NHS England

Evidence review:

Intervention: Bendamustine- Rituximab (BR)

Indication: First line treatment of advanced indolent/low grade Non-Hodgkin's Lymphoma (NHL)

Contents

1. Introduction

The technology Bendamustine (Levact, Napp Pharmaceuticals) is an alkylating antitumour agent. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. It is administered by intravenous infusion.

Low grade, indolent or slow-growing non-Hodgkin's Lymphoma (NHL) includes the following lymphomas: follicular, lymphoplasmacytic, small lymphocytic and marginal zone (gastric MALT, non-gastric MALT, splenic, nodal). These comprise 40% of NHL cases. mantle cell (aggressive nature) and chronic lymphocytic leukaemia (CLL) will be excluded from this list. The incidence of NHL in the UK was 13,413 cases (2013). Deaths were 4801. Age-specific incidence is seen to rise from 50-54 years. Median age at diagnosis is 70+ years. 5 year survival trends for both men and women have doubled since the mid 70's to two thirds, 10 year survival has increased 3 fold.

The most commonly used first-line treatment for symptomatic, advanced indolent NHL is rituximab plus combination chemotherapy, for example R-CVP (cyclophosphamide, vincristine, prednisolone and rituximab) or R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab). Chlorambucil with or without rituximab may be given to people who are unsuitable for R-CHOP/R-CVP regimens.

Rituximab maintenance therapy is often used following a response to induction therapy.

The optimal first-line treatment for advanced low grade NHL is still being debated. Bendamustine has become an important agent for the treatment of patients with lymphoid malignancies. Standard therapies eg R-CHOP and R-CVP are associated with peripheral neuropathy/paraesthesias, cardiac toxicities, myelosuppression and alopecia.

NICE has recently published guidance on Non-Hodgkin's lymphoma which inlcudes the following advice on follicular lymphoma https://www.nice.org.uk/guidance/ng52

Treating advanced-stage symptomatic follicular lymphoma

1.3.5 Rituximab, in combination with:

- *cyclophosphamide, vincristine and prednisolone (CVP)*
- *cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)*
- *mitoxantrone, chlorambucil and prednisolone (MCP)*
- *cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi)* ***or***
- *chlorambucil*

  is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people. [This recommendation is from rituximab for the first-line treatment of stage III–IV follicular lymphoma (NICE technology appraisal guidance 243).]

1.3.6 Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy. [This recommendation is

from rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma (NICE technology appraisal guidance 226).]

The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma, because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first-line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently suspended.

Bendamustine is a cytotoxic which is administered by intravenous infusion over 30 to 60 minutes on day 1 and day 2 of a 28 day cycle. The dose of rituximab used in R-Bendamustine is the same as that employed in R-CHOP and R-CVP.

R-Bendamustine treatment has been used by many haematologists in the first line setting (via CDF funding). The CDF received 689 applications for 1st line R-bendamustine for low grade lymphoma from M1-M10 inclusive in 2015/16, which correlates with about 827 patients per year.

Bendamustine is licensed for this in this indication in Switzerland and Australia. It is not licensed in UK for other conditions.

Research questions posed

- To evaluate the efficacy, safety, QOL and cost-effectiveness (all 4 parameters) of BR compared with the standard R-CHOP and R-CVP regimens for patients with treatment naïve indolent NHL
- To assess whether the treatment effect of BR is consistent across all the histological sub-types of indolent NHL
- To assess whether BR has a distinct safety and adverse event profile that is more favourable in comparison to R-CHOP and R-CVP
- To assess the potential of B-R as an alternative treatment regimen for the initial therapy of patients with low grade NHL.

Mantle Cell NHL is not considered in this evaluation.

2. Summary of results

The findings of this review are mainly based on two phase three studies that compared B-R to R-CHOP or R-CVP in patients with indolent NHL.

One of the studies (based on results in 514 patients) showed that B-R treated patients have a significantly longer period of progression free survival; B-R treated patients had a median PFS of 69.5 months compared to 31.2 months for R-CHOP.

The second study (based on results in 447 enrolled patients) showed that the complete response (CR) rate for B-R treatment was non-inferior to R-CHOP/R-CVP; CR was 31% in the B-R treatment group and 25% in the standard therapy group.

