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

Evidence Status Report: Bendamustine in combination with rituximab (MabThera®) for the treatment of previously untreated and relapsed indolent lymphomas
March 2017

KEY FINDINGS

Report background
Bendamustine is available through NHS England's Cancer Drugs Fund for off-label use in the treatment of untreated and relapsed low grade lymphoma, in people for whom standard treatment is unsuitable. According to the Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication[1].

A cohort of patients has been identified through data from individual patient funding request (IPFR) panels and clinicians in Wales consider there is an unmet need within the service. This cohort includes: young and fit people with aggressive, untreated and relapsed follicular lymphoma and marginal zone lymphoma, and Waldenstrom's macroglobulinaemia for whom anthracycline-based chemotherapy is unsuitable. Based on this unmet need, this medicine combination was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness
Data from two phase III studies showed that bendamustine plus rituximab is at least not inferior and may be superior to rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or CVP (cyclophosphamide, vincristine and prednisolone) in the first-line treatment of stage III or IV indolent lymphoma and mantle cell lymphoma, as assessed by progression-free survival or complete response rate[2]. However, in one study non-inferiority was not reached in the indolent non-Hodgkin's lymphoma group as a whole[3].

Data from a phase III study showed that bendamustine plus rituximab was more effective than fludarabine plus rituximab in treating relapsed indolent lymphomas, giving a longer progression-free survival and median overall survival[4].

Safety
Bendamustine plus rituximab is associated with high incidences of serious haematological toxicities, in common with other chemotherapy regimens used to treat indolent non-Hodgkin's lymphoma. The phase III studies showed that bendamustine plus rituximab has a safety profile that is distinct from those of the standard chemotherapy regimens, and has some favourable aspects[3]. In the first-line treatment of indolent lymphomas bendamustine plus rituximab showed a generally lower incidence of neutropenia, leukopenia, alopecia and neuropathy than seen in patients treated with rituximab plus CHOP, with a higher incidence of skin reactions and drug sensitivity[2]. A Cochrane review of bendamustine in treating indolent B cell lymphoid malignancies concluded that the risk of grade 3–4 adverse events was similar when bendamustine was compared with CHOP and fludarabine[5].

Patient factors
Health-related quality of life data showed that first-line treatment with bendamustine plus rituximab was associated with small improvements in functioning compared with standard therapy[6]. No evidence was identified to assess the health-related quality of life in the relapsed setting.

Cost effectiveness
One study was identified assessing the cost-effectiveness of bendamustine plus rituximab and rituximab plus CHOP, and rituximab plus CVP from the UK NHS perspective[7]. The estimated incremental cost-effectiveness ratio of bendamustine plus rituximab compared to rituximab plus CHOP was £5,249 per quality-adjusted life-year for England and Wales, and £8,092 for bendamustine plus rituximab compared to rituximab plus CVP.

Budget impact
Using national incidence data, the number of patients eligible for treatment has been estimated at 77 patients per annum. This is associated with an annual cost of £44,044 based on bendamustine acquisition costs only because rituximab would be included in any alternative treatment regimens. Additional resource costs for one extra day of medicine administration per cycle for bendamustine will be dependent upon current service capacity. However some patients are already receiving this regimen through IPFR and local arrangements. Sixteen patients across three health boards have accessed this regimen over the last 12 months which would decrease the annual budget impact to £34,892. Accurate figures were not available for the remaining health boards. In addition, comparator regimens are similarly priced and therefore the true net cost is likely to be significantly lower than the above estimates.

Welsh commercial access agreement
These medicines are currently not licensed for the indication under consideration (i.e. off-label). Therefore a commercial agreement cannot be offered by the relevant companies because the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine.

Impact on health and social care services
Using bendamustine plus rituximab to treat indolent lymphomas, including newly diagnosed and relapsed disease, is expected to have minimal impact on existing services.

Innovation and/or advantages
Bendamustine plus rituximab offers an anthracycline-free regimen for the treatment of indolent lymphomas. It therefore may be suitable for people who are unable to tolerate or who have a contraindication to an anthracycline-based regimen, or who may have reached the maximum cumulative dose of anthracycline at which the risk of chronic cardiotoxicity increases.

BACKGROUND

Target group

The indications being considered are follicular lymphoma, Waldenstrom's macroglobulinaemia and marginal zone lymphoma, including newly diagnosed and relapsed disease.

In the first-line setting, bendamustine plus rituximab are being considered for young and fit patients with aggressive follicular lymphoma and marginal zone lymphoma as an alternative to rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP). Bendamustine and rituximab may also be a suitable option for those relapsing after R-CVP where other licensed and health technology appraisal-approved regimens are unsuitable. Bendamustine plus rituximab is also being considered in the first-line and relapsed disease setting for the treatment of Waldenstrom's macroglobulinaemia in patients unsuitable for anthracycline-based regimens and/or where other licensed and health technology appraisal-approved regimens are unsuitable.

Technology

Bendamustine is an alkylating antitumor agent[8]. Its antineoplastic activity is based on cross-linking of DNA single and double strands by alkylation, which impairs DNA matrix functions and DNA synthesis and repair[8].

Rituximab (MabThera®) is a genetically engineered chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20 on pre-B and mature B lymphocytes[9]. This binding mediates B cell lysis by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and also induces cell death by apoptosis[9].

Marketing authorisation date: Not applicable, off-label

Bendamustine is indicated as monotherapy for indolent non-Hodgkin's lymphomas in patients who have progressed during or within six months of treatment with rituximab or a regimen containing rituximab[8].

The use of rituximab in combination with bendamustine for non-Hodgkin's lymphoma is therefore off-label. The license holder for the original bendamustine formulation have informed NICE that they will not be pursuing a license for this indication[10].

The European patent for rituximab (MabThera®) expired in 2013 and the US patent in 2016[11]. In December 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for a rituximab biosimilar for the first-line treatment of follicular lymphoma, as well as relapsed and refractory disease[12].

Dosing

Bendamustine is given by intravenous infusion over 30–60 minutes and administration must be supervised by a physician qualified and experienced in the use of chemotherapeutic agents[8]. In clinical studies it was given at a dose of 90 mg/m^2/day on days 1 and 2 of a four-week cycle, for up to six cycles[2-4,13].

The recommended dose of intravenous rituximab for the treatment of non-Hodgkin's lymphoma is 375 mg/m^2 body surface area per cycle, for up to eight cycles, which is the dose used in the clinical studies[9].

The recommended dose of rituximab subcutaneous formulation used as a maintenance treatment is 1,400 mg[14]. The dose is repeated once every two months for previously untreated follicular lymphoma and once every three months for relapsed/refractory follicular lymphoma (starting two months and three months after the last dose of induction therapy, respectively). Maintenance treatment is administered until disease progression or for a maximum period of two years[14].

Clinical background

Non-Hodgkin's lymphoma is a cancer that affects the lymphocytes in the blood[15]. Indolent or low-grade lymphomas represent 40% of all subtypes of non-Hodgkin lymphoma[4], of which follicular lymphoma is the most common and accounts for about 25% of lymphomas in the UK[16]. Follicular lymphoma affects B-cell lymphocytes and develops slowly, often without symptoms for many years[17]. Indolent lymphomas are characterised by a chronic relapse-remitting disease course and patients are often exposed to many and successive treatment regimens, eventually dying as a result of the disease[4]. Indolent lymphomas are more common in people aged over 50[18]. The most common symptom of non-Hodgkin's lymphoma is one or more painless swellings (enlarged lymph nodes) usually in the neck, armpit or groin[16].

