NHS England

Evidence review: Bortezomib for Relapsed/refractory Mantle Cell Lymphoma

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Contents

1. Introduction

- Mantle cell lymphoma (MCL) is a rare sub-type of indolent NHL. However it is one of the most challenging hematologic malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care. (Liu et al., 2015) Not all patients will be treated initially and not all will subsequently receive treatment at relapse.
- MCL accounts for approximately 6% of all newly diagnosed cases of non-Hodgkin lymphoma. Since non-Hodgkin lymphoma comprises approximately 4% of all cancers, MCL is rare. Around 500 patients were diagnosed with MCL in the UK between 2004-2011. (Cancer Research UK)
- The median age at presentation is 60-70 years, and typical survival is 4-5 years. Most patients are initially diagnosed with advanced-stage disease, and are often symptomatic at presentation. (McKay et al., 2012) Common features include widespread lymphadenopathy and splenomegaly, as well as bone marrow infiltration. Leukemic involvement and extranodal disease are common. The disease course can be highly variable. Some patients may have very aggressive disease, whereas others may have a much more indolent course. There is no consensus on its treatment.
- Although MCL often responds well to frontline chemo-immunotherapy with high overall response rates, the responses are not durable and often of relatively short duration and sequential therapies may be necessary. Effective treatment options in the frontline setting have included the addition of rituximab to bendamustine, or R-CHOP with maintenance rituximab following induction therapy.
- After first relapse, prognosis is considered to be very poor with median survival of approximately 1-2 years. (McKay et al., 2012) MCL is proving to be sensitive to novel therapies, for example, bortezomib, lenalidomide, temsirolimus and ibrutinib. (Dreyling et al., 2014) Each has single-agent efficacy in relapsed and refractory disease that may in the near future become useful adjuncts to standard regimens. Other agents in clinical trials include cladribine, idelalisib, and ABT-199. (Smith, 2015)
- Up-front consolidation of chemo-immunotherapy with cytarabine, high-dose therapy and autologous stem cell transplant remains an attractive option for those young, fit patients with chemosensitive disease, regardless of the induction regimen chosen. Reduced-intensity allogeneic stem cell transplant also remains a viable option in those with relapsed or refractory MCL. (McKay et al., 2012)
- The management of relapsed/refractory MCL remains a clinical challenge and standard second-line treatment for relapsed/refractory disease does not exist. Management of relapsed/refractory MCL requires an individualized treatment approach, incorporating factors such as functional status, prior treatments and response to them, and disease biology.
- Bortezomib (Velcade®, Janssen-Cilag Ltd) belongs to the group of drugs known as proteasome inhibitors. It is administered as either a subcutaneous or intravenous injection twice a week for the first two weeks of every three week cycle. Commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia. (Janssen-Cilag Ltd)
- Bortezomib is not licensed for treatment of relapsed mantle cell lymphoma, and therefore will not be considered for NICE appraisal.
- 29 applications for bendamustine in this indication were received by the national CDF in

2014/15, equating to an incidence of ~0.05 per 100,000 population per annum.

- As MCL is a disease with aggressive clinical course manifested by repeated relapsing disease, the key measures are progression-free survival and time to next treatment or treatment free interval.

2. Summary of results

- This evaluation found 5 clinical trials of bortezomib in people with relapsed or refractory mantle cell lymphoma (MCL). The most commonly reported outcomes were various types of treatment response (e.g. complete response, partial response, or stable disease).
- The main assessment of effectiveness in all 5 trials was overall response rate. This was defined as the number of patients who had at least a partial response to treatment. A partial response was defined as at least a 50% decrease in the size of the biggest disease masses, plus any lumps on the liver or spleen shrinking by at least half, no lumps increasing in size, no increase in size of the liver or spleen, and no new areas of the body developing disease.
- The biggest and longest trial found that around a third of the 155 people who took part had a partial response to treatment, or better. A further third had stable disease, meaning that while their health was not improved, it also did not worsen.
- Complete remission is defined as complete disappearance of all detectable evidence of disease. Only 6% of patients in the largest trial achieved this. Around a quarter of patients had disease which continued to progress despite treatment.
- Duration of response is an outcome which describes how long a patient can expect to remain well after responding to treatment. The largest study found that the duration of response to bortezomib in MCL was about 9 months.
- Progression-free survival is the amount of time that a patient can expect to live after treatment, without experiencing any worsening of disease. Progression-free survival was found to be roughly 6 months in patients with MCL who received bortezomib.
- None of the trials compared bortezomib to any other drugs or treatments for MCL. This means that it is not clear whether any benefits to the patient were due to the bortezomib, or whether they were due to the normal course of the disease or to chance.
- Adverse events were common, and were in line with what is already known about the safety of bortezomib. Side effects such as fatigue, neuropathy, and reduced platelet counts were common.
- Because bortezomib was not compared to any other treatments, or to standard care, it is not possible to tell whether bortezomib is any more or less safe than other drugs for MCL.

3. Methodology

- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by the NHS England Clinical and Public Health Leads of the Chemotherapy Clinical Reference Group (see section 10 below).
- The following sources were searched for relevant publications: EMBASE,

MEDLINE, Clinicaltrials.gov, NHS Evidence, Cochrane Library, and the National Institute for Health and Care Excellence (NICE) (see section 11 for search terms). National guidelines were examined and included where relevant.

- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. 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 was extracted from the selected trials and recorded in evidence summary tables (see section 7 below). Only outcomes specified in the PICO were extracted.
- All papers included in this evaluation were assessed as to their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. The evidence to support individual outcomes was graded, and quality was recorded in grade of evidence tables (see section 8 below).

4. Results

Five papers matching the PICO were identified, which reported the results of four trials of bortezomib for treatment of MCL. (Fisher et al., 2006, Goy et al., 2009, O'Connor et al., 2009, Belch et al., 2007, Zinzani et al., 2013) All of the trials were, early-phase, single-arm studies, which ranged in size from 30 to 155 participants. There was no randomisation or blinding in any trial, and no comparison with any other treatment for MCL. No cost-effectiveness studies or evidence on health-related quality of life were located.

Patients were adults with relapsed or refractory MCL despite ≥1 prior treatment. Bortezomib was administered at a dose of 1.3 mg/m^2 on days 1, 4, 8 & 11 of a 21 day cycle, but the number of cycles varied between trials.

Outcomes assessed included overall survival, progression-free survival (PFS), treatment response, disease progression and adverse events. Full details of the trial designs and outcomes are summarised in the evidence tables in section 7, below. Treatment response or remission was the most common measure of efficacy reported. All trials used definitions of treatment response as set out by the International Workshop for Response Criteria. (Cheson et al., 1999) These criteria require several conditions to be met for each category of complete remission (CR), unconfirmed CR (CRu), partial response (PR), stable disease (SD) and progressive disease (PD). For example, CR requires resolution of symptoms, normalisation of blood and biochemical markers, reduction in lymph node masses, resolution of any spleen enlargement, and normalised bone marrow histology. Full definitions are listed in the appendix, below.

Overall response rate

The main efficacy outcome of all four trials was overall response rate (ORR), a composite of CR, CRu and PR (see appendix for definitions of CR, CRu and PR). ORR was 32% (95% CI 24 – 40) in the updated report of PINNACLE, which was the

largest trial and also had the longest reported follow-up. (Goy et al., 2009) The other three studies all reported ORR in the region of 50%, however these are smaller trials and generally of lower quality. (Belch et al., 2007, O'Connor et al., 2009, Zinzani et al., 2013)

Complete remission of disease, either confirmed or unconfirmed, was not common. CR was reported for 6% of patients in the updated PINNACLE trial, while CR or CRu was reported for 8%. CRu is intended to intended to designate patients with curable histologies who have a large mass prior to therapy, and for whom treatment eradicated all but the single persistent mass, which had shrunk by ≥75%. This acknowledges that in most cases the remaining mass represents scar tissue or fibrosis. It should not be applied to patients with multiple masses which have decreased by 75% in total; this is more correctly a partial response. (Cheson, 2008) CRu can also apply to patients with indeterminate bone marrow biopsy post-treatment, and should not be applied to patients who have not had repeated biopsy.

PR was the most common response type in all of the published trials. It was not specifically reported by Goy et al, but given an ORR (CR + CRu + PR) of 32% and reported CR+CRu of 8% (95% CI 4-14), it can be inferred that the majority of treatment responses were defined as partial. The remaining trials all reported PR in 25-40% of patients.

Stable disease is also an important outcome; while not as desirable as full or partial treatment response, the absence of disease progression in this aggressive disease is still positive. SD was reported by three of the published trials (Fisher et al., 2006, Belch et al., 2007, O'Connor et al., 2009), and was 30-40% in each case. One trial (n=15) reported that stable disease was achieved by 6 patients (40%) and maintained for a median of 7.7 months (range 1.2 to 26.1).

Progressive disease despite treatment is the least desirable outcome, but unfortunately still common in the published trials. Fisher et al (n=155) reported PD in 26% of patients (95% CI), while O'Connor et al (n=40) reported the incidence as 8%.

Time to event outcomes

Time to event outcomes such as progression-free survival (PFS), duration of response (DOR) and time to next therapy (TTNT) are important in MCL, since they give information on how long a patient can expect to remain relatively well. DOR was the most commonly reported of these outcomes. The PINNACLE study found median DOR to be 9.2 months (95% CI 5.9-13.8). One other study found that DOR varied with response type. (Belch et al., 2007) One patient had CR with response duration of 24 months. Six patients had PR and a median DOR of 9.8 months (range 2.1 to 25.1) and an additional six patients had stable disease and a DOR of 7.7 months (range 1.2 to 26.1). It should be noted that these data should be interpreted with caution, due to the very small sample size in this trial (n=15).

Progression-free survival was reported by two trials. In the PINNACLE study median PFS was 6.5 months (95% CI 4.0-7.2), while O'Connor et al reported a very similar PFS of 6.2 months in their smaller trial (n=40).

PINNACLE also reported several other time-to-event outcomes which were not addressed by any other trial:

- Time to first response – median 1.4 months
- Time to progression – median 6.7 months (95% CI 4.0 – 7.3)
- Time to next therapy – median 7.4 months (95% CI 5.6 – 9.3)
- Overall survival – median 23.5 months (95% CI 20.3 – 27.9)

Safety

Safety events were reported in all four trials. The largest, PINNACLE, reported that 98% of patients experienced at least one adverse effect (AE) during treatment and 70% of patients experienced at least one AE of grade 3 (moderate) or higher. Commonly reported toxicities of grade ≥3 included peripheral neuropathy (13%), fatigue (12%) and thrombocytopenia (11%). In total 41 patients (26%) discontinued treatment due to an intolerable AE, most commonly peripheral neuropathy (10%) or fatigue (6%).

