NHS England

Evidence review: Bortezomib for Relapsed/Refractory Waldenstrom's Macroglobulinaemia

NHS England

Evidence review:

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1. Introduction

- Waldenstrom's macroglobulinaemia (WM) is a cancer which affects B lymphocytes. It is an indolent form of non-Hodgkin's lymphoma, characterized by accumulation of monoclonal cells and production of excessive monoclonal immunoglobulin M (IgM). WM cells have features of both plasma cells and lymphocytes and are called lymphoplasmacytoid. WM is therefore sometimes known as lymphoplasmacytic lymphoma (LL). (Orphanet)
- Symptoms of WM include hepatomegaly, splenomegaly, lymphadenopathy, cytopenia, bleeding, anaemia and fatigue. Excess IgM may also cause hyperviscosity syndrome, which may result in features such as nose bleeds, headaches, and seizures.
- WM is typically a disease of the elderly with a median age at presentation of >70 years and an overall median survival of approximately 60 months. It is relatively rare with an age standardized incidence rate of 0.55 per 100 000 per year in the UK. (Phekoo et al., 2008)
- Relapsed WM is disease which has initially responded to treatment, but then returned. Refractory WM is disease which has not responded to attempted treatment. There is no general standard approach to managing relapsed or refractory patients.
- The most recent UK guidelines for management of WM were published by the British Committee for Standards in Haematology. (Owen et al., 2014) The guidance recommends that patients with relapsed disease should not be treated until they become symptomatic. When treatment is indicated, choice of regimen should be guided by patient experience, duration of previous responses, tolerability of previous regimens, performance status, co-morbidities, potential for stem cell transplantation, and availability of clinical trial data. Regimens used for first-line treatment are also appropriate after relapse, and retreatment with previously-successful therapies may be appropriate in some patients. Bortezomib-containing regimens may be considered in relapsed patients, but patients with CD20-expressing disease should receive a regimen containing rituximab.
- More recent recommendations from the Eighth International Workshop on WM are also available. (Leblond et al., 2016) The advice is broadly in line with the UK guidance, stating that all interventions used for symptomatic, untreated patients may be considered in patients with relapsed disease. Re-treatment with the same regimen can be considered for patients who had treatment response lasting at least 2 years.
- Rituximab with or without combination chemotherapy with dexamethasone and cyclophosphamide remains the key treatment for relapsed WM in many cases, while haematopoietic stem cell transplantation (HSCT) is also considered to be an important tool in eligible patients. (NB: a commissioning policy for HSCT in WM has been agreed for routine commissioning).
- Bortezomib in this indication has been available via the national CDF since April 2013 and was available via many regional CDFs prior to this. A total of 36 applications for bortezomib in this indication were received by the national CDF in 2014/15. Bortezomib for LL was removed from the CDF in March 2015.
- The use of bortezomib for the treatment of relapsed WM is off-label use. Off-label use means clinicians prescribe licensed medications for uses other than those for which they are licensed. The evidence for this use is based on analysis of progression-free survival (PFS) which is the length of time during and after the treatment that a patient lives with the disease but it does not get worse.

2. Summary of results

- This evaluation found 5 clinical trials of bortezomib in people with relapsed or refractory Waldenstrom's macroglobulinaemia (WM), either alone or in combination with rituximab or bendamustine. The most commonly reported outcomes were various types of treatment response (e.g. complete response, partial response, or stable disease).
- Two trials treated patients with bortezomib alone. These found that between around one third and one half of patients had a partial or major response. This means that these patients had at least a 50% reduction in their serum monoclonal immunoglobulin M (IgM) levels, at least a 50% reduction in any enlargement of their lymph nodes, spleen, or other organs, and no new signs or symptoms of WM. Neither trial reported survival outcomes such as overall survival, or progression-free survival.
- One trial assessed bortezomib plus rituximab. Just over half of the 37 patients who took part had at least a partial response, with the same definition as used above. Median progression-free survival was 15.6 months.
- One trial compared weekly bortezomib to twice-weekly bortezomib. Nine out of 10 patients with WM had a partial response or better, but the study did not report which bortezomib regimen these patients were receiving.
- One trial assessed bortezomib plus bendamustine. However, only one patient of the 10 enrolled had WM, which means that this should be considered a case report rather than a clinical trial. The patient with WM had a partial response to treatment.
- There are several problems with the trials which limit how useful they are in making decisions about treating WM:
    - The trials were all very small; the largest trial enrolled 27 people. This means it is difficult to know if the results would also apply more widely to people with WM.
    - The trials used slightly different definitions of treatment response, which makes it difficult to compare the trials to see if bortezomib has a consistent effect.
    - None of the trials compared bortezomib to any other drugs or treatments for WM. 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, sensory neuropathy, reduced blood cell counts 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 WM.