There is insufficient data at this time to identify any difference between the treatments in overall survival. Neither study evaluated any differences in the ongoing response to rituximab maintenance therapy. There is insufficient data to make a full assessment of any differences in the quality of life of patients who receive B-R compared to R-CHOP/R-CVP.

Treatment costs are higher with B-R than standard therapy but incremental cost-effectiveness ratios are reasonable; £5249 per QALY and £8092 per QALY compared to R-CHOP and R-CVP respectively.

B-R appears to cause less alopecia and paraesthesia than the standard treatment but is more likely to cause allergic reactions and skin rashes.

3. Methodology

1. Scoping. A PICO was prepared by the Clinical and Public Health Leads for this policy area at NHS England (see section 10 below).
2. Appraisal. The following databases/sites were searched for relevant publications: NHS Evidence, The Cochrane Library, EMBASE, MEDLINE, National Guideline Clearinghouse (USA), UK National Library for Health guidelines database, the New Zealand Guidelines Group, the Australian National Health & Medical Research Council Guidelines Portal, the UK National Institute for Health and Care Excellence. (see section for search terms)
3. The titles and abstracts of the results from the literature searches were examined using the criteria from the PICO. Full text versions of papers that were deemed to be useful or potentially useful were obtained and a decision made on the appropriateness of including their findings in this review.
4. Generally, where reasonable or good quality phase 3 studies were available, they were used in preference to earlier phase 1 and 2 studies. Three studies on cost-effectiveness were considered but only one was directly relevant to the NHS in England and therefore included. A number of single case reports of adverse effects were also included to pick up on low frequency effects. Data published as conference abstracts were not included.
5. Major, authoritative guidelines were examined and included where relevant. All papers included in this evaluation were assessed as to their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria and for the applicability of the results to the specific questions posed in this review.
6. The evidence to support individual findings was graded.

4. Results

The efficacy of Bendamustine-Rituximab (B-R) compared to R-CHOP or R-CVP.

1. There are two randomised, controlled clinical trials that examine the effectiveness of B-R compared to R-CHOP or R-CVP in patients with indolent non-Hodgkins Lymphoma.
2. The Study Group for Indolent Lymphomas (StiL) study (Rummel 2013) included 274 patients that were assigned to B-R (261 assessed) and 275 to R-CHOP (253 assessed). These figures included 46 and 48 patients in each treatment group respectively with mantle cell Lymphoma. The primary outcome measure was progression free survival (PFS). Patients treated with B-R had a significantly longer median PFS (69.5 months) compared to R-CHOP (31.2 months) ($p<0.0001$). The secondary outcome measures included Overall Response (OR, no difference shown between the treatment groups), Complete Response (CR, significant increase seen for B-R 40% compared to R-CHOP 30% $p=0.021$). There did not appear to be any difference in overall survival (OS) but insufficient time had elapsed to assess this properly at publication.
3. The BRIGHT study (Flinn 2014) included 447 patients of which 224 were randomised to receive B-R and 223 to standard therapy (R-CHOP or R-CVP depending on clinical assessment). These included 36 and 38 patients in each treatment group respectively with mantle cell lymphoma. The primary outcome was CR rate and B-R (31%) demonstrated non-inferiority to standard treatment (25%) ($p=0.0225$ for non-inferiority). The OR rate did not differ significantly between the groups. Other secondary, time to event results (PFS, OS etc based on 5 year minimum follow up specified in protocol) were not sufficiently mature to report at time of publication.
4. A meta-analysis of treatments for newly diagnosed follicular NHL included data from StiL (Messori 2015). Data from BRIGHT was excluded due to the absence of PFS data. This analysis found no difference between B-R and R-CHOP. The most effective treatment reviewed was R-CHOP plus rituximab maintenance.

The Quality of Life (QoL) of Bendamustine-Rituximab (B-R) compared to R-CHOP or R-CVP.

1. The BRIGHT study (Flinn 2014) included an assessment of the impact on quality of life of B-R compared to R-CHOP/R-CVP. These results were published in a separate paper (Burke 2016). B-R treated patients reported a better quality of life in some areas assessed (cognitive, physical, emotional and social functioning) and some symptoms (constipation, dyspnoea and fatigue). Overall, despite reaching statistical significance in some cases, the clinical benefits of the differences were small.
2. A small study (Zimmer 2015) looked at cognitive performance within three months of B-R or R-CHOP induction therapy for patients with treatment naïve B-cell NHL.