Marginal zone lymphomas represent approximately 12% of all B cell lymphomas[16]. There are three types of marginal zone lymphoma:

- extranodal marginal zone lymphoma is the most common form. It occurs outside of the lymph nodes, in places such as the stomach, small intestine and salivary gland. Extranodal marginal zone lymphoma can be further divided into two categories: gastric, which develops in the stomach, and non-gastric which develops outside of the stomach[18].

- Nodal marginal zone lymphoma occurs within the lymph nodes[16].
- Splenic marginal zone lymphoma most often occurs in the spleen and blood[16].

Waldenstrom's macroglobulinaemia is a rare B-cell lymphoma that accounts for less than 2% of B-cell lymphomas[16]. The abnormal B-cells produce immunoglobulin M protein which can lead to thickening of the blood. This lymphoma usually affects people over the age of 65 and it is slightly more common in men than women[16].

Incidence/prevalence

In Wales in 2014 there were 595 new cases of non-Hodgkin's lymphoma and 239 deaths reported[19]. Assuming approximately 40% are indolent lymphomas[4] this gives an incidence of 238 cases per year in Wales. Assuming 64% of cases are diagnosed at an advanced or late-stage (stage III or IV)[20], an incidence of 238 cases per year in Wales equates to 153 patients eligible for first-line treatment. Intensive treatment is not suitable for around 50% of patients with mantle cell lymphoma[21]. There is no equivalent estimate for the proportion of patients with non-Hodgkin's lymphoma suitable for intensive treatment therefore 50% has been extrapolated from the mantle cell data; this equates to 77 patients in Wales. Health board data on patient numbers indicates that the population is likely to be lower than this anticipated figure however AWTTC have not been provided with data across all health boards.

Current treatment options

A watch and wait approach is standard for people with asymptomatic indolent lymphomas[15].

Follicular lymphoma:
For the first-line treatment of advanced-stage (stages III and IV) follicular lymphoma in people who are symptomatic, the National Institute for Health and care Excellence (NICE) recommends rituximab in combination with:

- cyclophosphamide, vincristine and prednisolone (CVP)
- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
- mitoxantrone, chlorambucil and prednisolone
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon alfa or
- chlorambucil[22].

The European Society for Medical Oncology (ESMO) recommends rituximab in combination with bendamustine or CHOP for advanced stage III and IV disease, with a high tumour burden[23]. CVP is not considered as effective as these two regimens with respect to progression-free survival . Full courses of purine analogue-based schemes (fludarabine and cyclophosphamide or fludarabine and mitoxantrone) are not recommended due to higher haematological toxicities, but a brief course of chemoimmunotherapy with full rituximab course is an alternative in elderly patients, with good efficacy and low toxicity[23].

If people have at least a partial response to induction chemotherapy, NICE recommends consolidation with autologous stem cell transplantation for people who are fit enough[22]. Rituximab maintenance therapy is recommended as an option to treat follicular lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy. Patients with refractory or relapsed disease may be given rituximab in combination with chemotherapy or rituximab monotherapy when all alternative treatment options have been exhausted. Guidelines suggest that the choice of treatment for relapsed disease depends on factors such as previous treatment regimens, duration of response and a patient's fitness for therapy[15,17,24,25]. Rituximab may also be used as maintenance therapy for people with relapsed stage III or IV follicular lymphoma in remission induced by

chemotherapy with or without rituximab[22]. Treatment pathways for double-refractory follicular lymphoma are not well defined and there is no standard of care.

Clinical experts in Wales consider rituximab plus CHOP or rituximab plus CVP to be current treatment options for the first line treatment of follicular lymphoma. For relapsed follicular lymphoma clinical experts consider the treatment options to be: rituximab plus CHOP; rituximab plus fludaribine, mitoxantrone and dexamethasone; rituximab plus fludaribine and cyclophosphamide; or retreatment with rituximab plus CVP.

Marginal zone lymphoma:
NICE recommends *Helicobacter pylori* eradication therapy for people with gastric extranodal marginal zone lymphoma[26]. For people with residual lymphoma after *H. pylori* eradication therapy who are at high risk of progression, NICE recommends chemotherapy (e.g. chlorambucil or CVP) in combination with rituximab or gastric radiotherapy. Chemotherapy in combination with rituximab is recommended for people with non-gastric extranodal marginal zone lymphoma for whom radiotherapy is not suitable or who have disseminated disease and need treatment[26].

There are no specific treatment recommendations for nodal marginal zone lymphoma[27]. These lymphomas are treated according to the recommended treatment options for follicular lymphoma. For splenic marginal zone lymphoma, treatment options include splenectomy, chemotherapy, rituximab alone or rituximab plus chemotherapy[27].

Clinical experts in Wales consider rituximab plus CVP or rituximab plus CHOP to be treatment options for first line treatment of marginal zone lymphoma. For people with relapsed disease rituximab plus CHOP is a treatment option.

Waldenstrom's macroglobulinaemia:
The British Society for Haematology (BSH) guidelines for Waldenstrom's macroglobulinaemia recommends rituximab-containing regimens for the first-line treatment for people who are symptomatic, and also for relapsed disease[28]. Appropriate regimens include:

- rituximab, dexamethasone plus cyclophosphamide
- bendamustine plus rituximab
- fludarabine plus rituximab, with or without cyclophosphamide
- cladribine plus rituximab[28].

The choice of regimen depends on the person's performance status, clinical features, co-morbidities and potential candidacy for stem cell transplantation[28]. According to the BSH guidelines, rituximab plus CHOP should not be used as primary therapy in Waldenstrom's macroglobulinaemia. Chlorambucil is a suitable first-line therapy for elderly and frail people[28]. If people cannot tolerate chemotherapy, rituximab monotherapy is a first-line option[29]. In addition to rituximab-containing regimens, bortezomib-containing regimens are suitable in the relapsed setting[28].

Clinical experts in Wales consider first line and second line treatment options to be: rituximab plus cyclophosphamide and dexamethasone; rituximab plus fludarabine (with or without cyclophosphamide); or rituximab plus cladribine.

Off-label bendamustine in combination with rituximab is available in NHS England through the Cancer Drugs Fund for the treatment of people with untreated and relapsed low grade lymphoma[1].

Guidance and related advice

Current guidance and advice:

- National Institute for Health and Care Excellence (NICE) Guideline NG52 (2016): Non-Hodgkin's lymphoma: diagnosis and management[15]
- NICE Pathway (2016): Non-Hodgkin's lymphoma[30]
- European Society for Medical Oncology (2016): Newly diagnosed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up[23]
- British Journal of Haematology (2014): Guidelines on the diagnosis and management of Waldenstrom macroglobulinaemia[28]
- National Comprehensive Cancer Network (2014): Clinical practice guidelines in oncology: non-Hodgkin's lymphomas[31]
- European Society for Medical Oncology (2013): Waldenstrom's macroglobulinaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up[29]

- The All Wales Medicines Strategy Group (AWMSG): recommended the use of subcutaneous rituximab (MabThera®) in combination with chemotherapy to treat stage III to IV follicular lymphoma that has not previously been treated, and as maintenance therapy for follicular lymphoma that responds to induction therapy[32].