The updated PINNACLE data reported by Goy et al suggested that the median time to onset of peripheral neuropathy was 4 cycles (12 weeks). It also reported that 67% of patients experienced lymphopenia, and 34% experienced lymphopenia of grade ≥3. There were four deaths considered to be treatment-related; three due to non-neutropenic sepsis, and one due to respiratory failure.

AEs reported by the other trials were in line with the pattern described above, with the most commonly reported events including fatigue, peripheral neuropathies, and haematological toxicities. One trial reported several serious AEs related to oedema or fluid retention, all of which occurred in patients known to have oedema or effusions at baseline. Oedema is a known common AE of bortezomib, and angioedema, lymphoedema, pulmonary oedema and brain oedema have all been reported. (Janssen-Cilag Ltd)

In summary, the pattern of AEs reported in these trials in line with the known AE profile of bortezomib. (Janssen-Cilag Ltd) Given the lack of comparative trial data and the symptoms commonly reported with MCL, it is difficult to determine what proportion of AEs is attributable to bortezomib therapy, and what proportion may be due to symptomatic disease.

5. Discussion

Published trials for bortezomib in relapsed MCL are generally small, of variable quality, and provide limited data on important outcomes such as overall survival and progression-free survival. Trials were single-arm phase 1 or 2 studies, and as such are non-comparative studies which cannot estimate treatment effect. Other important limitations include the small sample sizes; although the largest study (PINNACLE) enrolled 155 patients, others included only 15-40 patients with relapsed or refractory MCL. The trials all used definitions of treatment response as recommended by the International Workshop Response Criteria for non-Hodgkin's lymphomas. (Cheson et al., 1999)

The published evidence is generally of moderate quality. In addition to limitations of the studies themselves, there were problems with the reporting in several cases which limits the applications of any findings. These included:

- failing to specify inclusion/exclusion criteria for enrolled patients
- failing to account for all trial participants at the end of the trial
- failing to specify primary or secondary endpoints

Bortezomib appears to be active in the treatment of relapsed or refractory MCL, although the degree of effectiveness cannot be reliably estimated given the available evidence. There are no published studies comparing bortezomib with other treatments or standard care in patients with relapsed MCL, which further limits interpretation of the endpoints. Similarly, it is difficult to discern whether the adverse events reported are more likely attributable to the disease or to the bortezomib therapy, or whether both contributed to some degree. The PINNACLE trial is the most robust of the published studies and, despite its limitations, suggests that bortezomib may be a useful treatment option for people with relapsed or refractory disease.

Bortezomib is licensed for use in the USA for relapsed or refractory MCL, and current UK guidelines state that bortezomib may be considered for use in this indication. (McKay et al., 2012) Similarly, current European guidance lists bortezomib as an option in relapsed disease. (Dreyling et al., 2014) There is no single best option, and treatment choices should be made on a case-by-case basis. Factors which should be taken into consideration include the patient's age, performance status, bone marrow reserve, and initial treatment.

The published literature on the use of bortezomib to treat relapsed MCL is limited. The evidence in this case does not preclude use, but is too limited to make blanket recommendations. More evidence is required to inform robust treatment decisions.

6. Conclusion

The published evidence on bortezomib for treatment of relapsed MCL consists of several early-phase, non-randomised, non-comparative trials of variable quality. The literature appears to show that bortezomib is active to some extent in the treatment of relapsed mantle cell lymphoma. However, the published trials are very limited and there are no randomised controlled trials comparing bortezomib with other drugs or with standard care. It is therefore not clear whether bortezomib is any more or less effective than other drugs currently used for the treatment of relapsed or refractory disease. Similarly, adverse effects were common, but a lack of comparisons with other drugs or standard care means that it is not clear whether bortezomib is more or less safe than other regimens used in this indication.

In summary, while bortezomib may be a useful treatment option for relapsed or refractory MCL, there is insufficient evidence to make clear recommendations on factors such as patients most likely to benefit from treatment, or combinations with other drugs.

