NHS England

Evidence review: Bendamustine with Rituximab for relapsed low-grade Non-Hodgkin's Lymphoma

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1 Introduction

Introduction

- Lymphomas are cancers of the lymphatic system, which is a part of the body's immune system. Traditionally, lymphomas are divided into Hodgkin's disease (now known as Hodgkin's lymphoma) and non-Hodgkin's lymphoma (NHL) (NICE 2010).
- NHL is a heterogeneous group of lymphoproliferative malignancies that include all lymphomas except Hodgkin's lymphoma. They are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. Lymphomas are graded according to the rate at which the abnormal lymphocyte cells divide (NICE 2010).
- NHL is termed 'high-grade' (or aggressive) when they divide quickly and 'low-grade' (or indolent) when they divide slowly. Low-grade lymphomas tend to affect older people. Precise identification of the form of lymphoma and accurate staging is crucial both for choosing the optimum form of treatment and for monitoring disease progression (NICE 2010).
- There are 3 main subtypes of NHL. Diffuse large B-cell lymphoma (DLBCL), an aggressive subtype, is the most common type of NHL, constituting about one-third of all NHLs in the US. Follicular lymphoma (FL) is a slow-growing and the second most common type of NHL. Mantle cell lymphoma (MCL), which can be aggressive or indolent, is rare. Other NHL subtypes include peripheral T-cell lymphoma, lymphoplasmacytoid lymphoma (including Waldenstrom's macroglobulinaemia), Burkitt lymphoma and marginal zone lymphoma (Shankland et al 2012, Li et al 2017).
- The staging of NHL refers to how far the cancer has spread in the body. It is broken down into four stages: **stage 1** – the cancer is limited to one group of lymph nodes, either above or below the diaphragm; **stage 2** – two or more lymph node groups are affected, either above or below the diaphragm; **stage 3** – the cancer has spread to lymph node groups above and below the diaphragm; **stage 4** – the cancer has spread through the lymphatic system and is in organs or bone marrow (Macmillan 2018).
- Stages 1 and 2 are sometimes called early-stage, limited-stage or localised NHL. Stages 3 and 4 are sometimes called advanced NHL (Macmillan 2018).
- The most common symptom of NHL is one or more painless swellings in the neck, armpit or groin due to enlarged lymph nodes. Affected individuals may also have general symptoms (B symptoms) including heavy sweating at night, temperatures that come and go with no obvious cause, loss of weight and unexplained itching. There can be many other symptoms depending on where the NHL is in the body e.g. enlarged tonsils, liver or spleen. Symptoms can also be caused by enlarged lymph nodes pressing on an organ or nerve. Rarely, NHL can start in the brain and can cause headaches, fits and changes in personality (Cancer Research UK 2018).
- The clinical presentation, rate of disease progression and patterns of treatment vary widely. Low-grade lymphomas often grow very slowly and there may be long periods where there is very little, or no, change in the disease. For many people, regular check-ups are often the most appropriate option (known as active surveillance or watchful waiting), with appropriate interventions when symptoms develop. There may be multiple episodes of remission and relapse, and the nature of the disease can change at relapse, sometimes transforming to a more aggressive type (NICE 2010).

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- Whilst NICE have published guidance on the use of a number of interventions for the management of NHL, no published guidance on the use of bendamustine with rituximab was

identified.

- In October 2010, NICE stated that it was unable to recommend the use in the NHS of bendamustine for the treatment of low-grade (indolent) NHL that is refractory to rituximab or a rituximab-containing regimen because no evidence submission was received from the manufacturer or sponsor of the technology (NICE 2010). NICE did not specify whether this refers to monotherapy or combination therapy.
- In May 2016, NICE suspended the appraisal for bendamustine in combination with rituximab for the first-line treatment of advanced indolent non-Hodgkin's lymphoma announced from its work programme. This is because NICE was informed by the company that it will no longer be pursuing a licensing application for bendamustine in this indication (NICE 2016).
- A recently published NICE pathway for the diagnosis and management of NHL does not make any recommendations on the use of bendamustine plus rituximab (B-R) for relapsed or refractory NHL - the focus of this evidence review (NICE Pathways 2018).

The indication and epidemiology

- The exact cause of NHL is unknown but the risk of developing it is increased in conditions or treatments that affect the immune system, by certain viruses and people with a family history (Cancer Research UK 2018a).
- In 2015, there were just under 13,700 new cases of NHL in the UK. Approximately 60% of cases of NHL are diagnosed in people aged 65 years and over and more than 35% of new cases are in people aged 75 and over. However, it can occur at any age. NHL is slightly more common in men than in women; 7,500 and 6,200 new cases respectively in 2015 (Cancer Research UK 2018b).
- Low-grade lymphomas represent 40% of all non-Hodgkin lymphoma subtypes, with follicular lymphoma accounting for approximately 30% of all low-grade lymphomas (NICE 2010, Harris et al 1999).
- MCL is much less common and represents 3% to 10% of all newly diagnosed NHL cases although not all these are low-grade MCL (McKay et al 2012, Parrott et al 2017). The incidence of MCL is approximately 1 per 100,000 persons in Europe (Dreyling et al 2017).
- Across all ages, the 10-year survival rate is about 63% in England and Wales. NHL survival in England is highest in people diagnosed before the age of 40 years (Cancer Research UK 2018b).