Guidance in progress (at time of writing of this report):

- AWMSG: idelalisib for the treatment of adult patients with follicular lymphoma that is refractory to two prior lines of treatment[33].
- NICE: obinutuzumab (Gazyvaro®) in combination with bendamustine for the treatment of rituximab-refractory follicular lymphoma. The expected publication date was January 2017[34], however, this guidance is yet to be published.
- NICE: ibrutinib (Imbruvica®) for the treatment of adult patients with Waldenstrom's macroglobulinaemia who have received at least one prior therapy, or as first line treatment when chemo-immunotherapy is unsuitable, with advice expected in March 2017[35]
- NICE: obinutuzumab (Gazyvaro®) for untreated indolent non-Hodgkin's lymphoma, with advice expected in January 2018[36].

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC), together with information provided by the manufacturer of rituximab, identified three phase III studies and one retrospective study investigating the efficacy and safety of bendamustine plus rituximab compared to rituximab plus CHOP and rituximab plus fludarabine in untreated and relapsed patients, respectively. These studies are briefly described below. Phase II studies of bendamustine in relapsed or refractory indolent non-Hodgkin's lymphoma were identified but have not been included because of differences in the treatment regimen or prior exposure to rituximab.

Efficacy

Phase III studies:

These studies were open-label and aimed to demonstrate non-inferiority of bendamustine plus rituximab compared with rituximab plus CHOP, CVP and fludarabine[2-4]. The dosing regimens were as follows for a maximum of six cycles:

- bendamustine 90 mg/m^2 on days 1 and 2 plus rituximab 375 mg/m^2 on day 1 of a four week cycle,

- rituximab 375 mg/m^2 on day 1 plus cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2 on day 1 and prednisone 100 mg/day for 5 days (CHOP) of a three week cycle,
- rituximab 375 mg/m^2 on day 1 plus cyclophosphamide 750 mg/m^2 on day 1, vincristine at 1.4 mg/m^2 on day 1 and prednisone 100 mg/day for 5 days (CVP) of a three week cycle or
- rituximab 375 mg/m^2 on day 1 plus fludarabine 25 mg/m^2 on days 1–3 of a four week cycle.

Eligibility criteria included age over 18 years and a World Health Organization or an Eastern Cooperative Oncology Group performance status score of two or less[2-4].

STiL NHL1: Bendamustine plus rituximab versus CHOP plus rituximab – first-line treatment

This study was conducted in Germany in 549 patients with treatment-naive newly diagnosed stage III or IV indolent or mantle cell lymphoma[2].

Patients were stratified by lymphoma subtype then randomized 1:1 to receive rituximab plus either bendamustine or CHOP[2]. The primary endpoint was progression-free survival, with a non-inferiority margin of 10%. Analysis was per-protocol; 35 patients were excluded therefore 261 were treated with bendamustine plus rituximab and 253 with rituximab plus CHOP. Of the patients included in the analysis, 279 had follicular lymphoma, 67 had marginal zone lymphoma and 41 had Waldenstrom's macroglobulinaemia. Within the histological subgroups, the median age of patients was 60 years for those with follicular lymphoma, 66 years for those with marginal zone lymphoma and 64 years for those with Waldenstrom's macroglobulinaemia[2].

In the whole study population, at a median follow-up of 45 months, progression-free survival was significantly longer for patients treated with bendamustine plus rituximab than in those treated with rituximab plus CHOP (Table 1)[2]. This significant benefit was also seen in the sub-group of patients with follicular lymphoma and Waldenstrom's macroglobulinaemia (Table 1). Significant benefit was not demonstrated for marginal zone lymphoma (Table 1). The improvement in progression-free survival with bendamustine plus rituximab was independent of age (≤ 60 years: HR 0.52; 95% CI 0.33 to 0.79; p = 0.002; > 60 years: HR 0.62; 95% CI 0.45 to 0.84; p = 0.002)[2].

For the whole study population the rate of complete response was significantly higher in the bendamustine plus rituximab-treated patients (Table 1), and time to next anti-lymphoma treatment was significantly longer with bendamustine plus rituximab than with rituximab plus CHOP (HR 0.52; 95% CI 0.39 to 0.69; p < 0.0001)[2]. A seven year follow-up study showed no significant difference in the overall survival between the treatment arms for the whole study population[37]. There was a trend toward longer survival for the bendamustine plus rituximab group compared with the rituximab plus CHOP group. The estimated 10-year survival rates for patients with indolent lymphomas were 71.9% for bendamustine plus rituximab and 61.5% for rituximab plus CHOP (HR 0.70; 95% CI 0.48 to 1.04; p = 0.076)[37].

BRIGHT study: bendamustine plus rituximab versus rituximab plus CHOP or rituximab plus CVP – first-line treatment

This study was conducted in 447 patients with treatment-naive CD-20 positive indolent non-Hodgkin's lymphoma or mantle cell lymphoma with an estimated life expectancy of at least six months[3]. Histologic subtypes of patients were; follicular lymphoma (n = 314), marginal zone lymphoma (n = 46) and Waldenstrom's macroglobulinaemia (n = 11). Patients were preassigned to the most appropriate standard chemotherapy regimen, either rituximab plus CHOP or rituximab plus CVP, based on their performance status, co-morbidities and general

health. They were then randomised in a 1:1 ratio to receive either bendamustine plus rituximab (n = 224) or the standard chemotherapy (rituximab plus CHOP: n = 104; rituximab plus CVP: n = 119). During the assessment period no patient received maintenance rituximab treatment. Randomisation was stratified by the pre-determined chemotherapy and by lymphoma type[3].

The primary endpoint was complete response rate, with a non-inferiority threshold of 22%[3]. Complete response was defined by International Working Group criteria as disappearance of all evidence of disease[38], and was evaluated by an independent review committee in a blinded manner[3]. The analyses were conducted for evaluable patients in each treatment group: 213 patients who received bendamustine plus rituximab; 206 who received rituximab plus either CHOP or CVP[3].

Overall, the results showed that the bendamustine plus rituximab combination was statistically non-inferior to rituximab plus CHOP or rituximab plus CVP in the evaluable patient population, as assessed by complete response rate (Table 1)[3]. Overall response rates were 97% in the bendamustine plus rituximab group and 91% in the standard chemotherapy groups (complete response-rate ratio 1.04; 95% CI 0.99 to 1.09; p = 0.0102). In subgroup analysis non-inferiority was approached in the follicular lymphoma subset as assessed by complete response rate (Table 1). Non-inferiority was not reached in the indolent non-Hodgkin's lymphoma group as a whole (complete response: bendamustine plus rituximab 28% versus rituximab plus CHOP/CVP 25%; complete response-rate ratio 1.16; 95% CI 0.81 to 1.65; p = 0.1289).