7. Evidence Summary Table

Use of bortezomib to treat relapsed or refractory mantle cell lymphoma									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Fisher et al., 2006). PINNACLE study. JCO 2006, 24(30); 4867-74	P1 – prospective, open-label, multicentre, single-arm, single-agent, Phase 2. Efficacy assessed every 6 wks. (2 cycles) for 18 weeks then every 12 weeks until PD or alternative therapy. 35 centres in North America (n=151) and Europe (n=4)	155 patients with measurable/assessable pathologically confirmed MCL, with documented relapsed or progression following 1 or 2 prior lines of chemotherapy (including an anthracycline or mitoxantrone, and rituximab, each in ≥ 1 line); median age 65 years; 80% male; 92% white; Karnofsky performance status (KPS) of ≥50%; toxicities from previous therapy had to have resolved to grade 2 or lower	Bortezomib 1.3 mg/m2 IV on days 1, 4, 8, and 11 in 21-day cycles. (every 21 days until progression, up to a maximum of 17 cycles - approximately 1-year of treatment)	Secondary Clinical Efficacy	Overall Response Rate (ORR) (CR + CRu + PR))	141 (91%) of the 155 patients were assessable for response. In assessable patients, the ORR was 33% (95% CI 26 – 42).	6	Direct. The population studied appears representative of a relapsed MCL patient group.	This study does not strictly meet the PICO since it was published >10 years ago. However, it is the initial report of the trial published by Goy et al, 2009, and is included here for context. Original primary analysis was a comparison of TTP between bortezomib and historical controls; however, an appropriate cohort of historical control could not be found. Therefore the efficacy analyses are non-comparative (single-arm) assessments of disease response. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions. Disease response and progression were determined by International Workshop Response Criteria (IWRC, see appendix for definitions) 14 patients were not assessable for response; 9 had no post-baseline measurements, 5 had no measurable disease.
					Complete Response (CR + unconfirmed CR)	8% (95% CI 4 – 14).			
					Complete Response (CR)	6% (95% CI 3 – 12)			
					Partial response (PR)	26% (95% CI 26 – 42).			
					Stable disease	33% (95% CI 26 to 42)			
					Progressive disease	25% (95% CI 18 to 33)			
					Duration of response (DOR)	Median 9.2 months (95% CI 4.9 – 13.5).			
					Time to progression (TTP)	Median 6.2 months (95% CI 4.0 – 6.9).			
					Overall survival (OS)	Median OS was not reached after follow-up of 13.4 months.			
				Secondary Safety	Proportion with ≥1 AE	152 (98%)			
					≥1 drug-related AE	145 (94%)			
					Serious AE	60 (39%)			
					Death within 28 days of last bortezomib dose	12 (8%)			
					Treatment-related deaths	5 (3%)			

Use of bortezomib to treat relapsed or refractory mantle cell lymphoma									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					Discontinued treatment due to an AE Peripheral neuropathy Fatigue	41 (26%) 10% 6%			
					Grade ≥3 toxicities	Any 108 (70%) Fatigue 19 (12%) Peripheral neuropathy 20 (13%) Constipation 4 (3%) Diarrhoea 11 (7%) Nausea 4 (3%) Rash 4 (3%) Vomiting 4 (3%) Anorexia 5 (3%) Dizziness 5 (3%) Dyspnoea 7 (5%) Insomnia 1 (<1%) Thrombocytopenia 17 (11%) Musculoskeletal pain 3 (2%) Oedema lower limb 1 (<1%)			

Use of bortezomib to treat relapsed or refractory mantle cell lymphoma									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Goy et al., 2009) Additional follow-up of PINNACLE Ann Oncol 20: 520–525	P1 - Updated time-to-event analyses of the phase 2 PINNACLE study after a median follow-up period of 26.4 months 35 centres in North America (n=151) and Europe (n=4)	As above.	As above	Secondary Clinical Efficacy	Response Rate (CR + CRu + PR)	32% (95% CI 24 – 40)	6	Direct. The population studied appears representative of a relapsed MCL patient group.	These results are an update of the PINNACLE study (Fisher et al, 2006) after an additional 26.4 months follow-up. Design and population characteristics were as described above. Primary/secondary outcomes were not specified in the text, assumed to match those described by Fisher et al. Disease response and progression were determined by International Workshop Response Criteria (IWRC). No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions. Safety outcomes were poorly described. Given that treatment
					Time to first response	Median 1.4 months			
					Complete Response (CR + CRu)	8% (95% CI 4 – 14)			
					Duration of response (DOR)	Median 9.2 months (95% CI 5.9 – 13.8)			
					Time to progression (TTP)	Median 6.7 months (95% CI 4.0 – 7.3).			
					Overall survival (OS)	Median 23.5 months (95% CI 20.3 – 27.9).			
					Time to next therapy (TTNT)	Median 7.4 months (95% CI 5.6 – 9.3).			
					Progression-free survival (PFS)	Median 6.5 months (95% CI 4.0 – 7.2)			
				Secondary Safety	Most common grade ≥3 toxicity (non-haematologic)	Peripheral neuropathy, n=20 (13%)			
					Time to onset for peripheral neuropathy Any grade Grade ≥3	 Median 4 cycles Range 4-30 weeks			
					Lymphopenia Any grade Grade ≥3	 104 (67%) 52 (34%)			
					Death within 28 days of last bortezomib dose	12 (8%)			
					Treatment-related deaths	4 (3%)			

Use of bortezomib to treat relapsed or refractory mantle cell lymphoma									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(O'Connor et al., 2009) Br J Haematol 145(1); 34-9	Multicentre, phase II non-comparative non-randomised single arm study Response was routinely assessed after every 2 cycles, 1 month after finishing treatment, then every 3 months. No planned or actual follow-up duration was reported.	40 adult patients with heavily pre-treated MCL. 1 patient was treatment-naïve. Patients had MCL, measurable disease, ≤3 prior regimens of conventional cytotoxic therapy; no cytotoxic chemotherapy for ≥4 weeks prior to study enrolment; ≥3 months since last administration of any monoclonal antibody; life expectancy of ≥3 months, Karnofsky performance status >60%., no signs of congestive heart failure. Median time since diagnosis = 38 months, median prior treatments =	Bortezomib 1.5 mg/m^2 on days 1, 4, 8 and 11 of a 21 day cycle. Dose reduction to 1.3 mg/m^2 and then to 1.1mg/m^2 for Grade 3 or 4 non-haematological toxicity or Grade 4 haematological toxicity was allowed.	Secondary Safety	Toxicity profile	"Identical to what has been appreciated in this population"	4	Direct.	The bortezomib dose in this trial does not strictly meet PICO. Included here since protocol allowed dose reduction to the specified 1.3 mg/m^2. Full methods were not specified in the trial text. Previous reporting of a subset of these patients was used to determine some details. (O'Connor et al., 2005) Primary/secondary outcomes were not specified. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Insufficient evidence to guide treatment decisions.
				Primary Clinical effectiveness	Overall Response Rate (ORR) not defined.	50% (45% in intention-to-treat population, non-ITT population not defined)			
					Complete Response (CR + CRu)	6 (15%)			
					Partial response (PR)	12 (30%)			
					Median progression free survival (PFS)	All patients – 5.3 months. Patients with CR+ PR – 7.8 months			
					Stable disease (SD)	38%			
					Progressive disease (PD)	8%			