Standard treatment and pathway of care

- The aim of current management is to achieve the best possible remission for the longest period, and to prolong survival (NICE 2010).
- First-line treatment for low-grade NHL depending on extent of the disease usually consists of radiotherapy to the affected lymph nodes (NICE 2010). The most common chemotherapies containing alkylators used in the front-line treatment of low-grade non-Hodgkin’s lymphoma when required include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CVP (cyclophosphamide, vincristine, and prednisone) (Rummel et al 2016).
- Second-line treatments include single-agent chemotherapy and combination chemotherapy (with or without steroids and/or rituximab).
- Subsequent therapy options include rituximab monotherapy, or high-dose chemotherapy with stem cell support (NICE 2010).

The intervention (and licensed indication)

- Bendamustine is an active bifunctional alkylating agent that also has potential antimetabolite properties (Montillo and Tedeschi 2013). It is a cytotoxic agent that comprises the structural features of both an alkylating drug and a purine nucleoside analogue (Korycka-Wołowiec and Robak 2012).
- It is licensed in the UK for the following indications:
    - Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen (Electronic Medicines Compendium 2018).
- It is also licensed for first-line treatment of chronic lymphocytic leukaemia and multiple myeloma:
    - First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate (Electronic Medicines Compendium 2018).
    - Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment (Electronic Medicines Compendium 2018).
- The focus of this review is to consider evidence for the unlicensed use of bendamustine in combination with rituximab for the treatment of relapsed low-grade NHL.

Rationale for use

- There is evidence to suggest that bendamustine has very limited cross-resistance with other alkylating agents (Leoni et al 2008). It may therefore be useful in patients with alkylating agent resistant disease or those previously extensively treated with chemotherapy (Tageja and Nagi 2010).

2 Summary of results

- No studies that compared B-R with fludarabine, cyclophosphamide and rituximab (FCR) or any other regimen specified in the PICO were identified.
- One randomised, non-inferiority, open-label, phase 3 trial (StiL NHL 2–2003; n=230) that compared the efficacy and safety of bendamustine plus rituximab (B-R) with fludarabine plus rituximab (F-R) in patients with relapsed or refractory indolent, non-Hodgkin lymphoma and Mantle-cell lymphoma (MCL) was identified (Rummel et al 2016). It was not clear if the MCL patients included in the study had indolent disease.

Clinical Effectiveness.

- **Progression free survival (PFS).** Median PFS was longer for patients treated with bendamustine plus rituximab (B-R) compared to fludarabine plus rituximab (F-R): 34.2

months (95% CI 23.5 to 52.7) vs. 11.7 months (8.0 to 16.1) (HR 0.54 [95% CI 0.38 to 0.72], p<0.0001). The median follow-up was 96 months (interquartile range **(**IQR)[1] 73.2 to 112.9).

- At one year, a greater proportion of patients in the B-R group (76%) compared with the F-R group (48%) remained progression free (B-R vs. F-R: 0.76 (95% CI 0.68 to 0.84) vs. 0.48 (0.39 to 0.58), non-inferiority[2] p<0.0001).
- 152 patients responded to treatment with either B-R or F-R. Of these, 44 patients with follicular lymphoma (25 in the B-R arm, 19 in the F-R arm) also received rituximab maintenance therapy. The other 108 responders did not receive rituximab maintenance therapy (69 in the B-R arm, 39 in the F-R arm).The median PFS was significantly longer for patients who received rituximab maintenance than those who did not: 72.1 months [95% CI 54.1 to not reached] vs. 30.4 months [24.7 to 36.5], (HR 0.52 [95% CI 0.37 to 0.86], p=0.01).
- Among those 44 patients who received rituximab maintenance in addition to B-R or F-R , there was no difference in median PFS between those who received B-R (72.1 months [95% CI 52.7 to not reached]) and those who had F-R (93.6 months [45.0 to not reached], (HR 1.02 [95% CI 0.42 to 2.50], p=0.96).
- By contrast, patients who did not receive rituximab maintenance had significantly longer PFS if they were treated with B-R than with F-R: 25.0 months [95% CI 15.2 to 34.8] vs. 8.6 months [5.8 to 12.2], (HR 0.49 [95% CI 0.33 to 0.65], p<0.0001).
- **Overall survival (OS).** Of all the study participants, those receiving B-R had longer median overall survival than those receiving F-R (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 fewer deaths in the B-R group compared to the F-R group (55 deaths vs 71 deaths).
- **Response Rates.** Overall and complete response rates were greater for patients who received B-R compared to F-R: 82% vs. 51% (p<0.0001) and 40% vs.17% (p=0.0002) respectively.
- Twenty seven out of 230 patients recruited to the study were not bendamustine naïve. Thirteen of these were randomised to the B-R group and 14 to the F-R group. Results were reported separately for patients who had received previous bendamustine therapy in the B-R group but not for the F-R group. It is not clear to what extent the inclusion of a small number of patients who were not bendamustine naïve (and out of scope of this review) might have had an impact on the apparent non-inferiority of B-R compared to F-R.