Compared to healthy controls, treated patients, particularly those treated with B-R demonstrated a degree of cognitive impairment.

The cost-effectiveness of Bendamustine-Rituximab (B-R) compared to R-CHOP or R-CVP.

1. A cost-utility analysis (Dewilde 2014) used data from StiL (Rummel 2013) as well as other modelling from the Sheffield School of Health and Related Research (ScHARR) to develop a model that included B-R, R-CHOP, R-CVP as first line treatment of indolent NHL and maintenance rituximab for responders. B-R had the highest patient costs but due to better PFS, produced ICERs of £5249 per QALY and £8092 per QALY compared to R-CHOP and R-CVP respectively.

To assess whether the treatment effect of B-R is consistent across all the histological sub-types of indolent NHL

1. Sub-group analysis in the StiL study (Rummel 2013) looked at the PFS in four histological subtypes. The median PFS for B-R treated follicular lymphoma, mantle cell lymphoma and Waldenstrom's macroglobulinaemia were all significantly higher than with R-CHOP. The median PFS for marginal-zone lymphoma was not significantly different.
2. The BRIGHT study (Flinn 2014) showed that CR in patients treated with B-R was non-inferior to R-CHOP/R-CVP based on the whole study population results. In the sub-group analysis of patients with follicular lymphoma, B-R did not reach statistical significance for non-inferiority with R-CHOP/R-CVP (p=0.057). For mantle cell lymphoma B-R was superior to R-CHOP/R-CVP (p=0.018).

The safety of Bendamustine-Rituximab (B-R) compared to R-CHOP or R-CVP.

To assess whether B-R has a distinct safety and adverse event profile that is more favourable in comparison to CHOP-R and R- CVP

1. Both RCTs (Rummel 2013, Flinn 2014) found that the incidence of the following side effects were less frequent with B-R compared to R-CHOP/R-CVP
   - **a.** Peripheral neuropathy/paraesthesia
   - **b.** Alopecia
   - **c.** Stomatitis

Patients treated with B-R were more likely to suffer drug hypersensitivity and skin reactions (erythema or allergic reactions), nausea and vomiting.

A small case series from India (Malipatil 2011) describes a bendamustine associated rash as being erythematous and papular and that it resolves on completion of chemotherapy. In addition there are case reports of more serious rashes including fatal toxic epidermal necrolysis (Fallon 2015) and paraneoplastic pemphigus (Higo 2015).

B-R was associated with less Grade 3-4 leukocytopenia and neutropenia than R-CHOP in the both the StiL and BRIGHT studies ($p<0.0001$ vs r-CHOP). There were no differences in these parameters between B-R and R-CVP. B-R was associated with more grade 3-4 lymphocytopenia than R-CHOP and R-CVP

(p<0.0001) in the BRIGHT study. In both studies the use of colony stimulating factors was higher in patients receiving R-CHOP than B-R or R-CVP.
The incidence of infections was not statistically different between any of the groups in the BRIGHT study but B-R was associated with significantly less infectious episodes than R-CHOP (37% vs 50% p=0.0025) in the StiL study.

Case reports have been published linking B-R therapy with hepatitis B reactivation (Tsutsumi 2012), *Pneumocystis jirovecii* pneumonia (Carter 2011), Epstein Barr virus (Muroi 2015), liver damage/non-allergic bronchitis and eosinophilia (Jo 2014) and progressive multifocal leukoencephalopathy (Warsch 2012). There are insufficient data to ascribe a level of risk to these side effects occurring with B-R compared to other induction regimes.

The incidence of secondary malignancies was similar for B-R (20/274) and R-CHOP (23/275) treated patients in the StiL study. Numbers have not been reported for BRIGHT.

5. Discussion

The evidence provided from the two randomised controlled clinical trials of B-R compared to R-CHOP/R-CVP in treatment naïve indolent NHL is generally supportive of the effectiveness of B-R compared to R-CHOP or R-CVP. The StiL study demonstrated improved progression free survival (PFS) which would have clinical advantages given the size of the difference between the medians of 38 months (at the time of reporting). The BRIGHT study showed that B-R was non-inferior to R-CHOP/R-CVP based on the primary outcome measure of complete response (CR).

Neither RCT however has yet shown any treatment differences in overall survival.

The conclusion that B-R and R-CHOP are equally effective is also supported by the meta-analysis (Messori 2015).