Health-related quality of life data were collected during treatment using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[6]. Results showed that treatment with bendamustine plus rituximab was associated with improved functioning scores at several time points. Scores for Cognitive Functioning, Physical Functioning, Social Functioning, Emotional Functioning and Global Health Status, measured at various time points, were the same or improved with bendamustine plus rituximab compared with standard therapy. However, the clinical significance of the benefits was small and differences were not statistically significant at all time points[6].

Bendamustine plus rituximab versus fludarabine plus rituximab – relapsed disease

This study was conducted in Germany in 230 patients with relapsed or refractory stage III or IV indolent or mantle cell lymphomas[4].

Patients with lymphomas that were refractory to regimens that included rituximab, bendamustine or purine analogues were excluded[4]. The median number of previous treatments was 1; 15% had received more than two previous treatments and over 50% of these were CHOP-based chemotherapy. Patients were stratified by lymphoma subtype then randomised 1:1 to receive rituximab plus either bendamustine (n = 116) or fludarabine (n = 114)[4].

The primary endpoint was progression-free survival for the per-protocol population, with a non-inferiority margin of 15%[4]. Analysis was per-protocol: 11 patients were excluded, therefore the analysis included 114 patients treated with bendamustine plus rituximab and 105 treated with rituximab plus fludarabine. Of the 219 patients, 111 had follicular lymphoma, 24 had Waldenstrom's macroglobulinaemia and 18 had marginal zone lymphoma. During the study rituximab was approved for maintenance treatment of relapsed follicular lymphoma. The study protocol was then amended to give rituximab maintenance therapy to patients whose follicular lymphoma had responded to either treatment[4].

The median follow-up was 96 months[4]. For the whole study population the median

progression-free survival and overall survival was longer in patients treated with bendamustine plus rituximab than in those receiving fludarabine plus rituximab (Table 1). More patients did not respond to treatment and had progressive disease on fludarabine plus rituximab treatment than with bendamustine plus rituximab ($p < 0.0001$). Subgroup analysis showed that patients with follicular lymphoma had longer progression-free survival with bendamustine plus rituximab treatment compared with fludarabine plus rituximab (Table 1). Results were not provided for the subgroup of patients with marginal zone lymphoma. Additional subgroup analysis showed that progression-free survival and overall survival were longer in patients who received rituximab maintenance therapy than in those who did not receive maintenance treatment[4].

Table 1. The results from the phase III studies

	First-line				Relapsed	
	STiL NHL1[2]		BRIGHT[3]		Rummel et al. 2016[4]	
Overall population	**BR (n = 261)**	**R-CHOP (n = 253)**	**BR (n = 213)**	**R-CHOP/R-CVP (n = 206)**	**BR (n = 114)**	**RF (n = 105)**
Progression Free Survival (months)	69.5	31.2	NR		34.2	11.7
Hazard Ratio (95% CI)	0.58 (0.44–0.74)				0.54 (0.38–0.72)	
p value	p < 0.0001				p < 0.0001	
Complete Response	40%*	30%*	67%†	52%†	40%	17%
CR ratio (95% CI)	NR		1.26 (0.93–1.73)		NR	
p value	p = 0.021		p = 0.0225		p = 0.0002	
Overall Survival (years)	NR		NR		9	4
Hazard Ratio (95% CI)					0.64 (0.45–0.91)	
p value					p = 0.012	
Follicular lymphoma population[§]	**BR (n = 139)**	**R-CHOP (n = 140)**	**BR (n = 148)**	**R-CHOP/R-CVP (n = 149)**	**BR (n = 58)**	**RF (n = 53)**
Progression Free Survival (months)	Not reached	40.9	NR		54.5	22.9
Hazard Ratio (95% CI)	0.61 (0.42–0.87)				0.56 (0.34–0.87)	
p value	p = 0.0072				NR	
Complete Response	NR		30%†	25%†	NR	
CR ratio (95% CI)			1.27 (0.87–1.84)			
p value			p = 0.0569			
Marginal zone lymphoma[§]	**BR (n = 37)**	**R-CHOP (n = 30)**	**BR (n = 25)**	**R-CHOP/R-CVP (n = 17)**	**BR (n = 10)**	**RF (n = 8)**
Progression Free Survival (months)	57.2	47.2	NR		NR	
Hazard Ratio (95% CI)	0.70 (0.34–1.43)					
p value	p = 0.3249					
Complete Response	NR		20%†	24%†	NR	
Waldenstrom's macroglobulinaemia[§]	**BR (n = 22)**	**R-CHOP (n = 19)**	**BR (n = 5)**	**R-CHOP/R-CVP (n = 6)**	**BR (n = 13)**	**RF (n = 11)**
Progression Free Survival (months)	69.5	28.1	NR		NR	
Hazard Ratio (95% CI)	0.33 (0.11–0.64)					
p value	p = 0.0033					
Complete Response	NR		0%	17%†	NR	

BR: bendamustine plus rituximab; CI: confidence interval; CR: complete response; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP: rituximab plus cyclophosphamide, vincristine and prednisone; R-F: rituximab plus fludarabine; NR: not reported.
* Assessed by the World Health Organization response criteria.
† Assessed by an independent review committee.
§ Exploratory sub-group analyses

Retrospective study:
A retrospective study was conducted in European centres of 271 patients with low-grade non-Hodgkin's lymphoma, with the aim of comparing the efficacy and safety of rituximab plus bendamustine and rituximab plus CHOP[13].

Eligibility criteria included age over 18 years with newly diagnosed low grade non-Hodgkin's lymphoma and a WHO performance status of ≥ 2. Patients underwent first-line treatment with either rituximab plus bendamustine (n = 90) or rituximab plus CHOP (n = 173), as per the STiL NHL1 study, based on the physician's choice[13]. Patients were stratified by lymphoma subtype then randomized 1:1 to receive either treatment, with the exception of patients with follicular lymphoma: 54 were treated with rituximab plus bendamustine and 138 with rituximab plus CHOP[13].

There were several differences in the baseline characteristics between the treatment groups[13]. Patients who received bendamustine plus rituximab were older at the time of diagnosis (median age 65 years versus 57 years; $p < 0.001$), were more likely to be male (63% versus 48%; $p = 0.02$), had a higher rate of B-symptoms (32% versus 24%; $p = 0.05$) and bone marrow involvement (48% versus 36%; $p = 0.05$) and a higher rate of extranodal disease (61% versus 45%; $p = 0.05$) compared to patients that were given rituximab plus CHOP[13].

The median follow-up was 5.9 years for patients treated with bendamustine plus rituximab and 6.8 years for patients treated with rituximab plus CHOP[13]. The overall response rate (94% for bendamustine plus rituximab-treated patients compared with 92% for rituximab plus CHOP-treated patients) and complete remission (63% versus 66%) were similar in both groups[13]. There was no difference in the overall survival and progression-free survival between both groups. However, bendamustine plus rituximab increased progression-free survival in the subgroup of patients with follicular lymphoma compared to rituximab plus CHOP (152 months versus 132 months; $p = 0.05$)[13].

Safety

Bendamustine plus rituximab is associated with high incidences of serious haematological toxicities, in common with other chemotherapy regimens used to treat indolent non-Hodgkin's lymphoma.