Safety.

- No significant differences in the occurrence of adverse events between the patients who received B-R or those who received F-R therapy were reported. Actual results and p-values were not provided.
- 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). Clinical definitions or significance details were not provided.

Cost Effectiveness.

- No studies that evaluated the cost-effectiveness of bendamustine with rituximab for

[1] A measure of statistical dispersion; equal to the difference between 75th and 25th percentiles

[2] 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.

bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP were found.

Subgroups.

- Limited sub-group testing showed that the increase in PFS associated with B-R compared to F-R was evident in patients with follicular lymphoma (n=111, HR 0.56, 95% CI 0.34 to 0.87), mantle-cell lymphoma (n=47, HR 0.45, 95% CI 0.22 to 0.76) and small lymphocytic lymphoma sub-entities (n=17, HR 0.28, 95% CI 0.07 to 0.62). It is not clear if the other 55 patients in the study who had different types of NHL experienced any improvement in PFS as no further information or data on the sub-group testing was provided.

3 Methodology

- The methodology used to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: Embase, MEDLINE, Cochrane library, TRIP and NICE Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st January 2008 and 13th March 2018.The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO table. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence from the paper included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

No studies that compared B-R with fludarabine, cyclophosphamide and rituximab (FCR) or any other regimen specified in the PICO were identified.

However, one randomised, non-inferiority, open-label, phase 3 trial (StiL NHL 2–2003; n=230) that compared the efficacy and safety of bendamustine plus rituximab (B-R) with fludarabine plus rituximab (F-R) in patients with relapsed or refractory indolent, non-Hodgkin lymphoma and Mantle-cell lymphoma (MCL) was identified (Rummel et al 2016). It was not clear if the MCL patients included in the study had indolent disease.

This study was the only comparative study found for B-R therapy for bendamustine naïve patients with relapsed low-grade non-Hodgkin's lymphoma. The study recruited 230 adults (≥18 years)

with relapsed or refractory indolent NHL and MCL from 55 centres in Germany between October 2003 and August 2010. . Subjects were randomly assigned to B-R (n=114) or F-R (n=105). Eleven patients were excluded for protocol violations and not analysed; 219 patients were included in the per protocol analysis[3].

In 2006, following European Medicines Agency (EMA) approval, the study protocol was amended to include rituximab maintenance therapy for patients with follicular lymphoma who responded to either B-R or F-R. (n=44). Twenty-five and 19 patients received rituximab maintenance therapy in the B-R and F-R arms respectively.

What is the evidence on clinical effectiveness of using bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP?

Clinical effectiveness outcomes reported from the StiL NHL 2–2003 study (Rummel et al 2016) include progression-free survival (PFS), overall survival (OS), overall response, complete response, partial response, stable disease, and progressive disease.

Progression-free survival (PFS)

PFS was the primary endpoint in the StiL NHL 2–2003 study (Rummel et al 2016).

At median follow up of 96 months (interquartile range **(**IQR)[4] 73.2 to 112.9), the median PFS for patients treated with B-R was significantly longer than for those treated with F-R (B-R vs F-R: 34.2 months (95% CI 23.5 to 52.7) vs. 11.7 months (8.0 to 16.1), HR 0.54 [95% CI 0.38 to 0.72], p<0.0001). A greater proportion of patients treated with B-R compared to those treated with F-R were progression free at 1-year (B-R vs F-R: 0.76 (95% CI 0.68 to 0.84) vs. 0.48 (0.39 to 0.58) (non-inferiority[5] p<0.0001).

152 of the 219 patients analysed in the per protocol analysis responded to treatment with B-R or F-R. The 44 patients who responded to B-R or F-R and who also received rituximab maintenance therapy had significantly longer median PFS compared to the 108 patients who responded to B-R or F-R but did not receive rituximab maintenance therapy: (RM vs no RM: 72.1 months [95% CI 54.1 to not reached] vs. 30.4 months [24.7 to 36.5], HR 0.52[95% CI 0.37 to 0.86], p=0.01). In line with the EMA licence for rituximab, it is assumed that only patients with follicular lymphoma were given maintenance rituximab therapy but this was not explicitly stated in the paper.