Use of bortezomib to treat relapsed or refractory mantle cell lymphoma									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		2, including rituximab (70%), R-CHOP (62.5%), radiation (20%). Median age = 67.5; 72% male patients							

Use of bortezomib to treat relapsed or refractory mantle cell lymphoma									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Belch et al., 2007) Ann Oncol 18 (1); 116-21	Phase II non-randomised, non-comparative, single arm study. Blood counts were performed on days 1, 8 & 15 of each cycle, biochemistry tests were performed on day 1 of each cycle. Clinical assessment, performance status and lymph node measurements documented every 3 weeks.	30 adults, of whom 15 had relapsed disease and 13 had no prior treatment. Enrolled patients aged ≥18 with previously untreated or relapsed MCL with ≥2 previous treatments. Bi-dimensionally measurable disease, ECOG score of 0-2, no CNS involvement, ≥6 weeks since last dose of chemo-therapy and ≥4 weeks since completion of radiation therapy. ANC ≥1.5x10^9/L, platelets ≥75 x10^9/L, serum creatinine and	Bortezomib i.v. in a dose of 1.3 mg/m^2 by bolus injection for 3–5 seconds on days 1, 4, 8 and 11 of a 21-day cycle. Doses were to be reduced to 1.1 and then 0.9 mg/m2 for hematologic and other adverse events. If toxic effects resulted in more than two dose reductions, the patient discontinued protocol therapy and was treated at the discretion of the investigator. Median 4 cycles per patient (range = 1-9)	Primary Clinical Efficacy	Overall Response Rate (CR + CRu + PR))	46.7% (95% CI 21.3% to 73.4)	6	Direct.	Study enrolled patients who were treatment-naïve. Efficacy results are presented for patients with relapsed disease only. Safety results were not reported separately for patients with treatment-naïve or relapsed disease and are therefore presented for the trial population as a whole. Median follow-up not reported, but can be inferred to be at least 2 years given the reported median DOR. Patients with relapsed disease should be treated as a post-hoc subgroup, and interpreted with appropriate caution. Wide confidence intervals due to small sample size; increases uncertainty in outcome. Results only reported for 13 patients (1 CRu, 6 PR, 6 PD). 2 deaths were reported, but it is not clear if these are the same 2 patients for whom no response was recorded. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions.
					Unconfirmed complete Response (CRu)	1 (6.7%)			
					Complete Response (CR)	0			
					Partial response (PR)	6/15 (40%)			
					Stable disease (SD)	6/15 (40%)			
					Median duration of response (DOR) (range)	CRu – 24.2 months PR – 9.8 months (2.1 to 25.1) SD – 7.7 months (1.2 to 26.1)			
				Secondary Safety	Grade 3 toxicities	Congestive heart failure – 1 Fatigue – 7 Infection – 1 Diarrhoea – 1 Hyponatremia – 1 Dizziness – 1 Sensory neuropathy – 3 Abdominal pain – 2 Arthralgia – 2 Myalgia – 3 Neuropathic pain – 3 Granulocytes – 2 Platelets - 7			
					Grade 4 toxicities	Fatigue – 1			

Use of bortezomib to treat relapsed or refractory mantle cell lymphoma									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		bilirubin ≤1.5xULN, AST≤2.5xULN, ejection fraction ≥45%. Median age 67 years; 72% male; 4 (14%) with stage 3 disease, 25 (86%) with stage 4 disease.			Serious AEs – fluid retention or oedema	5, all in patients with oedema or effusion at baseline.			
					Deaths	2 (1 due to progressive lymphoma, 1 not specified)			
(Zinzani et al., 2013) Haematol Oncol 31(4); 179-82	Multicentre non-randomised non-comparative retrospective analysis. 9 centres, all in Italy	50 patients recruited, of whom 31 had MCL. Median prior treatments = 4 Patients aged ≥18 years with lymphoma progressed or relapsed after ≥2 previous therapies, and treated with bortezomib as salvage treatment in off-label setting. Median age 60; 60% male.	Bortezomib 1.3mg/m^2 administered on days 1, 4, 8 & 11 in 21 day cycles, for maximum of 6 cycles. 35 Patients received at least 4 cycles.	Primary Clinical efficacy	Overall Response Rate (CR + PR)	16 (51.6%)	4	Direct	Study enrolled patients who had other forms of lymphoma. Efficacy results are presented for patients with MCL only. Safety results were not reported separately different diagnoses and are therefore presented for the trial population as a whole. Patients with MCL should be treated as a post-hoc subgroup, and results interpreted with appropriate caution. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions.
					Complete Response (CR)	8 (25.8%)			
					Partial response (PR)	8 (25.8%)			
					Duration of response (DOR)	Not reported separately for mantle cell lymphoma.			
					Time to progression (TTP)	Not reported separately for mantle cell lymphoma.			
					Overall survival (OS)	Not reported separately for mantle cell lymphoma.			
				Secondary Safety outcomes	Grade ≥3 toxicities	Neutropenia – 3 (5.9%) Thrombocytopenia – 9 (17.6%)			
					Deaths	1 (sepsis)			

