disease (SD) was not defined by Rummel et al 2016. However a patient with lymphoma is usually considered to have SD when he or she fails to attain the criteria needed for a complete remission or partial response, but does not fulfil those for progressive disease (Cheson et al 2007). Fewer patients in the B-R group had SD than in the F-R group: 7 (6%) vs 16 (15%), p=0.0282. The study suggests that F-R therapy in patients with low-grade relapsed and/or refractory NHL is associated with a higher rate of disease stability compared to B-R therapy. It is difficult to interpret these results because the outcome was not defined and was subject to inter-assessor differences and individual interpretation. This is particularly noteworthy as the evaluations were carried out locally (55 centres) rather than centrally. It is not clear to what extent the inclusion of 27 patients who were not bendamustine naïve, as well as the inclusion of 44 patients who also received rituximab as maintenance therapy may have affected the comparative outcomes and the effect size. It is unknown how disease stability with B-R compares with that of standard treatments such as fludarabine, cyclophosphamide and rituximab (FCR).
5.	Progressive disease		Progressive disease (PD) was not defined by Rummel et al 2016. However a patient with lymphoma is usually considered to

			have PD when there is presence of a new lesion or increase by 50% or more of previously involved sites from nadir (Cheson et al 2007). Fewer patients with low-grade relapsed and/or refractory NHL in the B-R group had PD than in the F-R group: 8(7%) vs 30(29%), p<0.0001. The study suggests more patients with low-grade relapsed and/or refractory NHL are likely to experience disease progression if they are treated with F-R compared to B-R. However, how this compares with other standard treatments such as fludarabine, cyclophosphamide and rituximab (FCR) is unknown. It is difficult to interpret these results because the outcome was not defined and was subject to inter-assessor differences and individual interpretation. This is particularly noteworthy as the evaluations were carried out locally (55 centres) rather than centrally. It is not clear to what extent the inclusion of 27 patients who were not bendamustine naïve, as well as the inclusion of 44 patients who also received rituximab as maintenance therapy may have affected the comparative outcomes and the effect size.
	Adverse events		Adverse events (AE) were not specifically defined by Rummel et al 2016. However the WHO defines an AE as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention, in this case bendamustine and rituximab. There were no significant differences in the occurrence of adverse events between the study groups. The overall incidence of serious adverse events was similar for both treatment groups, with 23 events in the B-R group and 23 events in the F-R group. The most common adverse events were infections (B-R vs F-R: 11 vs 8) and myelosuppression (B-R vs F-R: 3 vs 2). The results suggest that the adverse effect profile in the two treatment arms is similar. The results need to be interpreted with caution as no clear description of the numbers reported or p-values were provided. It is not clear to what extent the

			inclusion of 27 patients who were not bendamustine naïve, as well as the inclusion of 44 patients who also received rituximab as maintenance therapy may have affected safety outcomes. It remains unclear how B-R compares with other standard therapies such as fludarabine, cyclophosphamide and rituximab (FCR) in terms of adverse effects.