In the STiL NHL1 study, patients treated with bendamustine plus rituximab had fewer toxic effects than those treated with rituximab plus CHOP; serious adverse events occurred in 49 patients (19%) treated with bendamustine plus rituximab and in 74 (29%) treated with rituximab plus CHOP[2]. Fewer incidences of grade 3–4 neutropenia and leukopenia were reported in patients treated with bendamustine plus rituximab than in those treated with rituximab plus CHOP ($p < 0.0001$). The use of granulocyte-colony stimulating factors was significantly reduced in the bendamustine plus rituximab group compared with the rituximab plus CHOP group (4% versus 20%; $p < 0.0001$). Infections were significantly less frequent in patients treated with bendamustine plus rituximab and neurotoxic effects, specifically peripheral neuropathy, were less common. No patients treated with bendamustine plus rituximab had alopecia, whereas all patients treated with rituximab plus CHOP did have alopecia. Drug-associated erythematous skin reactions were more common in patients treated with bendamustine plus rituximab ($p = 0.024$)[2]. The adverse events reported in this phase III trial were similar to those reported in the retrospective study[13].

In the BRIGHT study, patients treated with bendamustine plus rituximab had a higher incidence of nausea and vomiting, and drug hypersensitivity reactions than patients treated with the standard chemotherapy regimens[3]. Standard chemotherapy regimens plus rituximab were associated with a significantly higher incidence of peripheral neuropathy/paresthesia

and alopecia than bendamustine plus rituximab[3].

In the study of bendamustine plus rituximab versus rituximab plus fludarabine in treating relapsed indolent lymphomas, no substantial differences were noted between treatment groups for the occurrence of adverse events such as alopecia, stomatitis, erythema and allergic reactions or infections[4]. Haematological toxicities were also similar between the treatment groups. The most common adverse events were infections and myelosuppression[4].

In 2012 a Cochrane review of bendamustine in treating indolent B cell lymphoid malignancies based on five studies in 1,343 people (around 45% of whom had follicular lymphoma), concluded that the risk of grade 3 or 4 adverse events was similar when bendamustine was compared with CHOP and fludarabine, and higher when compared with chlorambucil[5].

Clinical effectiveness issues

Two of the phase III studies and the retrospective study showed that bendamustine plus rituximab is at least not inferior, and may be superior, to standard chemotherapy regimens for the treatment of previously untreated and relapsed indolent lymphomas. In the evaluable population of the phase III BRIGHT study, bendamustine plus rituximab was non-inferior to standard chemotherapy for the first-line treatment of indolent non-Hodgkins lymphoma. However, non-inferiority was not reached in the indolent non-Hodgkin's lymphoma group as a whole.

All the studies reported are open label, which could potentially introduce bias. However, blinding was not possible because of the different treatment regimens. The lack of blinding in the BRIGHT study may have influenced the health-related quality of life results[3]. The BRIGHT study included a blinded independent review committee to assess the complete response rate, the primary endpoint[6].

The three phase III studies were designed to demonstrate non-inferiority of bendamustine plus rituximab to the other treatments; any analyses for superiority were conducted *post hoc*. In all three, the analysis for the primary endpoint was per-protocol (evaluable patients only) rather than intention-to-treat. This could have introduced bias. In addition all sub-group analyses conducted in the phase III studies were exploratory rather than prospectively defined. The results of the sub-analyses should be interpreted with caution.

Limitations of the retrospective study were reported by the authors. Firstly, all participating centres performed independent pathology reviews and a central pathology review was not performed[13]. Secondly, the clinical factors assessed at the time of diagnosis were not well balanced between the two treatment groups as patients treated with bendamustine plus rituximab had a higher percentage of negative prognostic parameters than the rituximab plus CHOP group. This was expected, since in clinical practice bendamustine plus rituximab was initially reserved for elderly and patients unfit for rituximab plus CHOP treatment[13].

The studies in the first-line setting did not include patients with Waldenstrom's macroglobulinaemia unsuitable for anthracycline-based therapy. The clinical effectiveness of bendamustine plus rituximab and the associated adverse events have not been investigated in this fragile population.

The phase III study evaluating bendamustine plus rituximab versus rituximab plus fludarabine was conducted over a long period of time, and the study protocol was changed after three years to include rituximab maintenance therapy for those patients with follicular lymphoma (n = 111; 50%)[4], which is standard treatment. This was likely to have increased median progression-free survival. Additionally, only 42% of patients recruited were previously

treated with rituximab, which is not representative of current practice[4]. This was the only study identified of rituximab plus bendamustine in relapsed indolent lymphoma.

Rituximab plus fludarabine is considered by clinical experts in Wales to be a potential comparator for the treatment of Waldenstrom's macroglobulinaemia (first line and relapsed disease); however it is not deemed a relevant comparator for the treatment of follicular and marginal zone lymphoma. Therefore, the evidence to support head to head data in the relapsed setting of these lymphomas is lacking.

The median age of patients in the four studies ranged from 58 years to 70 years[2-4,13]. The incidence of non-Hodgkin lymphoma increases with age, with a median age at diagnosis of 67 years[2]. This shows that the patient groups were broadly representative of patients seen in clinical practice. A limitation common to the four studies includes the small number of patients[2-4,13].

The phase III studies showed that bendamustine plus rituximab has a safety profile that is distinct from those of the standard chemotherapy regimens, and has some favourable aspects[3]. In the first-line treatment of indolent lymphomas bendamustine plus rituximab showed a generally lower incidence of alopecia and neuropathy, with a higher incidence of skin reactions and drug sensitivity[2].

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

Cost-effectiveness evidence

The literature search by AWTTC identified two cost-effectiveness analyses relevant to this review. The first study was conducted in England and Wales and compared bendamustine plus rituximab and rituximab plus CHOP, and rituximab plus CVP as described below [7]. The second study was conducted in Spain, and therefore was not considered as relevant and will not be discussed further[39].

The UK study developed a cost-utility analysis comparing bendamustine plus rituximab with rituximab plus CHOP and rituximab plus CVP as a first-line treatment for indolent non-Hodgkin's lymphoma[7]. Health effects were expressed as quality-adjusted life years (QALYs). The analysis was conducted from the perspective of the NHS in England and Wales, with a lifetime time horizon[7].

It was assumed that patients followed the same treatment pathway irrespective of regimen[7]. Patients entered the model in a state of being progression-free at first line. They could receive induction therapy of: bendamustine plus rituximab or rituximab plus CHOP, each for a maximum of six cycles as per the STiL NHL1 study[2]; or rituximab plus CVP with a maximum of eight cycles. Responders to induction therapy were assumed to begin rituximab 375 mg/m^2 maintenance therapy eight weeks after completion of induction therapy. Maintenance therapy was administered every eight weeks for a maximum of 24-months. Non-responders (with stable or progressive disease) were not treated further, but were assumed to be monitored until disease progression, at which time they received second-line therapy[7].

Choice of second-line therapy was determined by first-line treatment, response, age and progression free state[7]. Second-line therapies were modelled as per the Sheffield School of Health and Related Research (ScHARR) approach[40]. Responders to induction were eligible for second-line rituximab maintenance as recommended by NICE, given every 12 weeks for 24 months. After a second progression event, patients entered a progressive disease state, where they resided until death. There was no explicit modelling of third-line treatment

outcomes.