8. Grade of evidence table

Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Overall response rate (CR + CRu + PR)	Fisher et al	6	Direct	B	NB, Goy et al is an extension study of Fisher et al, therefore for all outcomes these are counted as a single study for Grade of Evidence purposes. ORR is a composite of all patients with any treatment response to bortezomib, whether partial or complete; all studies assessed this outcome. See appendix for response definitions. ORR was reported as 32% (95% CI 24-40) by Goy et al (largest study, with longest reported follow-up) and as 47% (95% CI 21.3-73.4) These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
	Goy et al	6	Direct		
	Belch et al	6	Direct		
	Zinzani et al	4	Direct		
	O'Connor et al	4	Direct		
Complete response (CR + CRu)	Fisher et al	6	Direct	B	CRu is intended to designate patients with curable histologies with a large mass prior to therapy, and for whom treatment eradicated all but the single persistent mass, which had shrunk by ≥75%. This acknowledges that in most cases the remaining mass represents scar tissue or fibrosis. It should not be applied to patients with multiple masses which have decreased by 75% in total; this is partial response. (Cheson, 2008) CRu is also intended to apply to patients with indeterminate bone marrow biopsy post-treatment, and should not be applied to patients who have not had repeated biopsy. Complete response was reported as 8% (95% CI 4-14) by Goy et al. These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
	Goy et al	6	Direct		
	Belch et al	6	Direct		
	O'Connor et al	4	Direct		
Complete response (CR only)	Fisher et al	6	Direct	B	CR refers to resolution of detectable disease including resolution of symptoms, blood and biochemical markers, lymph node masses, any spleen enlargement, and bone marrow histology. (See appendix for full definition). CR was reported in 6% of patients (95% CI 3-12) by Fisher et al (largest study, longest reported follow-up). Goy et al did not report this outcome separately from CRu. These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
	Belch et al	6	Direct		
	Zinzani et al	4	Direct		
Partial response	Fisher et al	6	Direct	B	Partial response requires reduction in size of the spleen and liver nodules and the largest lymph node masses, no increase in other nodes and no increase in the size of liver or spleen, and no new sites of disease (see appendix for full definition). PR was reported for 26% of patients by Fisher et al (largest study, longest reported follow-up). Goy et al did not report this outcome. These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
	Belch et al	6	Direct		
	Zinzani et al	4	Direct		
	O'Connor et al	4	Direct		
Stable disease (SD)	Fisher et al	6	Direct	B	Stable disease refers to disease which has not responded to treatment, but has also not worsened during treatment (see appendix for full definition). SD was reported for 33% (95% CI 26 to 42) of patients by Fisher et al. Results were similar (38-40%) in the remaining trials. These trials were not randomised or comparative, and there is therefore no evidence that bortezomib is any better or worse than other treatments for this outcome.
	Belch et al	6	Direct		
	O'Connor et al	4	Direct		

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of Evidence	Interpretation of Evidence
Progressive disease (PD)	Fisher et al	6	Direct	B	Progressive disease refers to disease which has continued to worsen during treatment (see appendix for full definition). PD was reported by Fisher et al for 25% of patients (95% CI 18 to 33). These trials were not randomised or comparative and there is therefore no evidence that bortezomib is any better or worse than other treatments for this outcome.
	O'Connor et al	4	Direct		
Duration of response	Fisher et al	6	Direct	B	MCL is a disease of relapse and remission. Median DOR is a measure of how long patients can expect their response to treatment to last. Median DOR was reported as 9.2 months (95% CI 4-7.3) by Goy et al (largest study, longest reported follow-up). These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
	Goy et al	6	Direct		
	Belch et al	6	Direct		
Progression-free survival (PFS)	Goy et al	6	Direct	C	MCL is a disease of relapse and remission. Median PFS is a measure of how long following treatment patients can expect to remain both alive and free of disease progression. Patients may not be disease or symptom free during this period. PFS is preferred to TTP since it accounts for patients who have died. Median PFS was 6.5 months (95% CI 4.0 to 7.2), as reported by Goy et al (largest study, longest reported follow-up). These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
	O'Connor et al	4	Direct		
Time to progression (TTP)	Fisher et al	6	Direct	C	MCL is a disease of relapse and remission. Median TTP is a measure of how long following treatment patients can expect to remain free of disease progression. Patients may not be disease or symptom-free during this period. It is similar to PFS but does not capture data on patients who have died. Median TTP was 6.7 months (95% CI 4.0-7.3), as reported by Goy et al (largest study, longest reported follow-up). These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
	Goy et al	6	Direct		
Overall survival	Fisher et al	6	Direct	C	OS is a measure of how long following treatment patients are expected to live. It is not restricted to deaths that are disease-related; deaths of any cause are accounted for. Median OS was 23.5 months (95% CI20.3-27.9) as reported by Goy et al. These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
	Goy et al	6	Direct		
Time to first response	Goy et al	6	Direct	C	Median TTFS is a measure of how long after starting treatment patients may expect to first see a treatment response. Goy et al found the median to be 1.4 months. This result should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
Time to next therapy	Goy et al	6	Direct	C	Time to next therapy is an indicator of how long following bortezomib treatment patients remain free of need to other drugs. This is an indicator of quality of life, and clinical benefit. Goy et al found median TTNT to be 7.4 months (95% CI 5.6-9.3). This result should be interpreted with caution; trial was not randomised or