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

Literature searches returned 146 publications. The titles and abstracts of these results were reviewed, and 24 publications were considered to potentially match the PICO. In total 19 of these were rejected for reasons including:

- Enrolled patients were treatment-naïve, and did not have relapsed disease.
- Assessed interventions other than bortezomib, bortezomib + rituximab, or bortezomib + bendamustine.
- Available as conference abstract only, with no full publication of results.
- Paper older than 10 years.

The five studies included were all small, early-phase, trials, the largest enrolling 27 patients. Patients were adults with relapsed or refractory WM. All received bortezomib, but doses varied from 0.7 mg/m^2 twice weekly to 1.6 mg/m^2 once weekly. Two trials assessed bortezomib alone, two assessed bortezomib + rituximab, and one assessed bortezomib + bendamustine. Four trials were non-comparative and non-randomised, but the fifth compared weekly bortezomib + rituximab to twice weekly bortezomib + rituximab in a randomised manner.

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. Definitions of response varied slightly between trials in line with changing guidance from the bi-annual International Workshop on WM, but were broadly similar. All trials required a measure of serum IgM levels as part of their evaluation of efficacy, with some also requiring symptom resolution, reduction in size of tumour lesions or masses, or evidence of normal bone marrow.

Bortezomib monotherapy

Two studies assessed bortezomib alone for treatment of WM. One recruited patients who had failed treatment with at least one first-line therapy (n=27), (Treon et al., 2007) while the second recruited both relapsed and treatment-naïve patients (n=27). (Chen et al.,

2007) A total of 15/27 patients (56%) had relapsed disease in this trial; this cohort should be considered a post-hoc subgroup.

No participants in either trial achieved a complete response. Treon et al defined a major response as ≥50% reduction in serum IgM, which was achieved by 13 patients (48%). Chen et al reported a similar endpoint of partial response, which had a stricter definition of ≥50% reduction in serum IgM, plus confirmation of the reduction 6 weeks later and reduced lesion size. Only 4 patients (27%) with relapsed disease met this more stringent definition.

The remaining patients in these trials had a minor response (≥25% reduction in serum IgM) or stable disease. Again, Chen et al had a stricter definition of stable disease, requiring ≤50% change in serum IgM, plus no new lesions or sites of disease. This led to a greater proportion of patients in this trial being classified as stable (70% vs. 0), but these data are confounded by the inclusion of treatment-naïve patients.

Chen et al reported a median PFS of 16.3 months, while Treon et al reported a median time to progression of 6.6 months. Time to progression is similar to PFS, but does not capture instances where a patient has died. Treon et al did not report any deaths, so in this case the two outcomes are likely to be similar. The difference may reflect the uncertainty that is inevitable with such small sample sizes, or the confounding influence of the inclusion of treatment-naïve patients in the study by Chen et al. Chen et al also found the median duration of response was 10 months, and median duration of stable disease was 14.3 months. As before, these data may be confounded.

Grade III (moderate) or IV (severe) toxicities were reported frequently. Neuropathy is a particular concern with bortezomib, and was reported by 11-22% of patients. Other commonly reported adverse drug reactions (ADRs) were fatigue, myalgia, leukopenia, neutropenia, thrombocytopenia, neuropathic pain, dizziness, diarrhoea and dyspnoea.

Weekly bortezomib plus rituximab

One trial (n=37) assessed the effectiveness of bortezomib plus rituximab in patients with relapsed or refractory WM.(Ghobrial et al., 2010) The primary endpoint was the proportion of patients with at least a minor response to treatment (as defined by the Third International Workshop on Waldenstrom's Macroglobulinaemia). (Kimby et al., 2006) After a median follow-up of 16 months, this outcome was achieved by 30 patients (81%, 95% CI 65% to 92%), including one patient (3%) with complete remission, one with near complete remission. The remainder of patients meeting the primary endpoint had partial remission (n=17, 46%) or a minor response (n=11, 30%). Four patients (11%) maintained stable disease and one had disease progression.

Median PFS was 15.6 months (95% CI 11.2 to 21.1), and median time to progression was 16.4 months. Median time to next therapy was reported to account for the fact that guidance recommends patients with relapsed disease should not be treated until they become symptomatic, despite clinical evidence of relapsed disease. The median time to next therapy was 17.6 months (range 1 to 25 months). PFS was 58% and 45% at 12 and 18 months respectively. Median overall survival was not reached during the follow-up period, but the estimated 12 month survival was 94% (95% CI 86% to 100%).