The model inputs were based on the ScHARR model developed during the NICE appraisal of rituximab for the first-line treatment of follicular lymphoma[40] with the addition of the indolent lymphoma population from STiL NHL1[2]. The BRIGHT study was excluded as it was only available as a conference abstract[41]. The time to progression for rituximab plus CVP was assumed to be equivalent to rituximab plus CHOP for a given response category, which clinical experts judged to be conservative as rituximab plus CHOP is considered to provide better disease control than rituximab plus CVP[7].

Utility values were obtained from a study of 222 patients with follicular lymphoma, which used the EQ-5D questionnaire[42]. This study was carried out in patients with follicular lymphoma, whereas this analysis included patients with other indolent non-Hodgkin's lymphoma sub-types. Clinical experts were consulted and their opinion was that different disease states will be associated with equivalent quality-of-life, regardless of histology. Disutility for adverse events was calculated as a decrement of 15% for 45 days[7].

Costs were taken from the British National Formulary, NHS reference costs 2010-2011, and ScHARR[7]. In cases where multiple chemotherapies were administered in a single day, the highest administration cost was applied and assumed to cover administration of all chemotherapy drugs. Delivery of chemotherapy and maintenance therapy was assumed to occur on a day-case basis. 15% of bendamustine plus rituximab and 35% of rituximab plus CHOP patients received granulocyte colony stimulating factor in the model. The expected treatment cost per cycle was £3,358 for bendamustine plus rituximab, £2,381 for rituximab plus CHOP, and £2,174 for rituximab plus CVP. Drug acquisition costs were calculated assuming a mean body surface area of 1.8 m^2. Costs and utilities were discounted at 3.5% per annum. Where necessary, costs were inflated to 2012 prices using the Hospital and Community Health Services Pay and Prices Index[7].

The key sensitivity analyses explored the impact of using utility values depending on the depth of response and stage of treatment, and the impact of assuming equal progression free survival for first line rituximab plus CHOP and rituximab plus CVP[7]. A probabilistic sensitivity analysis was also conducted[7].

Results

Table 2. Base case results – bendamustine plus rituximab compared to rituximab plus CHOP, and bendamustine plus rituximab compared to rituximab plus CVP[7]

	B-R	R-CHOP	Difference
Total costs	£63,453	£59,627	**£3,836**
Total life-years	9.05	8.20	**0.85**
Total QALYs	7.19	6.46	**0.73**
ICER	**£5,249**		
	B-R	**R-CVP**	**Difference**
Total costs	£63,453	£58,532	**£4,921**
Total life-years	9.05	8.32	**0.72**
Total QALYs	7.19	6.58	**0.61**
ICER	**£8,092**		

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year; B-R:bendamustine plus rituximab; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP: rituximab plus cyclophosphamide, vincristine and prednisone.

At a £20,000 QALY threshold, the probability of bendamustine plus rituximab being cost effective was 94% compared with rituximab plus CHOP and 78% compared with rituximab plus CVP in the probabilistic sensitivity analysis[7].

Table 3. Results of deterministic sensitivity analyses[7]

	Parameter	ICER	
		B-R vs R-CHOP	B-R vs R-CVP
Increasing the hazard of progression for R-CVP vs R-CHOP	HR, PFS, R-CVP versus R-CHOP[43]	£5,249	£4,733
Length of treatment benefit	80 months	£7,796	£12,061
Impact of time cut-off for early relapse	−6 months	£5,254	£7,955
No death as progression event in first progression free state	0	£5,381	£9,479
No clinical effect of rituximab maintenance	$HR_{R\text{-}maint} = 1.0$	£6,082	£11,890
Applying primary utility scores[42].	Wild et al.[42]	£4,400	£6,000
ICER: incremental cost effectiveness ratio; B-R: bendamustine plus rituximab; HR: hazard ratio; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP: rituximab plus cyclophosphamide, vincristine and prednisone; R-maint: rituximab maintenance.			

Overall, the model predicted that indolent non-Hodgkin's lymphoma patients treated with bendamustine plus rituximab at first line will have a longer survival time than those treated with rituximab plus CHOP and rituximab plus CVP[7]. The STiL NHL1 study did not show any difference between treatments in overall survival, as discussed in the efficacy section[2]. A long-term survival benefit of bendamustine plus rituximab was considered plausible by clinical experts.

Health economic issues

The limitations discussed in the published papers include:

- no head-to-head studies of rituximab plus CVP and bendamustine plus rituximab
- a lack of mature overall survival data in the STiL NHL1 study and,
- a lack of health-related quality of life data. The health-related quality of life scores used did not differentiate between having a complete or partial response, or between being in first or second remission.

The model is based on a model submitted to NICE[40] with a few variations that are explained, with inputs taken from published sources.

BUDGET IMPACT

The budget impact focuses on the costs of bendamustine because patients with indolent lymphoma would receive rituximab as part of any alternative regimen and therefore the use of rituximab in combination does not represent a change in costs. The list price of bendamustine is £6.85 for 25 mg and £27.77 for 100 mg[44]. The dose of bendamustine is 90 mg/m^2 body surface area on days 1 and 2 of a cycle. Clinical experts indicate that a cycle is 28 days in length and on average a patient will have six cycles. Patients are already receiving this regimen through IPFR and local applications. Sixteen patients across three health boards have accessed this regimen over the last 12 months. Excluding these patients from the estimated 77 eligible patients (see incidence/prevalence section) leaves 61 patients. Data from other health boards are unavailable. Table 4 details the estimated annual budget impact in Wales. This excludes VAT and any local contracting agreements.

Table 4. Estimated Annual Budget Impact in Wales (costs are not discounted)

	Year 1	Year 2	Data Source
Bendamustine [*] [†] [§]	£572	£572	BNF
Number of eligible patients per annum	77	77	Welsh Cancer Intelligence and Surveillance Unit[19] Cancer Research UK[20] Nazeef et al[21]
Number of patients known to have already received bendamustine plus rituximab	**16**	**16**	**Local Health Board and IPFR data**
Patients treated per annum	**61**	**61**	
Net medicine cost	**£34,892**	**£34,892**	

[*] This assumes vial sharing and zero wastage.
[†] This assumes a body surface area of 1.91 m^2.
[§] This assumes six cycles of treatment.

Bendamustine is administered by intravenous infusion on two days of a cycle, for the other rituximab-containing regimens intravenous administration is on one day of a treatment cycle. One extra day of medicine administration per cycle may incur additional resource cost, this will depend upon current service capacity

Budget impact issues

- The budget impact has not considered the discontinuation of therapy and mortality rates.
- The analysis does not include costs of adverse events.
- The analysis does not consider treatment switching.
- In current practice there are a proportion of patients already receiving bendamustine in combination with rituximab in these settings, in the absence of a suitable alternative treatment. Bendamustine in combination with rituximab is accessed through local agreements and individual patient funding requests. We do not have accurate figures for the total number of these patients in Wales. Where information has been provided the number has been taken from the estimated total eligible patients.

Welsh commercial access agreement

These medicines are currently not licensed for the indication under consideration (i.e. off-label). Therefore, because the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the relative companies.