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of Evidence	Interpretation of Evidence
					comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
Any adverse event	Fisher et al	6	Direct	B	All trials reported on adverse events. Due to lack of any comparison with other treatments or standard care, it is not possible to determine what proportion of events are attributable to bortezomib treatment and what proportion are likely to be a direct consequence of the disease. Similarly, there is no evidence that bortezomib is more or less safe than other treatments. The PINNACLE trial reported that 98% of patients experienced at least 1 adverse event.
	Goy et al	6	Direct		
Grade ≥3 toxicities	Fisher et al	6	Direct	B	All trials reported on adverse events. Due to lack of any comparison with other treatments or standard care, it is not possible to determine what proportion of events are attributable to bortezomib treatment and what proportion are likely to be a direct consequence of the disease. Similarly, there is no evidence that bortezomib is more or less safe than other treatments. The PINNACLE trial reported that 70% of patients experienced at least one toxicity of grade ≥3. Commonly reported grade ≥3 toxicities included fatigue and peripheral neuropathy.
	Goy et al	6	Direct		
	Belch et al	6	Direct		
	Zinzani et al	4	Direct		
	O'Connor et al	4	Direct		

9. Fact Sheet

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

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

10. Literature Search Terms

Search strategy *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with relapsed/refractory MCL, with previous systemic treatment for treatment of mantle cell lymphoma. e.g. 1-3 prior therapies (chemotherapy (+/- immunotherapy)
I – Intervention Which intervention, treatment or approach should be used?	Bortezomib 1.3 mg/m^2 administered on days 1, 4, 8, and 11 of a 21-day cycle,
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	No restrictions applied
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* Overall Response Rate and type of response (CR,CRu,PR etc.), median time to first response, median duration of response, OS, Time to Progression, Time to next treatment, safety and toxicity profile, HRQOL
Assumptions / limits applied to search	
Inclusion Criteria	**Adult patients with confirmed diagnosis of MCL with progression/relapsed disease after 1-3 lines of therapy +/- ASCT.**
Exclusion Criteria	**Studies older than 10 years**

11. Search Strategy

1. EMBASE, Medline; Bortezomib.ti,ab; 17889 results.
2. EMBASE, Medline; (Mantle AND Cell AND Lymphoma).ti,ab; 11001 results.
3. EMBASE, Medline; Relapsed.ti,ab; 75531 results.
4. EMBASE, Medline; refractory.ti,ab; 236595 results.
5. EMBASE, Medline; 1 AND 2; 932 results.
6. EMBASE, Medline; 3 AND 5; 414 results.
7. EMBASE, Medline; 4 AND 5; 340 results.
8. EMBASE, Medline; 6 AND 7; 289 results.
9. EMBASE; (Relapsed OR refractory).ti,ab; 174690 results.
10. EMBASE, Medline; 5 AND 9; 465 results.
11. EMBASE,Medline; Duplicate filtered: [5 AND 9]; 465 results.

12. Evidence selection

- Total number of publications reviewed: 465
- Total number of publications considered relevant: 23
- Total number of publications selected for inclusion in this briefing: 5

13. References

BELCH, A., KOUROUKIS, C. T., CRUMP, M., SEHN, L., GASCOYNE, R. D., KLASA, R., POWERS, J., WRIGHT, J. & EISENHAUER, E. A. 2007. A phase II study of bortezomib in mantle cell lymphoma: the National Cancer Institute of Canada Clinical Trials Group trial IND.150. *Ann Oncol,* 18**,** 116-21.

CANCER RESEARCH UK Non-Hodgkin lymphoma incidence statistics. February 2016. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence#heading-Zero. Accessed 14/09/16.

CHESON, B. D. 2008. New response criteria for lymphomas in clinical trials. *Ann Oncol,* 19 Suppl 4**,** iv35-8.

CHESON, B. D., HORNING, S. J., COIFFIER, B., SHIPP, M. A., FISHER, R. I., CONNORS, J. M., LISTER, T. A., VOSE, J., GRILLO-LOPEZ, A., HAGENBEEK, A., CABANILLAS, F., KLIPPENSTEN, D., HIDDEMANN, W., CASTELLINO, R., HARRIS, N. L., ARMITAGE, J. O., CARTER, W., HOPPE, R. & CANELLOS, G. P. 1999. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol,* 17**,** 1244.

DREYLING, M., GEISLER, C., HERMINE, O., KLUIN-NELEMANS, H. C., LE GOUILL, S., RULE, S., SHPILBERG, O., WALEWSKI, J., LADETTO, M. & GROUP, E. G. W. 2014. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol,* 25 Suppl 3**,** iii83-92.