Reported grade III or IV toxicities were lymphopenia (24%), neutropenia (16%), leukopenia (14%), thrombocytopenia (13%), anaemia (11%), and peripheral neuropathy (5%). One patient died of viral pneumonia.

Weekly bortezomib plus rituximab vs. twice-weekly bortezomib plus rituximab

One trial (n=49) with a combined phase 1/2 design compared the effectiveness of weekly bortezomib plus rituximab to twice-weekly bortezomib. (Agathocleous et al., 2010) Enrolled patients had follicular lymphoma, of whom 1 of 7 in the phase 1 stage and 10 of 42 in the phase 2 stage had WM. Patients in the phase 2 stage of the trial were randomised to receive bortezomib 1.3 mg/m^2 twice weekly in 21 day cycles (Arm A), or bortezomib 1.6 mg/m^2 once weekly (Arm B) in 35-day cycles. Patients in both arms received rituximab 375 mg/m^2 was administered on the same days as bortezomib in both treatment arms, but only during cycles 1 and 4.

The primary outcome was safety; however events were not reported for the subgroups of patients with different diagnoses. It is therefore not known how many events occurred in patients with WM. Overall, grade 3 or 4 events were relatively common in both treatment arms. The most common were lymphopenia (24-38%), thrombocytopenia (10-29%) and neutropenia (14-24%). Neuropathy of grade 3 or 4 was reporting in 14% of patients in arm A, and 19 % in arm B.

Efficacy outcomes were secondary endpoints. While results were reported for WM patients as a subgroup, the study did not confirm which arm the WM patients were treated in. Nine of the ten patients treated with bortezomib achieved at least a partial response, but the doses these patients were receiving were not specified. The remaining patient had stable disease. Four of the 10 WM patients had no disease progression 2-2.5 years following treatment, while five had progressive disease. The remaining patient was not accounted for.

Bortezomib plus bendamustine

One trial assessed the effectiveness of bortezomib plus bendamustine for treatment of relapsed WM. (Moosmann et al., 2010) However, this study enrolled patients with several types of indolent non-Hodgkin's lymphoma, and only one participant had a diagnosis of WM. The study should therefore be considered a case report for purposes of assessing efficacy in WM treatment, and extreme caution should be used when extrapolating the results to other patients.

The WM patient this trial was a 59 year old male with refractory stage IV disease who had failed treatment with seven prior therapies, including several rituximab-containing regimens. The patient achieved partial remission of disease, but no definition of partial remission was supplied. The only safety event reported was bendamustine dose-limiting thrombocytopenia. The authors of this study highlight that it is beyond the scope of the data to determine the efficacy of this combination.

5. Discussion

Published trials for bortezomib in relapsed WM are small, of variable quality, and provide limited data on important outcomes such as overall survival and progression-free survival. Trials were generally phase 1 or 2, and as such are non-comparative studies which cannot estimate treatment effect. Other important limitations include the small sample sizes, with the largest trial recruiting only 37 patients, and heterogeneous trial populations.

The 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 adequately describe the dose or administration schedule for some medicines
- failing to specify primary or secondary endpoints
- failing to clearly define efficacy endpoints such as complete response, partial response, etc.

Bortezomib appears to be active in the treatment of relapsed WM, but the degree of effectiveness, or effectiveness compared to other regimens, cannot be estimated. The most commonly reported efficacy outcome was treatment response, but use of slightly different definitions of response by each trial confound efforts to make a pooled estimate of the treatment effect. These differences, together with the diversity of endpoints used, mean that many outcomes reported only have evidence from a single trial. There are no published studies comparing bortezomib with other treatments or standard care in patients with relapsed WM, which further limits interpretation of the endpoints. Similarly, the adverse events reported cannot be readily generalised to other populations.

Current guidance on the management of WM includes use of bortezomib where appropriate, but treatment choices should be made on a patient-by-patient basis. The published literature on the use of bortezomib to treat relapsed WM is extremely limited, which is to be expected for a rare disease. As highlighted by the treatment recommendations made by the Eighth Annual International Workshop on Waldenstrom's Macroglobulinaemia, WM is an uncommon disease and there is rarely randomised trial data to support decision-making. (Leblond et al., 2016) Treatments must therefore often be derived from early phase studies such as those available in this case.

The evidence in this case does not preclude use of bortezomib for treatment of relapsed Waldenstrom's macroglobulinaemia, but is too limited to make blanket recommendations. While conducting trials in rare conditions is challenging, more evidence is required in order to make robust treatment decisions.

6. Conclusion

The literature appears to show that bortezomib is active to some extent in the treatment of relapsed Waldenstrom's macroglobulinaemia. 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 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, there is insufficient evidence to make clear recommendations on use of bortezomib in terms of dose, schedule or combinations with other drugs.