Comparative unit costs

Table 5 provides the approximate cost per patient for medicines that could be used in patients with indolent lymphomas based on advice from clinical experts in Wales. The following assumes a body surface area of 1.91 m^2.

Table 5. Examples of medicine acquisition costs

Regimens	Example doses per cycle or 28 days*	Cost per patient per cycle
Bendamustine plus rituximab (MabThera®)[45]	Rituximab 375 mg/m^2 IV on day 1, bendamustine 90 mg/m^2 IV on days 1 and 2 of a 4-week cycle	£1,346
Rituximab (MabThera®) plus CHOP[46]	Rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1; oral prednisolone 100 mg on days 1–5, every 21 days	£1,486
Rituximab (MabThera®) plus CVP[3]	Rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1; oral prednisolone 100 mg on days 1–5, every 21 days	£1,309
Idelalisib (Zydelig®)	150 mg orally twice daily for 28 days*	£2,907
Rituximab (MabThera®) plus FC[47]	Rituximab 375 mg/m^2 IV on day 1, cyclophosphamide 120 mg/m^2 orally on days 1–4, fludarabine 25 mg/m^2 orally on days 1–4	£1,661

*costs are given per cycle for all regimes except idelalisib; for idelalisib cost given is for 28 days of treatment.
IV: intravenous
Costs are based on Monthly Index of Medical Specialities (MIMS) and British National Formulary list prices[44,48].
Where generic medicines are available the lowest cost is used.
Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[8,9,49-53] .
Assuming vial sharing and zero wastage.
Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Bendamustine plus rituximab is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

REFERENCES

1. NHS England. National Cancer Drugs Fund List. v1.21 2nd March 2017. 2017. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/03/national-cdf-list-v1-21.pdf. Accessed Mar 2017.
2. Rummel M, Niederle N, Maschmeyer G et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomise, phase 3 non-inferiority trial. *The Lancet.* 2013;381(6):1203-1210. Available at: http://www.sciencedirect.com/science/article/pii/S0140673612617632. Accessed Jan 2017.
3. Flinn I, van der Jagt R, Kahl B et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood.* 2014;123(19):2944-2952. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260975/. Accessed Jan 2017.
4. Rummel M, Kaiser U, Balser C et al. 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.* 2016;17(1):57-66. Available at: http://www.sciencedirect.com/science/article/pii/S1470204515004477. Accessed Jan 2017.
5. Vidal L, Gafter-Gvili A, Gurion R et al. Bendamustine for patients with indolent B cell lymphoid malignancies including chronic lymphocytic leukaemia. *Cochrane Database of Systematic Reviews.* 2012;9:CD009045. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009045.pub2/full. Accessed Feb 2017.
6. Burke JM, van der Jagt RHC, Kahl BS et al. Differences in quality of life between bendamustine-rituximab and R-CHOP/R-CVP in patients with previously untreated advanced indolent non-Hodgkin lymphoma or mantle cell lymphoma. *Clin Lymphoma Myeloma Leuk.* 2016;16(4):182-190. Available at: http://ac.els-cdn.com/S2152265016000203/1-s2.0-S2152265016000203-main.pdf?_tid=a165eb1e-dc8e-11e6-a815-00000aacb35f&acdnat=1484641763_8bfc2fc4642d89d8373e86cce2f08974.
7. Dewilde S, Woods B, Castaigne JG et al. Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales. *Journal of Medical Economics.* 2014;17(2):111-124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24308372. Accessed Feb 2017.
8. Napp Pharmaceuticals Limited. Levact®. Summary of Product Characteristics. Feb 2015. Available at: https://www.medicines.org.uk/emc/medicine/23469#PHARMACOLOGICAL_PROPS. Accessed Jan 2017.
9. Roche Products Limited. MabThera® 100 mg and 500 mg concentrate for solution for infusion. Summary of Product Characteristics. June 2016. Available at: https://www.medicines.org.uk/emc/medicine/2570. Accessed Jan 2017.
10. National Institute for Health and Care Excellence. Technology Appraisal Suspended ID434. lymphoma (non Hodgkin's) - bendamustine (with rituximab). May 2016. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag278. Accessed Mar 2017.
11. Derbyshire M. Patent expiry dates for best-selling biologicals. *Generics and Biosimilars Initiative Journal.* 2015;4(4):178-179. Available at: http://gabi-journal.net/patent-expiry-dates-for-best-selling-biologicals.html. Accessed Feb 17.
12. European Medicines Agency. Summary of opinion; Initial authorisation: Truxima®. Procedure No.: EMA/CHMP/813387/2016. Dec 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004112/WC500218017.pdf. Accessed Feb 2017.
13. Mondello P, Steiner N, Willenbacher W et al. Bendamustine plus rituximab versus R-CHOP as first-line treatment for patients with indolent non-Hodgkin's lymphoma: evidence from a multicenter, retrospective study. *Annals of Hematology.* 2016;95(7):1107-1114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27103007. Accessed Jan 2017.
14. Roche Products Limited. MabThera® 1400 mg solution for subcutaneous injection. Summary of Product Characteristics. June 2016. Available at: https://www.medicines.org.uk/emc/medicine/28732. Accessed Feb 2017.
15. National Institute for Health and Care Excellence. NICE Guideline, NG52. Non-Hodgkin's lymphoma: diagnosis and management. July 2016. Available at: https://www.nice.org.uk/guidance/ng52. Accessed Jan 2017.
16. Cancer Research UK. Non Hodgkin lymphoma. July 2015. Available at: http://www.cancerresearchuk.org/about-cancer/type/non-hodgkins-lymphoma/. Accessed Jan 2017.
17. National Institute for Health and Care Excellence. Technology Appraisal 243. Rituximab for the first-line treatment of stage III-IV follicular lymphoma. Jan 2012. Available at: https://www.nice.org.uk/guidance/ta243. Accessed Jan 2017.
18. Lymphoma association. Non-Hodgkin lymphoma. April 2016. Available at: https://www.lymphomas.org.uk/about-lymphoma/types/non-hodgkin-lymphoma. Accessed Jan 2017.
19. Welsh Cancer Intelligence and Surveillance Unit. Interactive cancer statistics tool. Feb 2016. Available at: http://www.wcisu.wales.nhs.uk/interactive-cancer-statistics-tool. Accessed Jan 2017.
20. Cancer Research UK. Non-Hodgkin lymphoma (NHL) incidence by stage at diagnosis. 2014. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence#heading-Three. Accessed Mar 2017.