The StiL study was liable to a degree of bias as patients, investigators and assessors were unblinded to which treatment was being used. The BRIGHT study addressed this by using two blinded assessors from an Independent Review Committee (IRC) to assess images and clinical data for the assessment of the primary outcome measure of complete response (CR). There is some evidence from BRIGHT that unblinded assessors may have judged complete response rate to be greater for B-R treated patients than the IRC. This may explain the size of the differences between the CR rates between the two studies.

Table CR Rates from StiL and BRIGHT

Complete Response Rate	B-R	R-CHOP	p
StiL (investigator assessed)	40%	30%	p=0.021 for superiority
BRIGHT (IRC assessed)	31%	25%	p=0.025 for non-inferiority

The other limitations from both studies relate to the non-availability of longer term, time-dependent outcomes (e.g. overall survival) and the fact that neither study included the option of continued maintenance therapy with rituximab (as currently advised as an option by NICE). Hence there are no data on how B-R treated patients respond to rituximab maintenance compared to those treated with R-CHOP/R-CVP.

The cost-utility analysis of B-R compared to R-CHOP and R-CVP indicated favourable ICERs of £5249 per QALY and £8092 per QALY compared to R-CHOP and R-CVP respectively.

There are limited data on differences in quality of life in B-R treated patients. The data is limited to assessments made during the course of induction treatment; the clinical significance of the benefits was small, and the differences between the groups were not statistically significant at all points in time.

The side effect profile of B-R is qualitatively different to that of R-CHOP/R-CVP in some respects. Some individual drug specific side effects seen with CHOP and CVP are less likely with bendamustine. These include alopecia, peripheral neuropathy/paraesthesia and stomatitis. Whilst being associated with less leukopenia and neutropenia than R-CHOP and R-CVP, B-R is associated with more lymphocytopenia.

B-R is associated with a higher incidence of drug hypersensitivity and skin rashes than R-CHOP or R-CVP. A small case series from India (Malipatil 2011) describes a bendamustine associated erythematous and papular rash that resolves on completion of chemotherapy.

Other reports of serious side effects have been published but there are insufficient data to ascertain if they are more or less likely to occur with B-R compared to other regimens.

The European Society for Medical Oncology clinical practice guidelines includes B-R as an alternative to R-CHOP and R-CVP for first line treatment of follicular lymphoma (Dreyling 2014).

NICE has not considered the role bendamustine in its recent guideline on NHL (July 2016).

Bendamustine has approval for use in this indication in Australia (Bendamustine for previously untreated CD-20 positive stage III-IV NHL in combination with rituximab) and Switzerland.

Some areas of uncertainty exist about,

- longer term, time dependent outcomes (for example overall survival)
- possible bias arising from the unblinded assessment of primary outcomes in one of the major RCTs
- how B-R treated patients respond after rituximab maintenance therapy compared to those treated with R-CHOP/R-CVP

There is however evidence that, compared to R-CHOP/R-CVP,

- B-R is non-inferior in its effect on complete response to induction therapy
- B-R has a superior effect on progression free survival
- B-R is reasonably cost-effective
- B-R is relatively safe
- B-R has a different side effect profile particularly for alopecia and peripheral neuropathy

On that basis B-R has potential as an alternative treatment regimen for the initial therapy of patients with low grade NHL.

6. Conclusion

The available data indicate that in patients with treatment naïve indolent NHL, compared to R-CHOP and R-CVP regimes

- B-R is non-inferior in its effect on complete response to induction therapy and has a superior effect on progression free survival
- B-R is reasonably cost-effective and relatively safe with a different side effect profile particularly with reduced risk of alopecia and peripheral neuropathy and increased risk of skin rash

The differences between the two induction regimes in the various histological subtypes are inconsistent between the two main phase three studies.

There is insufficient data to make a full assessment of any differences in the quality of life of patients who receive B-R compared to R-CHOP/R-CVP

B-R has potential as an alternative treatment regimen for the initial therapy of patients with low grade NHL but there are some areas on uncertainty because of the lack of data on longer term, time dependent outcomes (for example overall survival). There is possible bias arising from the unblinded assessment of progression free survival in one of the major RCTs. Neither of the two phase three studies assessed how B-R treated patients respond after rituximab maintenance therapy compared to those treated with R-CHOP/R-CVP.