7. Evidence Summary Tables

Use of bortezomib to treat relapsed or refractory Waldenstrom's macroglobulinaemia (WM)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Treon et al., 2007) Clin Cancer Res 2007;13 (11)	P2 – prospective non-randomised, non-comparative trial Efficacy assessed every 2 cycles, then every 3 months for 2 years or until disease progression	27 patients with WM who failed ≥1 first line of therapy (i.e. an alkylator, drug alone or with steroids, nucleoside analogue or rituximab), baseline platelet count ≥50,000x10^9/L, absolute neutrophil count ≥0.75 x 10^9/L, CrCl ≥30 mL/min and no ≥grade 2 peripheral neuropathy. Median age 62; 66% male, median prior therapies 2 (range 0-3).	Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 in cycles (cycle length not specified). Up to 8 cycles, with follow-up of 2 years or until disease progression. Median follow-up was 18.2 months.	Primary Clinical response	Complete response (resolution of all symptoms, normalised serum IgM)	0	6	Direct study. Population appears to be representative of WM patients, although ethnicity of patients was not specified. Small study size limits generalisability	• No comparator group, and therefore no randomisation or blinding • No evidence of safety or efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions. • Bortezomib cycle length was not specified and cannot be inferred. • Primary/secondary outcomes were not clearly specified in the text; study simply specified that it would assess response and effects on peripheral blood effector cells. • Response definitions are in line with those suggested by the 3rd International Workshop on WM (see appendix for full definitions) • Time to progression was reported in place of progression-free survival. No deaths were explicitly reported so these two end points likely to be similar in this case.
					Major response (≥50% reduction in serum IgM)	13 (48.1%)			
					Minor response (≥25% reduction in serum IgM)	10 (37.0%)			
					Stable disease	Not specified			
					Progressive	Not specified			
					Time to progression	Median 6.6 months (range 2.9 to 21.4+)			
				Secondary Safety	Reported grade III or IV toxicities	Sensory neuropathy (22.2%) Leukopenia (18.5%) Neutropenia (14.8%) Dizziness (11.1%) Thrombocytopenia (7.4%) Pleural effusion, diarrhoea, infection, anorexia, fatigue, nausea, hypotension (3.7% each)			
					Deaths	Not specified			

Use of bortezomib to treat relapsed or refractory Waldenstrom's macroglobulinaemia (WM)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Chen et al., 2007) J Clin Oncol 25:1570-1575	P2 – prospective non-randomised, non-comparative trial Efficacy assessed every cycle (3 weeks), then every 3 months until relapse or death	27 patients with symptomatic WM, either untreated with IgM of ≥20 mg/dL or relapsed with IgM of ≥5 mg/dL. 15 (56%) had relapsed after ≥1 prior therapy. ECOG performance status ≤2, neutrophil count ≥1x10^9/L, platelets ≥50x10^9/L, serum creatinine or bilirubin ≤1.5xULN, AST or ALT ≤2.5xULN. Patients with neurotoxicity grade ≥2 were excluded. Median prior treatments = 2, median age 65, 14 (52%) male.	Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 in 21 day cycles. No limit to number of cycles; treatment continued until: partial response stable for at least 2 cycles, or stable disease for at least 4 cycles, or disease progression Median number of cycles was 6	Primary Clinical response	Complete response	0	7	Direct study. Population appears to be representative of WM patients. Small study size limits generalisability	• No comparator group, and therefore no randomisation or blinding. • No evidence of safety or efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions. • Data from relapsed patients should be considered a post-hoc subgroup analysis, and treated with appropriate caution. • Most endpoints were reported for the entire population, and not only relapsed patients. Applicability to patients with relapsed WM is therefore not clear. Data included here due to paucity of other evidence. • Wide confidence intervals, likely due to small sample size. • Response definitions are in line with those suggested by the 2nd International Workshop on WM (see appendix for full definitions)
					Partial response Treatment-naïve Previously-treated	7 (26%, 95% CI 11% to 46%)) 3/12 (25%) 4/15 (27%)			
					Stable disease	19 (70%)			
					Progressive disease	1 (4%)			
				Secondary Survival and relapse	Median progression-free survival	16.3 months (95% CI 14.2 to ∞)			
					Median duration of response	10 months (range 1.4 to 14.9)			
					Duration of stable disease	14.3 months (1.2 to 28.5)			
				Secondary Safety	Treatment-related grade III toxicities	Fatigue, sensory neuropathy, myalgia (11% each) Neuropathic pain, diarrhoea, dyspnoea (7% each) Non-neutropaenic infection, abdominal pain, dizziness, stomatitis, pancreatitis, hypertension (4% each)			
					Treatment-related grade IV toxicities	Anaemia, thrombocytopenia (4% each)			