Among the 44 patients who received rituximab maintenance, there was no difference in between the 25 patients who received B-R (72.1 months [95% CI 52.7 to not reached]) and the 19 patients who received F-R (93.6 months [45.0 to not reached], HR 1.02 [95% CI 0.42 to 2.50], p=0.96).

In contrast, patients who did not receive rituximab maintenance had significantly longer PFS if they were treated with B-R than with F-R (25.0 months [95% CI 15.2 to 34.8] vs. 8.6 months [5.8 to 12.2], HR 0.49 [95% CI 0.33 to 0.65], p<0.0001).

The authors reported that 27 out of the 230 patients recruited to the study were not bendamustine naïve. Thirteen were randomised to the B-R group and 14 to the F-R group. Results were reported separately for patients who had received previous bendamustine therapy in the B-R

[3]Per-protocol analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated.

[4] A measure of statistical dispersion; equal to the difference between 75th and 25th percentiles

[5] 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.

group but not for the F-R group. Results for bendamustine naive patients were not reported separately; it is therefore not clear whether patients who have had previous bendamustine therapy have a different outcome to those who have not and the extent to which this may have confounded the overall results.

Overall survival (OS)
OS was a secondary endpoint in StiL NHL 2–2003 study (Rummel et al 2016). Patients receiving B-R had longer median OS than those receiving F-R (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). The authors reported that there were 55 deaths in the B-R group and 71 deaths in the F-R group.

In the subgroup analysis of B-R and F-R responders, rituximab maintenance therapy significantly increased the median OS compared to no additional rituximab maintenance therapy (RM vs no RM: not reached (95% CI 93.6 to not reached) vs. 69.7 months (49.4 to not reached, HR 0.52, 95% CI 0.34 to 0.92, p=0.03).

Overall response (OR)
OR was a secondary endpoint in StiL NHL 2–2003 study (Rummel et al 2016); however the definition for this endpoint was not stated. More patients treated with B-R compared with those treated with F-R achieved an overall response (B-R vs F-R: 82% vs. 51%, p<0.0001).

Complete response (CR)
CR was a secondary endpoint in StiL NHL 2–2003 study (Rummel et al 2016); however a definition for this endpoint was not stated. More patients treated with B-R compared with those treated with F-R achieved a complete response (B-R vs F-R: 40% vs. 17%, p=0.0002).

Partial response (PR)
Although PR was not pre-specified as a secondary endpoint or defined, the StiL NHL 2–2003 study reported no difference in the PR rate between patients treated with either bendamustine-rituximab or fludarabine-rituximab (B-R vs F-R: 42% vs. 34%, p=0.2345).

Stable disease (SD)
SD was not pre-specified as a secondary endpoint or defined; fewer patients in the B-R group had SD than in the F-R group (B-R vs F-R: 7(6%) vs. 16(15%), p=0.0282).

Progressive disease (PD)
PD was not pre-specified as a secondary endpoint or defined; fewer patients in the B-R group had PD than in the F-R group (B-R vs F-R: 8 (7%) versus 30 (29%), p<0.0001).

What is the evidence relating to the safety of bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP?
Safety was evaluated in StiL NHL 2–2003 study (Rummel et al 2016).

Toxic effects were pre-specified as a secondary endpoint in the StiL NHL 2–2003 study. 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 (B-R vs F-R: 23 vs 23 events). 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 definitions of adverse events and detailed description of the numbers or p-values were inadequately reported.

What is the evidence on the cost effectiveness of bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP?

No studies that evaluated the cost-effectiveness of bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade NHL who are chemotherapy-refractory or unsuitable for R-CHOP were identified.

From the evidence retrieved from the preceding questions are there any subgroups of bendamustine naive patients with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP who would gain greater benefit from using bendamustine with rituximab?

i. **Follicular lymphoma;**
ii. **Marginal zone lymphoma;**
iii. **Lymphoplasmacytoid lymphoma;**
iv. **Stage on treatment pathway / line of treatment;**
v. **Other**.

The only subgroup analysis which attempted to differentiate between types of NHL was reported that the increase in PFS reported in the B-R group was evident in patients with follicular lymphoma (HR 0.56, (95% CI 0.34 to 0.87), mantle-cell lymphoma (HR 0.45, (95% CI 0.22 to 0.76) and small lymphocytic lymphoma sub-entities (HR 0.28, (95% CI 0.07 to 0.62). It is not clear if this means that the other 55 patients in the study who had different types of NHL experienced any improvement in PFS or not as the authors did not state whether the PFS of any other subtypes. No further information or data on the sub-group testing was provided.