7. Evidence Summary Table

Use of Bendamustine plus Rituximab versus CHOP plus rituximab to treat indolent and mantle-cell lymphomas									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Rummel et al 2013 StiL NHL1 study	P1- an open-label, multicentre, randomised, controlled, phase 3 non-inferiority trial	Recruitment 2003-08 Sample size, numbers randomised into each arm if applicable, severity of disease, sub groups etc. 274 patients were assigned to bendamustine plus rituximab (261 assessed) and 275 to R-CHOP (253 assessed) Patients aged 18 years or older with a WHO performance status of 2 or less were eligible if they had newly diagnosed previously untreated advanced indolent (stage III or IV disease) or mantle-cell lymphoma. Indolent lymphoma	81 centres in Germany participated. 549 patients enrolled and randomised to BR or R-CHOP. Bendamustine IV 90mg/m^2 over 30-60 minutes on days 1 and 2 of a 4 week cycle for up to six cycles. CHOP three weekly cycles of cyclophosphamide 750mg/m^2, doxorubicin 50mg/m^2, vincristine 1.4mg/m^2 (max 2mg) on day 1 and prednisolone 100mg daily for 5 days for up to 6 cycles. All patients received rituximab 375mg/m^2 on day 1 of each cycle. All patients received standard anti-emetic prophylaxis but no prophylactic antibiotics. G-CSF was allowed according to ASCO guidelines. Treatment could be delayed due to blood results or	Primary Clinical effectiveness	Progression-Free Survival (PFS) defined as the time between first treatment and one of the following events Progressive disease, relapse after response or death from any cause.	Median PFS (Inter-quartile range [IQR] months): B-R 69.5 (26.1-not reached) months R-CHOP 31.2 (15.2-65.7) months Significant benefit for all histological subtypes apart from marginal-zone lymphoma	7	Distribution of cell types in line with expectations. Standard practice now includes routine maintenance with rituximab. Not used in this trial. Single country study (Germany) but no obvious reason why this should affect applicability.	Patients, treating physicians and assessors were not blinded to allocation so there could be a degree of bias in favour of investigational treatment. Note – upper IQR not reached for some parameters - the study will continue to follow these patients over time until they can establish the median overall survival. Median follow-up time was 45 months (IQR 29-57). Full follow up not reported at time of publication. Overall survival data was not published at this time as median was not reached in either group but no clear difference apparent.
				Secondary Clinical effectiveness	Overall Response (OR)	OR did not differ. B-R - 93% R-CHOP – 91%			
				Secondary Clinical effectiveness	Complete Response (CR)	Increased in B-R group B-R – 40% R-CHOP -30% p= 0.021			
				Secondary Safety	Acute and late toxic effects.	Fewer serious adverse events in B-R group (19%) than R-CHOP group (29%). Lower haematological toxicity in B-R Grade 3-4 leucopenia and neutropenia lower in B-R group (p<0.0001). Grade 3-4 lymphocytopenia higher in B-R (74% vs 43%) Reduced use of G-CSF in B-R (4% of cycles) compared to R-CHOP (20% of cycles) p<0.0001. Less alopecia,			

		included CD20 subtypes; Follicular (grade 1 and 2); Lymphoplasmacytic; Small lymphocytic Marginal-zone.	doses reduced. Vincristine could be stopped due to neurological effects. Physical, blood and radiographic tests carried out at pre-treatment. Tumour responses were assessed after cycles 3, 6 or at end of treatment. WHO toxicity criteria used to assess treatment toxic effects. CT/sonography repeated every 3 months for two years to assess remission			paraesthesia, infection and sepsis. More skin allergy and erythema. Similar numbers of secondary malignancies.			
				Secondary Clinical effectiveness	Overall survival	No difference but not fully assessed at publication B-R – 43 deaths R-CHOP – 45 deaths			
				Secondary	Time to next lymphoma treatment (months)	B-R: Median not yet reached; IQR 35.1 to not yet reached R-CHOP: Median 42.3 months; IQR 18.2 to not yet reached			
				Secondary	Event Free Survival (progression of disease, death from any cause, not achieving a partial response after 3 cycles, starting salvage therapy)	Not reported			
Flinn et al 2014	P1 an open-label, multicentre, controlled, randomised, phase 3 non-inferiority trial. Internati	Eligible adult patients (≥18 years of age) with CD20-positive indolent NHL or mantle cell lymphoma. Untreated subtypes of indolent NHL included follicular (grade 1 or 2)	Investigators pre-assigned patients to either R-CHOP or R-CVP based on their disease and health. They were then randomised to their standard treatment or B-R All patients received rituximab 375mg/m^2 on day 1 of each cycle. Six cycles were planned with a	Primary Clinical effectiveness	Complete response rate	B-R was non-inferior (NI) to standard therapy. CR was 31% in the B-R treatment group and 25% in the standard-therapy group. CR rate ratio = 1.26; *P* = 0.0225 for NI P = 0.1269 for superiority	8	Distribution of cell types in line with expectations. Standard practice now includes routine maintenance with rituximab. This was not used in this trial.	Non-blinded treatment but blinded validation assessment of CR rate. Two standard treatments – results from two subgroups (R-CHOP and R-CVP) combined to give number of randomised patients = 223 Differences were seen in investigator and independent assessor evaluations of response. Possibly suggestive of potential bias in investigator assessment of investigational treatment.
				Secondary Clinical effectiveness	Overall response rate (complete plus partial)	B-R = 97% R-CHOP/R-CVP = 91% p = 0.0102			