FISHER, R. I., BERNSTEIN, S. H., KAHL, B. S., DJULBEGOVIC, B., ROBERTSON, M. J., DE VOS, S., EPNER, E., KRISHNAN, A., LEONARD, J. P., LONIAL, S., STADTMAUER, E. A., O'CONNOR, O. A., SHI, H., BORAL, A. L. & GOY, A. 2006. Multicenter phase II study of

bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol,* 24**,** 4867-74.

GOY, A., BERNSTEIN, S. H., KAHL, B. S., DJULBEGOVIC, B., ROBERTSON, M. J., DE VOS, S., EPNER, E., KRISHNAN, A., LEONARD, J. P., LONIAL, S., NASTA, S., O'CONNOR, O. A., SHI, H., BORAL, A. L. & FISHER, R. I. 2009. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. *Ann Oncol,* 20**,** 520-5.

JANSSEN-CILAG LTD Summary of Prodcut Characteristics Velcade 3.5 mg powder for solution for injection. Date of revision of the text 25/01/2016. https://www.medicines.org.uk/emc/medicine/17109

LIU, Y., ZHANG, X. & ZHONG, J. F. 2015. Current approaches and advance in mantle cell lymphoma treatment. *Stem Cell Investig,* 2**,** 18.

MCKAY, P., LEACH, M., JACKSON, R., COOK, G., RULE, S. & BRITISH COMMITTEE FOR STANDARDS IN, H. 2012. Guidelines for the investigation and management of mantle cell lymphoma. *Br J Haematol,* 159**,** 405-26.

O'CONNOR, O. A., MOSKOWITZ, C., PORTLOCK, C., HAMLIN, P., STRAUS, D., DUMITRESCU, O., SARASOHN, D., GONEN, M., BUTOS, J., NEYLON, E., HAMELERS, R., MAC-GREGOR CORTELLI, B., BLUMEL, S., ZELENETZ, A. D., GORDON, L., WRIGHT, J. J., VOSE, J., COOPER, B. & WINTER, J. 2009. Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: results of a multicentre Phase 2 clinical trial. *Br J Haematol,* 145**,** 34-9.

O'CONNOR, O. A., WRIGHT, J., MOSKOWITZ, C., MUZZY, J., MACGREGOR-CORTELLI, B., STUBBLEFIELD, M., STRAUS, D., PORTLOCK, C., HAMLIN, P., CHOI, E., DUMETRESCU, O., ESSELTINE, D., TREHU, E., ADAMS, J., SCHENKEIN, D. & ZELENETZ, A. D. 2005. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol,* 23**,** 676-84.

SMITH, S. M. 2015. New drugs for the treatment of non-Hodgkin lymphomas. *Chin Clin Oncol,* 4**,** 14.

ZINZANI, P. L., PELLEGRINI, C., MERLA, E., BALLERINI, F., FABBRI, A., GUARINI, A., PAVONE, V., QUINTINI, G., PUCCINI, B., VIGLIOTTI, M. L., STEFONI, V., DERENZINI, E., BROCCOLI, A., GANDOLFI, L., QUIRINI, F., CASADEI, B., ARGNANI, L. & BACCARANI, M. 2013. Bortezomib as salvage treatment for heavily pretreated relapsed lymphoma patients: a multicenter retrospective study. *Hematol Oncol,* 31**,** 179-82.

14. Appendix

Definitions of disease response as recommended by an international working group on non-Hodgkin's lymphoma. (Cheson et al., 1999)

Outcome	International Workshop Response Criteria (IWRC)
Complete response (CR)	All of the following criteria must be met: 1. Disappearance of all detectable clinical and radiographic evidence of disease and disease-related symptoms, with normalisation of biochemical abnormalities. 2. All lymph nodes and nodal masses regressed to normal size: ○ Nodes >1.5 cm regressed to ≤1.5 cm in greatest transverse diameter ○ Nodes 1.1 cm to 1.5 cm regressed to ≤1 cm in greatest transverse diameter, or by more than 75% in the SPD. 3. If evidence of splenomegaly prior to treatment, spleen must have regressed in size and must not be palpable. 4. If extant bone marrow involvement prior to treatment, infiltrate must be cleared on repeat bone marrow aspiration and biopsy of the same site (biopsy ≥20 mm required).
Complete response (CRu)	Features 1 and 3 of a complete response, plus ≥1 of the following: • A residual lymph node <1.5 cm in greatest transverse diameter that has regressed by >75% in SPD. Individual nodes that were previously confluent must have regressed by >75% in their SPD compared with the size of the original mass • Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).
Partial response (PR)	All of the following criteria must be met: 1. ≥50% decrease in SPD of six largest dominant nodes or nodal masses 2. No increase in size of other nodes, liver or spleen 3. Splenic and hepatic nodules must regress by ≥50% in the SPD 4. Involvement of organs other than spleen and liver is considered assessable and not measurable disease. 5. Bone marrow involvement is considered assessable and not measurable disease, however if positive, the cell type should be specified 6. No new sites of disease
Stable disease (SD)	Disease does not fulfil criteria for a partial response, but is not progressive disease
Progressive disease (PD, non-responder)	1. ≥50% increase from nadir in SPD of any previously identified abnormal node for PRs or non-responders 2. Appearance of any new lesion during or at the end of therapy
Relapsed disease (following CR or CRu)	1. Appearance of any new lesion, or increase by ≥50% in size of any previously involved sites 2. ≥50% increase in greatest diameter of any previously identified node >1cm in its short axis, or in the SPD of more than one node

SPD – sum of the products of the greatest diameters.