Use of bortezomib plus rituximab to treat relapsed or refractory WM									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Ghobrial et al., 2010) J Clin Oncol 28:1422-1428.	P2 – prospective non-randomised, non-comparative phase II trial Efficacy assessed every 28 days during treatment cycles, then every 3 months until disease progression or starting another therapy, or death.	37 patients with symptomatic WM who failed ≥1 first line of therapy, with measurable monoclonal IgM on serum electrophoresis, IgM 2 x ULN, evidence of relapsed or refractory disease, presence of lymphoplasma-cytic cells in the bone marrow, AST or ALT less than 3 x ULN, serum bilirubin <2 mg/dL, creatinine <2.5 x ULN, platelets ≥75,000/mm^2, absolute neutrophil count ≥1,000/mm^2. Median age 64, 70% male, 100% white. Prior treatments: 1 (30%), 2 (22%), 3 (19%) or >3 (30%).	Bortezomib 1.6 mg/m^2 IV (reduced to 1.3 or 1.0 mg/m^2 in case of toxicity) on days 1, 8 and 15 in 28 day cycles for up to six cycles, plus rituximab 375 mg/m^2 on days 1, 8, 15 and 22 of cycles 1 and 4. Treatment was stopped in patients with progressive disease after two cycles. Median follow-up was 16 months.	Primary Proportion of patients with at least minor treatment response	Minor response or better (CR + nCR + PR + MR)	30 (81%, 95% CI 65% to 92%)	7	Direct study. Population appears to be representative of WM patients. Small study size limits generalisability	• No comparator group, and therefore no randomisation or blinding. • No evidence of safety or efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions. • Wide confidence intervals, likely due to small sample size. • Response definitions are in line with those suggested by the 3rd International Workshop on WM (see appendix for full definitions).
					Complete remission (CR)	1 (3%)			
					Near complete remission (no monoclonal protein in serum, but disease evident by immune-fixation) (nCR)	1 (3%)			
					Partial remission (PR)	17 (46%)			
					Minor response (MR)	11 (30%)			
					Stable disease	4 (11%)			
					Progressive disease	1 (3%)			
				Secondary Efficacy	Progression-free survival (PFS) (median)	15.6 months (95% CI 11.2 to 21.1)			
					12 month PFS (estimated)	58% (95% CI 39% to 75%)			
					18 month PFS (estimated)	45% (95% CI 27% to 63%)			
					Overall survival (median)	Not reached			
					Estimated 12 month overall survival	94% (95% CI 86% to 100%)			
					Time to progression (median)	16.4 months			
					Time to next therapy (median)	17.6 months (range 1 to 25 months)			
				Secondary Safety	Deaths reported	3			
					Treatment-related grade III or IV toxicities affecting ≥10% of	Anaemia – 4 (11%) Leukopenia – 5 (14%)			

Use of bortezomib plus rituximab to treat relapsed or refractory WM									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					patients	Lymphopenia – 9 (24%) Neutropenia – 6 (16%) Thrombocytopenia – 5 (13%) Peripheral neuropathy – 2 (5%)			
					Treatment-related grade V toxicities	Viral pneumonia – 1 (3%)			

Use of weekly bortezomib plus rituximab vs. twice weekly bortezomib plus rituximab to treat relapsed or refractory WM									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Agathocleous et al., 2010) Br J Haematol. 2010 Nov;151(4):346-53	Prospective, randomised, dose comparison phase 1/2 study.	<u>Phase I</u>: 1 patients with WM, from total of 7 with follicular lymphoma, mantle cell lymphoma or WM. Median age 54, 3 (43%) male, median 4 prior treatments. <u>Phase II</u>: 10 patients with WM, from total of	<u>Phase I</u> Bortezomib 0.7 mg/m^2 twice weekly (n=3) vs. 1.0 mg/m^2 twice weekly (n=2) vs. bortezomib 1.3 mg/m^2 once weekly (n=2) <u>Phase II</u> Arm A (n=21): Bortezomib	Primary Toxicity	Reported toxicities (any grade)	Not reported for WM patients as a subgroup.	5	Direct study Small study size limits generalisability	• No evidence of safety or efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions. • Primary/secondary outcomes were not clearly specified in the text. • No other patient inclusion/exclusion criteria specified. • Response definitions are in line with those suggested by the 3rd International Workshop on WM (see appendix for full definitions). • WM patients in this trial can be considered a post-hoc subgroup. All conclusions drawn should therefore be
				Secondary Treatment response	Overall response (complete response + partial response)	9/10 (90%) (Bortezomib dose not specified)			
					Stable disease	1/10			
				Secondary Progression (NB: no timescale	Patients with no disease progression	4/10 (2-2.5 years following treatment)			
					Patients with progressive disease	5/10			