	onal 7 countries .	lymphoplasmacytic and marginal-zone B cell. Of 447 patients enrolled, 224 were randomized to receive B-R and 223 to standard therapy; 104 were treated with R-CHOP and 119 with R-CVP. Nine patients in the B-R group and 3 patients in the standard-therapy treatment group withdrew because of AEs.	maximum of 8. Bendamustine IV 90mg/m^2 over 30 minutes on days 1 and 2 of a 4 week cycle. R-CHOP/R-CVP day 1, cyclophosphamide IV 750 mg/m^2 (with the option of 1000 mg/m^2 for patients assigned to R-CVP) on day 1, vincristine IV at 1.4 mg/m^2 (2mg maximum) on day 1, and prednisone orally at 100 mg/d on days 1 to 5; patients assigned to R-CHOP doxorubicin IV at 50 mg/m^2 on day 1. Cycles of R-CHOP or R-CVP were repeated every 21 days.	Secondary Clinical effectiveness	Progression free survival (PFS) - the time from randomization to disease progression or relapse, or death from any cause	Time to event results not sufficiently mature at time of publication (based on 5 year minimum follow up specified in protocol). Follow up ongoing.			
				Secondary Clinical effectiveness	Event-free survival, or time from randomization to treatment failure				
				Secondary Clinical effectiveness	Median duration of response				
				Secondary Clinical effectiveness	Overall survival				
				Secondary	Quality of life	Reported separately (Burke 2016)			
				Secondary Safety	Safety and tolerability	B-R associated with higher incidence ($p<0.05$) of drug hypersensitivity, nausea and vomiting compared to R-CVP. R-CHOP/R-CVP associated with more peripheral neuropathy and alopecia ($p<0.05$) No significant difference in infections. Grade 3-4 reductions in lymphocytes more common in B-R. Grade 3-4 reductions in neutrophils more common in R-CHOP/R-CVP			