21. Nazeef M KB. Mantle cell lymphoma: first-line therapy in pateints not eligible for stem cell transplantation. *Current Treatment Options in Oncology.* 2015;16(29). Available at: https://www.ncbi.nlm.nih.gov/pubmed/25975443. Accessed Mar 2017.
22. National Institute for Health and Care Excellence. Treating follicular lymphoma. 2016. Available at: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma#path=view%3A/pathways/non-hodgkins-lymphoma/treating-follicular-lymphoma.xml&content=view-index. Accessed Jan 2017.
23. Dreyling M, Ghielmini M, Rule S et al. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2016;27(5):83-90. Available at: http://www.esmo.org/Guidelines/Haematological-Malignancies/Newly-Diagnosed-and-Relapsed-Follicular-Lymphoma. Accessed Jan 2017.
24. National Institute for Health and Care Excellence. Technology Appraisal 137. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma. Feb 2008. Available at: https://www.nice.org.uk/guidance/ta137. Accessed Nov 2016.
25. South Wales Cancer Network. Follicular lymphoma haematological pathway. 2013. Available at: www.cancerservicesdirectory.wales.nhs.uk/opendoc/266969. Accessed Nov 2016.
26. National Institute for Health and Care Excellence. Treating MALT lymphoma. 2016. Available at: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma/treating-malt-lymphoma. Accessed Feb 2017.
27. Dreyling M, Thieblemont C, Gallamini A et al. ESMO Consensus conferences: guidelines on malignant lymphoma, part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Annals of Oncology.* 2013;24(4):857-877. Available at: http://www.esmo.org/Guidelines/Haematological-Malignancies/Marginal-Zone-Lymphoma-Mantle-Cell-Lymphoma-Peripheral-T-cell-Lymphoma. Accessed Feb 2017.
28. Owen R, Pratt G, Auer R et al. Guidelines on the diagnosis and management of Waldenstrom macroglobulinaemia. *British Journal of Haematology.* 2014;165(3):316-333. Available at: http://onlinelibrary.wiley.com/doi/10.1111/bjh.12760/pdf. Accessed Jan 2017.
29. Buske C, Leblond V, Dimopoulos M et al. Waldenstrom's macroglobulinaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2013;24(6):55-59. Available at: http://oncologypro.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines/Haematological-Malignancies/Waldenstrom-s-Macroglobulinemia. Accessed Jan 2017.
30. National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma. 2016. Available at: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma. Accessed Jan 2017.
31. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-Hodgkin's lymphoma. 2014. Available at: https://www.nccn.org/about/nhl.pdf. Accessed Jan 2017.
32. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 3414. Rituximab (MabThera®) 1,400 mg solution for subcutaneous injection. Jan 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1048. Accessed Feb 2017.
33. All Wales Medicines Strategy Group. Idelalisib (Zydelig®) 100 mg and 150 mg film-coated tablets. Reference number: 2597. Appraisal information. Jan 2017. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2597. Accessed Jan 2017.
34. National Institute for Health and Care Excellence. Technology Appraisal in development. Lymphoma (follicular, rituximab-refractory)-obinutuzumab (with bendamustine) [ID841]. Expected publication date: Jan 2017. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10020. Accessed Jan 2017.
35. National Institute for Health and Care Excellence. Technology Appraisal in development. Waldenstrom's macroglobulinaemia - ibrutinib [ID884]. Expected publication date: March 2017. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10046. Accessed Jan 2017.
36. National Institute for Health and Care Excellence. Technology Appraisal in development. Obinutuzumab for untreated indolent non-Hodgkin lymphoma [ID1020]. Expected publication date: Jan 2018. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10137. Accessed Feb 2017.
37. Rummel M, Maschmeyer G, Ganser A et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent and mantle cell lymphomas (MCL) - 7 year updated results from the StiL NHL1 study. *Blood.* 2014;124:4407. Available at: http://www.bloodjournal.org/content/124/21/4407?sso-checked=true. Accessed March 2017.
38. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology.* 2007;25(6):579-586. Available at: http://ascopubs.org/doi/pdf/10.1200/JCO.2006.09.2403. Accessed Jan 2017.
39. Sabater E, Lopez-Guillermo A, Rueda A et al. Cost-effectiveness analysis of bendamustine plus rituximab as a first-line treatment for patients with follicular lymphoma in Spain. *Applied Health Economics and Health Policy.* 2016;14(4):465-477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27090915. Accessed Feb 2017.
40. Papaioannou D, Rafia R, Rathbone J et al. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of technology appraisal no. 110): a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England).* 2012;16(37):1-253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23021127. Accessed Feb 2017.
41. Flinn I, Van der Jagt R, Kahl B et al. An open-label, randomized study of bendamustine and rituximab (BR) compared with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in first-line treatment of patients

with advanced indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma (MCL): the bright study. Presented at American Society of Hematology annual meeting. 8-11 Dec 2012. *Blood* 120; 902. http://www.bloodjournal.org/content/120/21/902?sso-checked=true. Accessed Feb 2017.

42. Wild D, Pettengell R, and Lewis G. Utility elicitation in patients with follicular lymphoma. Presented at ISPOR 9th Annual European Congress. 28-31 Oct 2006. *Value in Health*. http://www.valueinhealthjournal.com/article/S1098-3015(10)63491-2/abstract. Accessed Feb 2017.
43. Federico M, Luminari S, and Dondi A. CVP-R vs. CHOP-R vs. R-FM for the initial treatment of patients with advanced-stage follicular lymphoma. Final results of the F0LL05 trial from the Fondazione Italiana Linfomi. Presented at ASCO Annual meeting. 1-5 Jun 2012. http://issuu.com/spom/docs/1_8006_federicorev. Accessed Feb 2017.
44. British Medical Association, and Royal Pharmaceutical Society of Great Britain. British National Formulary. Feb 2017. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Feb 2017.
45. Regional Strategic Chemotherapy Group. R-Bendamustine-90 for lymphoma. 2013. Available at: http://stlukescanceralliance.co.uk/wp-content/uploads/2015/10/R-Bendamustine-90-for-low-grade-NHL-V4-8.16.pdf. Accessed 2016.
46. Surrey West Sussex and Hampshire Cancer Network. R-CHOP. 2015. Available at: http://stlukescanceralliance.co.uk/wp-content/uploads/2015/10/R-CHOP-V13-8.16.pdf. Accessed 2016.
47. Derby-Burton Local Cancer Network. Oral fludarabine + cyclophosphamide + rituximab [R-FC-Lite] (PACIFICO Trial - investigational arm). 2014. Available at: http://www.derbyhospitals.nhs.uk/. Accessed Feb 2017.
48. Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Available at: http://www.mims.co.uk/. Accessed Mar 2017.
49. Sandoz Ltd. Cyclophosphamide 1000 mg Powder for Solution for Injection or Infusion. Summary of Product Characteristics. Dec 2014. Available at: http://www.medicines.org.uk/emc/medicine/29592. Accessed Mar 2017.
50. Teva Pharma. Myocet 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion. Summary of Product Characteristics. Apr 2015. Available at: http://www.medicines.org.uk/emc/medicine/28863. Accessed Mar 2017.
51. Hospira UK Ltd. Vincristine Sulphate 1 mg/ml Injection. Summary of Product Characteristics. Mar 2017. Available at: http://www.medicines.org.uk/emc/medicine/7298. Accessed Mar 2017.
52. Gilead Sciences Ltd. Zydelig (Idelalisib) 100 mg®▼. Summary of Product Characteristics. Dec 2016. Available at: http://www.medicines.org.uk/emc/medicine/29202. Accessed Mar 2017.
53. Sanofi. Fludara® oral 10 mg film-coated tablet. Summary of Product Characteristics. Jan 2016. Available at: http://www.medicines.org.uk/emc/medicine/4240. Accessed Mar 2017.