Use of weekly bortezomib plus rituximab vs. twice weekly bortezomib plus rituximab to treat relapsed or refractory WM									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		42, as above. Median age 60, 30 (71%) male, median 2 prior treatments.	1.3 mg/m^2 on days 1, 4, 8 & 11 of a 21 day cycle for a maximum of 6 cycles, vs. Arm B (n=21): bortezomib 1.6 mg/m^2 on days 1, 8, 15 & 22 of a 35 day cycle, for a maximum of 6 cycles. Both groups received rituximab on all 4 treatment days of cycles 1 and 4. Total follow-up time not specified.	for progression given in trial)	Unaccounted for	1/10			treated with appropriate caution. Results not generalizable.

Use of bortezomib plus bendamustine to treat relapsed or refractory Waldenstrom's macroglobulinaemia (WM)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
(Moosmann et al., 2010) Leuk Lymphoma 2010; 51(1):149-52	P2 – prospective non-randomised, non-comparative dose-finding study	1 patient with WM, from total of 12 with relapsed/ refractory indolent NHL, Karnofsky score ≥50%, life expectancy ≥3 months, platelet count ≥50x10^9/L, haemoglobin ≥75 g/L, ANC ≥0.75x10^9/L, AST, ALT & bilirubin <2.5x ULN. Male WM patient aged 59, refractory stage IV disease, 6 years post-diagnosis with 7 prior therapies (inc R-COP, R-CHOP, R-fludarabine).	Bortezomib 1.6 mg/m^2 on days 1, 8, 15 and 22 of a 35-day cycle, for a maximum of 3 cycles. Bendamustine started at 60 mg/m^2, with dose escalation to 80 mg/m^2 if tolerated. Administered on days 1, 8 & 15 of each cycle.	Secondary Treatment response	Partial remission	1 (100% of WM patients)	5	Direct. Only 1 WM patient involved, so essentially only a case report; not generalizable.	• Only 1 WM patient enrolled; therefore study is very limited in what it can tell us regarding bortezomib + bendamustine for WM. Should be considered a case report for this purpose. • As noted by the authors, "*It was beyond the scope of this trial to characterize the efficacy of a weekly bortezomib and bendamustine combination therapy. The sample size is too small and the cohort too heterogeneous to draw meaningful conclusions*." • No comparator group, and therefore no randomisation or blinding. • No evidence of efficacy or safety compared to other treatment options • Primary outcome was to determine feasibility of weekly co-administration of bortezomib and bendamustine. • Partial remission was not defined.
				Secondary Safety	Bendamustine dose-limiting toxicity	Thrombocytopenia			

8. Grade of evidence tables

Use of bortezomib to treat relapsed or refractory WM					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Complete response (CR)	Treon et al, 2007	6	Direct	B	• CR was defined as normalisation of serum IgM, resolution of adenopathy or splenomegaly. Chen et al also required normal bone marrow biopsy • Chen et al included patients who were treatment-naïve. Population of relapsed patients should be considered a post-hoc subgroup and results treated with appropriate caution. • There were no CRs in either trial • Very small sample sizes (both n=27, n=15) means that possibility of CR occurring in a small % of patients cannot be ruled out • No comparison with standard care or other active drug. Therefore cannot determine whether this outcome is due to chance or demonstrates a true treatment effect. This applies to all outcomes for these trials.
	Chen 2007	7	Direct		
Major response	Treon 2007	6	Direct	C	• Defined as ≥50% reduction in serum IgM, with no requirement for improvement in any other signs or symptoms of WM. • This is likely to be the same outcome as Partial Response below, since the IWWM-3 does not provide a definition for “Major Response”, and the details given in the trial roughly match the IWWM-3 definition of Partial Response. Poor reporting of the trial methods prevents confirmation of this. • Achieved by 13 patients (48%)
Partial response	Chen 2007	7	Direct	B	• Defined as ≥50% reduction in serum IgM, confirmed at least 6 weeks later, plus ≥50% reduction in the sum of the products of the diameters of dominant nodes/masses • Similar to Major response as reported by Treon et al, 2007, but with requirement for bidimensional evidence of disease response • Achieved by 4 patients (15%)
Minor response	Treon 2007	6	Direct	C	• Defined as ≥25% reduction in serum IgM , with no requirement for improvement in any other signs or symptoms of WM • Achieved by 10 patients (37%)
Stable disease (≤25% change in serum IgM)	Treon 2007	6	Direct	C	• Defined as ≤25% change in serum IgM, with no requirement for improvement in any other signs or symptoms. • Achieved by 0 patients.
Stable disease (<50% change in serum IgM plus no new lesions)	Chen 2007	7	Direct	B	• Defined as <50% change in serum IgM for at least 6 weeks plus no new lesions or sites of disease • Achieved by 19 patients (70%) • More stringent definition than Treon et al, 2007 likely led to the increased chance of this outcome in this study as opposed to minor/partial response.
Progressive	Treon 2007	6	Direct	B	• Chen et al, 2007 defined PD as any 1 of: ≥25% increase in serum IgM, increase of 5g/L in IgM from baseline, ≥50% increase in sum of the products of the