Burke et al 2016	P3 Additional results from Flinn et al 2014. Analysis of quality of life study.	A total of 209 patients were preassigned to R-CHOP (105 patients randomized to B-R and 104 to R-CHOP) and 238 to R-CVP (119 patients each randomized to B-R and R-CVP).	EORTC QLQ-C30 tool was used at baseline and after cycles 1,3,6 and 8 or at end of treatment if induction was not completed.	Primary Superior quality of life (QoL) for B-R over R-CHOP/R-CVP	EORTC-QLQ-C30 Addressing global health status, functioning and symptoms and signs	A mixture of differences seen in specific scores at different time points. In sub-group analysis overall, B-R led to more QOL improvements when compared with R-CVP than it did when compared with R-CHOP.	6	QoL assessments only carried out during the induction treatment phase.	This analysis involved the results from patient unblinded treatments. In general, patients receiving B-R reported greater improvement across selected QoL domains compared with patients receiving standard therapy, though the clinical significance of the benefits was small, and the differences between the groups were not statistically significant at all points in time. Analysis only covered period of induction chemotherapy.
Zimmer et al 2015	P3 Group comparison. Patients on active treatment with B-R or R-CHOP and healthy volunteers	30 patients on active, first line treatment for B-cell NHL (16 on B-R and 14 on R-CHOP) and 10 healthy volunteers.	Participants were assessed once within 3 months of their induction treatment.	Primary Cognitive impairment following chemotherapy	Objective cognition assessments Subjective cognition assessments (using EORTC-QlQ-C30) EEG Serum parameters (IL-6 and BDNF)	Patients performed less well than controls. B-R treated patients performed less well than R-CHOP for some parameters. Overall, patients had lower scores than controls. Only R-CHOP sub-group had significantly lower scores that controls (p=0.005) No significant difference in EEG IL-6 significantly elevated in patients; only significantly so in B-R sub-group No significant differences in BDNF	6	Limited applicability	This was a single point assessment rather than a longitudinal study. The results could be biased by the presence of other factors (e.g. depression). This is a small study with limited applicability.
Dewilde et al 2014	S2 Cost-utility analysis to determine the cost-utility of	A patient-level simulation based on 15,000 patients and the results from StiL (Rummel 2013) plus	The model was based on induction therapy and, depending on response, rituximab maintenance or high dose therapy or alternative chemotherapy.	Primary Cost utility of B-R compared to R-CHOP/R-CVP.	Treatment costs Cost-utility Incremental cost-	B-R patients accumulated the highest costs. B-R £63,453 R-CHOP £59,627 R-CVP £58,532 ICERs	10	The NHS/BNF based costs make this analysis relevant.	The NHS/BNF based costs make this analysis relevant. The inclusion of rituximab maintenance presents a more realistic approach in line with recent NICE guidance. The lack of OS data from any RCT limits the model. Suggestions of improved quality of life

	B-R compared to R-CHOP or R-CVP	expert clinical opinion.	PFS data was taken from StiL study. Treatment costs were based on BNF and NHS reference costs		effectiveness ratios (ICER)	B-R vs R-CHOP: £5,249 per QALY B-R vs R-CVP: £8,092 per QALY			with B-R would improve these ICERs.
Messori et al 2015	S1	Bayesian meta-analyis comparing four first line treatments for new diagnosed follicular NHL. CHOP, R-CHOP, B-R and R-CHOP with Rituximab maintenance	Analysed results from 3 trials (1773 patients in six treatment arms). Each treatment choice was ranked relative to the other three based on PFS data.	Primary outcome measure Efficacy	Progression free survival (PFS) at 2 years	Ranks for individual treatments (95% CI) 1 - R-CHOP + R (1-1) 2 - R-CHOP (3-2) 3 - B-R (3-2) 4 - CHOP (4-4) All difference were significant except between R-CHOP and B-R	6	Didn't include data from BRIGHT.	Some approximations were made to data from some studies. There were differences in entry criteria for one of the studies included regarding the histological sub-type grading which may have affected PFS rates.

8. Grade of evidence table

Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Progression Free Survival (PFS)	Rummel 2013	7	PFS was primary outcome measure. Trial did not assess outcomes with follow up rituximab.	B	Progression free survival is the time between the first treatment and one of the following; progressive disease, relapse after response or death from any cause. B-R has a superior effect on progression free survival (median 69.5 vs 31.2 months) compared to R-CHOP. This is likely to represent a benefit to patients although this evidence comes from an un-blinded study.
	Messori 2015	6	Data from BRIGHT not included.		
Complete Response (CR)	Flinn 2014	8	CR was primary outcome measure.	B	Complete response was defined according to international criteria as a complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy. B-R is non-inferior in its effect on CR to induction therapy compared to R-CHOP/R-CVP. In terms of initial outcome to induction treatment, patients on either treatment would be expected to experience a similar level of effectiveness,
	Rummel 2013	7	CR was secondary outcome measure.		
Overall Response (OR)	Rummel 2013	7	OR was secondary outcome measure.	B	Overall response rate is the complete response rate plus the partial response rate (which includes at least a 50% decrease in sum of the product of the diameters of up to six of the largest dominant nodes or nodal masses). Overall response rate to B-R was superior to R-CHOP/R-CVP B-R = 97%, R-CHOP/R-CVP = 91% (p = 0.0102). These data from a double blinded study indicate a statistical difference but one that in clinical terms may be small.
	Flinn 2014	8	OR was a secondary outcome measure.		
Safety	Rummel 2013	7	Trial did not assess outcomes with follow up rituximab.	B	B-R has a different side effect profile to R-CHOP/R-CVP greatly reducing the incidence of alopecia and peripheral neuropathy. B-R caused less leukopenia and neutropenia but more lymphocytopenia. B-R has a higher risk of drug hypersensitivity and skin rash The risk of secondary malignancies for B-R and R-CHOP/R-CVP does not appear to be different.
	Flinn 2014	8	Trial did not assess outcomes with follow up rituximab.		
Quality of Life	Burke et al 2016	6	This study included QoL assessment during induction chemoimmunotherapy.	C	B-R showed some advantages in QoL compared to R-CHOP/R-CVP but the clinical significance of the benefits was small, and the differences between the groups were not statistically significant at all points in time.
	Zimmer	6	Small study which made a single time point assessment of post chemotherapy cognitive impairment (partly based on EORTC-QLQ-C30).		
Cost-effectiveness	Dewilde 2014	10	Highly applicable. Based on NHS prices and costs for England and Wales	A	The cost-utility analysis of B-R compared to R-CHOP and R-CVP indicated favourable ICERs of £5249 per QALY and £8092 per QALY compared to R-CHOP and R-CVP respectively.