5 Discussion

The limited research evidence identified suggests that bendamustine with rituximab for the treatment of bendamustine naïve patients with refractory and/or relapsed low-grade NHL is safe and improves progression free survival, overall survival, overall response and complete response compared with F-R. However, the study which supports this evidence has a number of limitations. These include the non-inferiority study design, how the outcomes were assessed, how the results were reported, the generalizability of the study results to the population of interest and the comparators specified in the PICO.

There were a number of potential sources of bias including the fact that this was an open-label study. Patients, physicians, and individuals assessing outcomes and analysing data were not blinded to treatment allocation. In addition, the outcomes were investigator-assessed; evaluations were completed locally at each of the 55 participating centres and were not centrally reviewed.

The authors carried out a per-protocol analysis rather than an intention to treat analysis – this only included those patients who completed the treatment originally allocated. This may have exaggerated the effects of the treatment. In addition the primary outcome, the between group difference in progression free survival, was analysed using a Kaplan-Meier plot of the per-protocol population. We noted that at the median follow up of 96 months, only 32 out of 219 patients recruited to the study were at risk i.e. had had treatment for 96 months or more.

Twenty-seven out of 230 patients included in study had received previous bendamustine therapy

(13%) and the results for the bendamustine naïve patients were not reported separately. It is not clear whether patients who have had previous bendamustine therapy have a different outcome to those who have not and to what extent this confounds the overall outcomes and the overall effect size.

Subgroup analysis of patients with different types of NHL showed that patients with low-grade follicular lymphoma who received rituximab maintenance therapy in addition to B-R had a longer progression free survival than those who had B-R alone. This happened irrespective of whether they are treated with B-R or F-R. It is therefore not clear how much of the apparent PFS benefits attributed to bendamustine plus rituximab were due to rituximab maintenance therapy.

Several of the outcomes measured including overall response, complete response, stable disease and progressive disease were not defined and could have been open to individual interpretation particularly as evaluations were completed locally at each of the 55 participating centres and were not centrally reviewed.

The patients in the control arm were treated with F-R, however, nowadays fludarabine, cyclophosphamide and rituximab (FCR) is more widely used. Therefore, the comparative results (both outcomes and effect size) for B-R versus F-R cannot be considered generalisable to any of the four contemporary comparators of interest:

- FCR (fludarabine, cyclophosphamide and rituximab)
- Rituximab + chlorambucil (RCbl)
- Rituximab + CVP (cyclophosphamide, vincristine and prednisolone)
- Cyclophosphamide and dexamethasone

We do not know if the improvement in PFS associated with B-R compared to F-R for follicular lymphoma, small lymphocytic lymphoma and mantle cell lymphoma is achieved in any other subtype of NHL. The PFS of those patients in the study with Waldenstrom's macroglobulinaemaia (n=24), marginal zone lymphoma (n=18) or low-grade, unclassifiable lymphoma (n=2) was not reported.

The adverse effect profile for B-R appears to be similar to that of the control arm (F-R) however, no clear description of the numbers reported, definitions or p-values were provided.

It should also be noted that the study was funded by manufacturers of the intervention.

6 Conclusion

There is moderate evidence to suggest that bendamustine plus rituximab in patients with relapsed and/or refractory low-grade NHL is safe, and may be as effective as fludarabine plus rituximab at improving progression free survival, overall survival, overall and complete response.

However, there is no published evidence for the unlicensed use of bendamustine plus rituximab compared with current standard treatments of interest:

- FCR (fludarabine, cyclophosphamide and rituximab)
- Rituximab + chlorambucil (RCbl)
- Rituximab + CVP (cyclophosphamide, vincristine and prednisolone)
- Cyclophosphamide and dexamethasone

The effectiveness of bendamustine plus rituximab in bendamustine naïve patients is still

uncertain, as is the comparative effectiveness for different subtypes of NHL. In addition, the study by Rummel et al 2016 introduces an important question about the extent to which improved outcomes might be achieved by rituximab maintenance therapy.