Use of bortezomib to treat relapsed or refractory WM					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
disease (PD)	Chen 2007	7	Direct		diameters of dominant nodes/masses or appearance of new node/lesion. • Treon et al, 2007 defined PD simply as ≥25% increase in serum IgM. • PD reported by 1 patient in Chen et al, 2007. Not specified in Treon et al, 2007.
Time to progression	Treon 2007	6	Direct	C	• Time to progression is a similar measure to PFS, but does not account for deaths occurring before progression. PFS is therefore the preferred outcome. • Median time to progression was 6.6 months (range 2.9 to 21.4+ months) • Very wide range increases uncertainty in this outcome. Larger sample size required. • Untreated WM can remain stable for months or years without progression
Progression-free survival (PFS)	Chen 2007	7	Direct	B	• Median 16.3 months (95% CI 14.2 to infinity) • Very wide confidence interval increases uncertainty in this outcome. Larger sample size required.
Duration of partial response	Chen 2007	7	Direct	B	• Median 10 months (range 1.4 to 14.9) • Wide range increases uncertainty in this outcome. Larger sample size required.
Duration of stable disease	Chen 2007	7	Direct	B	• Median 14.3 months (range 1.2 to 28.5) • Very wide range increases uncertainty in this outcome. Larger sample size required.
Reported toxicities	Treon 2007	6	Direct	B	• Without comparison groups it cannot be determined what proportion of reported ADRs are attributable to treatment, or whether many are reflective of underlying disease symptoms. • Common grade 3 or 4 toxicities included sensory neuropathies (11-22%), leukopenias, fatigue, dizziness.
	Chen 2007	7	Direct		

Use of bortezomib plus rituximab to treat relapsed or refractory WM					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Minor response or better	Ghobrial 2010	7	Direct	B	• Defined as CR + nCR + PR + MR. Designated as primary endpoint. • Achieved by 30 patients (81%, 95% CI 65% to 92%). • Very small sample sizes (n=37) means that results should be interpreted with caution, and contributes to wide confidence interval. • No comparison with standard care or other active drug. Therefore cannot determine whether this outcome is due to chance or demonstrates a true treatment effect. This applies to all outcomes for this trial.
Complete response (CR)	Ghobrial 2010	7	Direct	B	• Defined as disappearance of monoclonal IgM, resolution of adenopathy/organomegaly, signs and symptoms of WM, and malignant bone marrow cells. Confirmation required after 6 weeks. See appendix for full definition. • Achieved by 1 patient.

Use of bortezomib plus rituximab to treat relapsed or refractory WM					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Near complete response (nCR)	Ghobrial 2010	7	Direct	B	• Defined as patients who have no monoclonal IgM evident in serum, but remain disease-positive by immunofixation. • Achieved by 1 patient.
Partial response (PR)	Ghobrial 2010	7	Direct	B	• Defined as ≥50% improvement in both serum monoclonal IgM and adenopathy/organomegaly, plus no new signs or symptoms of disease. See appendix for full definition. • Achieved by 17 patients (46%).
Minor response (MR)	Ghobrial 2010	7	Direct	B	• Defined as ≥25% but <50% reduction in monoclonal IgM, plus no new signs or symptoms of active disease. See appendix for full definition. • Achieved by 11 patients (30%)
Stable disease	Ghobrial 2010	7	Direct	B	• Defined as <25% change in serum monoclonal IgM, plus no progression of adenopathy/splenomegaly, or other clinically significant signs or symptoms of WM. See appendix for full definition. • Reported for 4 patients (11%)
Progressive disease	Ghobrial 2010	7	Direct	B	• Defined as ≥25% increase in monoclonal IgM, confirmed by either a second measurement or clinically significant findings or symptoms. See appendix for full definition. • Reported for 1 patient
Progression-free survival (PFS)	Ghobrial 2010	7	Direct	B	• PFS is the time from a specified start date until either disease progression or death occurs. • Median 15.6 months (95% CI 11.2 to 21.1 months) • Estimated PFS at 12 months 58% (95% CI 39% to 75%) • Estimated PFS at 18 months 45% (95% CI 27% to 63%) • Wide confidence intervals increase uncertainty in this endpoint. • Start date for measurement of PFS was not specified. Date of trial enrolment or first day of treatment are commonly used.
Time to progression	Ghobrial 2010	7	Direct	B	• Time to progression is a similar measure to PFS, but does not account for deaths occurring before progression. PFS is therefore the preferred outcome. • Median time to progression was 16.4 months • Untreated WM can remain stable for months or years without progression
Overall survival	Ghobrial 2010	7	Direct	B	• Median overall survival was not reached during the trial (median follow-up 16 months). Longer follow-up required to capture this information
Time to next therapy (TTNT)	Ghobrial 2010	7	Direct	B	• This endpoint was included since WM patients may meet criteria for PD but remain asymptomatic. These patients are not treated until symptomatic. • Median TTNT 17.6 months (range 1 to 25 months) • Wide range increases uncertainty in this endpoint.
Deaths	Ghobrial 2010	7	Direct	B	• 3 deaths recording during study follow-up (median 16 months) • Lack of comparator means it cannot be determined whether this is superior or inferior to current standard care.
Reported toxicities	Ghobrial 2010	7	Direct	B	• Without comparison groups it cannot be determined what proportion of reported ADRs are attributable to treatment, or whether many are reflective of underlying disease symptoms. • Reported grade 3 or 4 toxicities included anaemia, leukopenias, thrombocytopenia, and peripheral neuropathy.