9. Fact Sheet – to be completed

Intervention Fact Sheet	
What is the intervention for?	
Who might consider taking it?	
Who should not take it?	
Other things to consider	

	Placebo/comparator	**Intervention**
Benefits **What difference did the intervention make?** *Include questions based on outcomes measures report* • ***For. e.g. What was the change in pulmonary vascular resistance?*** •	*Present results from studies*	
Harms **Did the intervention have side effects?** *Include questions based on outcomes measures report* • ***For. e.g. Were there life-threatening side effects?*** •	*Present results from studies*	

10. Literature Search Terms

Search strategy *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with untreated, advanced indolent NHL who have been assessed as requiring treatment eg B symptom, large tumour mass, presence of lymphoma related complications or hyperviscosity syndrome
I – Intervention Which intervention, treatment or approach should be used?	First line Bendamustine- Rituximab combination. Bendamustine being delivered on days 1 and 2 at 4 weekly intervals over a median of 6 cycles.
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Standard first line chemotherapy regimens such as R-CHOP (Cyclophosphamide, doxorubicin, vincristine ,prednisone or R-CVP (cyclophosphamide, vincristine, prednisone)
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	**Critical to decision-making:** Complete response rates, overall response rates (complete, partial response rates), median duration of response,consistent treatment effect, ,time to disease response, time to disease progression, PFS, OS, QOL, safety and tolerability of treatment regimen **Important to decision-making:** Non- inferiority to standard treatments and toxicity profile compared to that of standard treaments
Assumptions / limits applied to search	
Inclusion Criteria	Pts receiving first line treatment for advanced low grade NHL with R- Bendamustine Adult patients with a diagnosis of CD20 positive indolent NHL Treatment naïve Patients with a need for treatment Peer reviewed journals English language Last 10 years
Exclusion Criteria	Patients with relapsed disease Mantle Cell Lymphoma

11. Search Strategy

1. EMBASE; *LYMPHOMA/; 39117 results.
2. EMBASE; *FOLLICULAR LYMPHOMA/; 5109 results.
3. EMBASE; *MARGINAL ZONE LYMPHOMA/; 1349 results.
4. EMBASE; *LYMPHOBLASTOMA/; 1102 results.
5. EMBASE; 1 OR 2 OR 3 OR 4; 46147 results.
6. EMBASE; *BENDAMUSTINE/; 1162 results.
7. EMBASE; *RITUXIMAB/; 12680 results.
8. EMBASE; *CYCLOPHOSPHAMIDE/; 47285 results.
9. EMBASE; 6 AND 7 AND 8; 23 results.
10. EMBASE; 5 AND 9; 6 results.
11. EMBASE; 5 AND 6; 185 results.
12. EMBASE; 5 AND 6 AND 7; 108 results.
13. Medline; *BENDAMUSTINE HYDROCHLORIDE/; 29 results.
14. Medline; BENDAMUSTINE HYDROCHLORIDE/; 464 results.
15. Medline; RITUXIMAB/; 10028 results.
16. Medline; 14 AND 15; 160 results.
17. Medline; exp LYMPHOMA/; 154292 results.
18. Medline; 16 AND 17; 107 results.

Other non-bibliographic databases; Bendamustine, Rituximab

12. Evidence selection

- Total number of publications reviewed: 43
- Total number of publications considered relevant: 33
- Total number of publications selected for inclusion in this briefing: 16

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