7 Evidence Summary Table

For abbreviations see list after each table

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent NHL and MCL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Rummel et al 2016	P1-Randomised, non-inferiority, open-label, phase 3 trial 55 centres in Germany Median follow-up was 96 months (IQR 73.2 to 112.9)	230 patients aged 18 years or older with a WHO performance status of 0 to 2 & relapsed or refractory indolent NHL or MCL treatment groups **B-R arm (n=116)** FL:51%; MCL:21% WM:11%; MZL:9%; LL:7%; unclassifiable :1% **F-R arm (n=114)** FL:50%; MCL:22% WM:10%; MZL:8%; LL:9%; unclassifia	Randomised centrally under concealment Rituximab (375 mg/m², day 1) + bendamustine (90 mg/m², days 1 & 2); max six cycles **OR** Rituximab (375 mg/m², day 1) + Fludarabine (25mg/m², days 1 to 3) every 28 days: max six 28-day cycles. After approval in 2006 of rituximab for maintenance therapy for follicular lymphoma, protocol was amended for patients who responded to	Primary Clinical effectiveness	Progression free survival (PFS)	Median PFS **B-R vs. F-R** At median follow-up of 96 months 34.2 months (95% CI 23.5 to 52.7) vs. 11.7 months (8.0 to16.1), HR 0·54 [95% CI 0·38 to 0·72], p<0·0001 1-year PFS 0.76 (95% CI 0.68 to 0.84) vs. 0.48 (0.39 to 0.58), non-inferiority p<0.0001 Exploratory sub-group testing FL: HR 0.56 (95% CI 0.34 to 0.87) SLL: HR 0.28 (95% CI 0.07 to 0.62 MCL: HR 0.45 (95% CI 0.22 to 0.76) P values not reported Sub-analysis - Patients who received rituximab maintenance (n=44) vs. those who did not (n=108) Median PFS = 72.1	6/10	Direct	Randomisation and allocation of concealment methods used were well documented. There were a number of potential sources of bias including the fact that this was an open-label study, patients, physicians, and individuals assessing outcomes and analysing data were not masked to treatment allocation. In addition the outcomes were investigator-assessed. Evaluations were completed locally at participating centres and were not centrally reviewed. Not all the patients included in the study were bendamustine naïve. About 13% of the patients had received previous bendamustine therapy; it is not clear what effect this has on the overall results. Although results were reported for patients previously exposed to bendamustine in the B-R group this was not done for the F-R group it was therefore not possible to isolate the results. Outcome measures were not defined which meant that they could have been interpreted differently by the different assessors. Evaluations were completed locally at participating centres and were not centrally reviewed. Data on adverse events were not clearly reported. Results may not be generalizable as FCR is currently more widely used than F-R. An unplanned subset analysis reported no differences in PFS were observed between those who had received rituximab maintenance in the B-R or F-R arms. Current management strategies mean

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent NHL and MCL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		ble :1% B-R + RM (n=25) F-R + RM (n=19)	B-R or F-R therapy. Rituximab maintenance (RM) dose= 375 mg/m² every 3 months for up to 2 years			months [95% CI 54.1to not reached] vs. 30.4 months [24.7 to 36.5]; HR 0.52,[95% CI 0.37 to 0.86], p=0.01 <u>Patients who received rituximab maintenance therapy</u> - Median PFS **B-R (n=25) vs. F-R (n=19)** 72.1 months [95% CI 52.7 to not reached] vs. 93.6 months [45.0 to not reached], HR 1.02 [95% CI 0.42 to 2.50], p=0.96 <u>Sub-group analysis</u> Patients who **<u>did not</u>** receive rituximab maintenance therapy - Median PFS **B-R (n= 69) vs. F-R (n= 39)** 25.0 months [95% CI 15.2 to 34.8] vs. 8.6 months [95% CI 5.8 to12.2], HR 0.49 [95% CI 0.33 to 0.65], p<0.0001			that many patients would be exposed to rituximab maintenance therapy early in the treatment pathway. Only those patients who completed the treatment originally allocated were included in the analysis. This may have exaggerated the effects of the treatment. It should also be noted that the study was funded by the manufacturers of the intervention.
				Secondary Clinical effectiveness	Overall response (OR)	**B-R vs. F-R:** 94 (82%) vs. 54 (51%), p<0.0001 Previous bendamustine therapy: B-R: n=13 vs F-R:			

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent NHL and MCL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						n=14: 77% vs no results reported.			
				Secondary Clinical effectiveness	Complete response (CR)	**B-R vs. F-R:** 46 (40%) vs. 18 (17%), p=0.0002			
				Secondary Clinical effectiveness	Partial response (PR)	**B-R vs. F-R:** 48 (42%) vs. 36 (34%), p=0.2345			
				Secondary Clinical effectiveness	Stable disease (SD)	**B-R vs. F-R** 7 (6%) vs.16 (15%) p=0.0282			
				Secondary Clinical effectiveness	Progressive disease (PD)	**B-R vs. F-R:** 8 (7%) vs. 30 (29%), p<0.0001			
				Secondary Clinical effectiveness	Median Overall survival (OS)	**B-R vs. F-R:** 109.7 months [95% CI 50.2–not reached] vs. 49.1 months [36.2 to 59.0], HR 0.64, (95% CI 0.45 to–0.91), p=0.012 Deaths 55 deaths vs. 71 deaths No p-values were reported <u>Sub-group analysis</u> RM subgroup vs. non RM subgroup: Not			

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent NHL and MCL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						reached (95% CI 93.6 to not reached) vs. 69.7 months (49.4 to not reached), HR 0.52 (95% CI 0.34 to 0.92), p=0.03			
				Secondary Safety	Adverse effects	**B-R vs. F-R** <u>Infections</u> 11 events vs. 8 events <u>Myelosuppression</u> 3 events vs. 2 events <u>G-CSF use</u> 13% of patients vs. 12% of patients No drug related treatment discontinuation. Dose reductions 20 patients vs. 20 patients <u>Serious adverse events – this was not clearly defined</u> 23 events vs.23 events **No clear details or p values were reported for adverse events**			

B-R – bendamustine + rituximab; CI -confidence interval; CR-complete response; EMA - European Medicines Agency; FL-Follicular lymphoma; F-R- fludarabine + rituximab; G-CSF – granulocyte colony-stimulating factor; HR –hazard ratio; LL- lymphocytic lymphoma; MCL- mantle cell lymphoma; MZL – marginal zone lymphoma; NS-not significant; OR-overall response; OS overall survival; PFS-progression free survival; RM – rituximab maintenance; SLL- small lymphocytic lymphoma; WHO-World Health Organisation; WM- Waldenstrom macroglobulinemia

8 Grade of Evidence Table

For abbreviations see list after each table

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Progression free survival (PFS)	Rummel et al 2016	6/10	Direct	B	PFS was defined 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[6] 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.

[6] 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.

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival (OS)	Rummel et al 2016	6/10	Direct	B	Overall survival 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 96 months follow-up, patients with low-grade relapsed and/or refractory NHL treated with B-R had longer median OS than those receiving F-R (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 F-R group. 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.
Overall response (OR)	Rummel et al 2016	6/10	Direct	B	Overall response refers to patients who respond to treatment. The criteria for meeting this outcome was 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.

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Complete response (CR)	Rummel et al 2016	6/10	Direct	B	Complete response 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.
Partial response (PR)	Rummel et al 2016	6/10	Direct	B	Partial response 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. 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.

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					It is unknown how B-R compares with standard treatments such as fludarabine, cyclophosphamide and rituximab (FCR).
Stable disease (SD)	Rummel et al 2016	6/10	Direct	B	Stable disease 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).
Progressive disease (PD)	Rummel et al 2016	6/10	Direct	B	Progressive disease 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.

Bendamustine with Rituximab vs. Fludarabine with Rituximab for relapsed or refractory indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Adverse events	Rummel et al 2016	6/10	Direct	B	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

9 Literature Search Terms

<table>
<tr><td colspan="2">Search strategy Indicate all terms used in the search</td></tr>
<tr><td>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?</td><td>Patients with relapsed low-grade non-Hodgkin’s lymphoma (advanced, stage 3, stage 4) who have not previously been treated with bendamustine and who are also:

● chemotherapy-intolerant or unsuitable for R-CHOP (and not suitable for stem cell transplant)</td></tr>
<tr><td>I – Intervention
Which intervention, treatment or approach should be used?</td><td>Bendamustine with rituximab</td></tr>
<tr><td>C – Comparison
What is/are the main alternative/s to compare with the intervention being considered?</td><td>● FCR (fludarabine, cyclophosphamide and rituximab)
● Rituximab + chlorambucil (RCbl)
● Rituximab + CVP (cyclophosphamide, vincristine and prednisolone)
● Cyclophosphamide and dexamethasone</td></tr>
<tr><td>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; return to work, physical and social functioning, resource use.</td><td><u>Critical to decision-making:</u>
• Overall survival
• Progression free survival
• Overall response rate
• Disease control rate
• Adverse events (including secondary malignancies)
• Quality of life (HRQoL)
• Cost effectiveness
Any other relevant outcome from included studies.

<u>Important to decision-making:</u></td></tr>
<tr><td colspan="2">Assumptions / limits applied to search
<u>Inclusion criteria</u>
Patients with relapsed low-grade non-Hodgkin’s lymphoma (advanced, stage 3, stage 4) following previous treatment with chemotherapy
English language peer reviewed publications

<u>Exclusion criteria</u>
Previous treatment with bendamustine.
Trials including comparison arms with R-CHOP or stem cell transplants.
Comparisons of bendamustine and rituximab with oltertuzumab (not licensed).
Comparisons of bendamustine and rituximab with obinatuzumab (NICE approved).
Comparisons of bendamustine and rituximab with FMD (not current standard practice).
Comparisons of bendamustine and rituximab with lenalidomide and rituximab (not commissioned by NHSE).
Abstracts.
Conference papers.
Letters and commentaries
Uncontrolled studies
Papers published greater than 10 years ago.</td></tr>
</table>

10 Search Strategy

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in England from **1 January 2008 date to 13 March 2018**. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 13 March 2018

Embase Search

1 *bendamustine/
2 (bendamustine or levact or treanda or bendeka).ti,ab.
3 1 or 2
4 *rituximab/
5 (rituximab or mabthera or rchop or r-chop or rituxan).ti,ab.
6 4 or 5
7 exp nonhodgkin lymphoma/
8 ("non-hodgkin* lymphoma*" or "nonhodgkin* lymphoma*").ti,ab.
9 7 and 8
10 3 and 6 and 9
11 limit 10 to (english language and yr="2008 -Current")
12 limit 11 to "reviews (maximizes specificity)"
13 limit 11 to "therapy (best balance of sensitivity and specificity)"
14 limit 11 to "economics (best balance of sensitivity and specificity)"

11 Evidence Selection

- Total number of publications reviewed: 130
- Total number of publications considered potentially relevant: 29
- Total number of publications selected for inclusion in this briefing: 1

12 References

Cancer Research UK 2018a. Symptoms | non-Hodgkin lymphoma | Cancer Research UK. [online] Available at: http://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/symptoms [Accessed 17 Apr. 2018].

Cancer Research UK 2018b. Non-Hodgkin lymphoma statistics. [online] Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma [Accessed 17 Apr. 2018].

Dreyling M, Geisler C, Hermine O, Kluin-Nelemans H, Le Gouill S, Rule S, Shpilberg O, Walewski J. and Ladetto, M. 2014. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 25(suppl 3): 83-92

Electronic Medicines Compendium. 2018. Levact 2.5 mg/ml powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (eMC). [online] Available at: https://www.medicines.org.uk/emc/product/5656/smpc [Accessed 17 Apr. 2018].

Harris N, Jaffe E, Diebold J, Flandrin G, Muller-Hermelink H, Vardiman J, Lister T. and Bloomfield, C. 1999. The World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues. Annals of Oncology. 10(12):1419-1432.

Korycka-Wołowiec A and Robak T. 2012. Pharmacokinetic evaluation and therapeutic activity of bendamustine in B-cell lymphoid malignancies, Expert Opinion on Drug Metabolism & Toxicology. 8:11;1455-1468

Leoni L, Bailey B, Reifert J, Bendall H, Zeller R, Corbeil J, Elliott G. and Niemeyer C. 2008. Bendamustine (Treanda) Displays a Distinct Pattern of Cytotoxicity and Unique Mechanistic Features Compared with Other Alkylating Agents. Clinical Cancer Research. 14(1): 309-317.

Li M, Dave N, Salem A. and Freise, K. 2017. Model-based meta-analysis of progression-free survival in non-Hodgkin lymphoma patients. Medicine. 96(35):e7988.

Macmillan Cancer Support 2018. Staging non-Hodgkin lymphoma - Understanding cancer - Macmillan Cancer Support - Understanding - Macmillan Cancer Support. [online] Available at: https://www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-non-hodgkin/treating/treatment-decisions/understanding-your-diagnosis/staging-non-hodgkin-lymphoma.html [Accessed 17 April 2018].

McKay P, Leach M, Jackson R, Cook G. and Rule S. 2012. Guidelines for the investigation and management of mantle cell lymphoma. British Journal of Haematology. 159(4):405-426.

Montillo M. and Tedeschi A. 2013. 'Use it again!': retherapy with bendamustine in indolent B-cell lymphoproliferative disorders. Expert Review of Hematology. 6(3): 247-250.

NICE 2010. Bendamustine for the treatment of non-Hodgkin's lymphoma. [online] Available at: https://www.nice.org.uk/guidance/ta206/documents/lymphoma-nonhodgkins-bendamustine-draft-scope-for-consultation2 [Accessed 17 April 2018].

NICE 2016. Lymphoma (non Hodgkin's) - bendamustine (with rituximab). [online] Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag278 [Accessed 18 May 2018]

NICE Pathways 2018. Non-Hodgkin's lymphoma - NICE Pathways. [online] Available at: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma [Accessed 17 April 2018].

Parrott M, Rule S, Kelleher M. and Wilson J. 2018. A Systematic Review of Treatments of Relapsed/Refractory Mantle Cell Lymphoma. Clinical Lymphoma Myeloma and Leukemia. 18(1):13-25.

Rummel M, Kaiser U, Balser C, Stauch M, Brugger W, Welslau M, Niederle N, Losem C, Boeck H, Weidmann E, von Gruenhagen U, Mueller L, Sandherr M, Hahn L, Vereshchagina J, Kauff F, Blau W, Hinke A. and Barth J. 2016. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. The Lancet Oncology. 17(1): 57-66.

Shankland K, Armitage J. and Hancock B. 2012. Non-Hodgkin's lymphoma. The Lancet. 380:.848-857.

Soini E, Martikainen J, Vihervaara V, Mustonen K. and Nousiainen T. 2012. Economic Evaluation of Sequential Treatments for Follicular Non-Hodgkin Lymphoma. Clinical Therapeutics. 34(4):915-925.

Tageja N. and Nagi J. 2010. Bendamustine: something old, something new. Cancer Chemotherapy and Pharmacology. 66(3): 413-423.