Use of weekly bortezomib plus rituximab vs. twice weekly bortezomib plus rituximab to treat relapsed or refractory WM					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Reported toxicities	Agathocleous, 2010	5	Direct	C	• Without comparison groups it cannot be determined what proportion of reported ADRs are attributable to treatment, or whether many are reflective of underlying disease symptoms. • ADRs were not reported by subgroup; it is not clear what ADRs were experienced by patients with WM. • Reported grade 3 or 4 toxicities included neuropathy (14-19%), leukopenias, thrombocytopenia.
Overall response (complete response + partial response)	Agathocleous, 2010	5	Direct	C	• Only 10 patients in this trial had a diagnosis of WM; it should be considered a post-hoc sub-group analysis for purposes of evidence-based medicine. • Overall response was defined as CR + PR. These were not defined in the text, but used the definitions from the 3rd International Workshop on WM (text specified 4th workshop, but reference is to 3rd). See appendix for full definitions. • IWWM-3 defines CR as disappearance of monoclonal IgM, plus resolution of adenopathy/organomegaly, signs and symptoms of WM, and malignant bone marrow cells. • IWWM-3 defines PR as ≥50% improvement in both serum monoclonal IgM and adenopathy/organomegaly, plus no new signs or symptoms of disease. • Overall response was reported in 9 patients with WM (90%). • Any extrapolation from these patients to other people with WM should be made with extreme caution; these results are not generalizable.
Stable disease	Agathocleous, 2010	5	Direct	C	• Stable disease was not defined in the text but specified that definitions from the 3rd International Workshop on WM were used (text specified 4th workshop, but reference is to 3rd). See appendix for full definition. • IWWM-3 defines stable disease as <25% change in serum monoclonal IgM, plus no progression of adenopathy/splenomegaly, or other clinically significant signs or symptoms of WM. • 1 patient with WM had stable disease. Time point for this assessment not clearly specified.
Disease progression	Agathocleous, 2010	5	Direct	C	• Disease progression was defined as >25% increase in IgM. • 4 patients (40%) remained asymptomatic for 2-2.5 years. • 5 patients had disease progression. • The remaining patient was not accounted for.

Use of bortezomib plus bendamustine to treat relapsed or refractory Waldenstrom's macroglobulinaemia (WM)					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Partial remission	Moosmann 2010	5	Direct	C	• Only 1 patient in this trial had a diagnosis of WM; it should be considered a case report or sub-group analysis for purposes of evidence-based medicine. • No extrapolation can be made from this patient to other people with WM. • The one WM patient had a partial remission of disease.

					• No definition of partial remission was specified.
Reported toxicities	Moosmann 2010	5	Direct	C	• Bendamustine dose was limited by dose-limiting thrombocytopenia

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	

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

10. Literature Search Terms

Search strategy *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with relapsed or refractory disease
I – Intervention Which intervention, treatment or approach should be used?	Bortezomib, used alone or in combination with rituximab or bendamustine.
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Rituximab single agent or in combination with dexamethasone and cyclophosphamide (DCR)
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 survival Progression free survival *Important to decision-making:* Treatment-related morbidity/mortality Clinical response Disease relapse
Assumptions / limits applied to search	
Inclusion Criteria	**Studies published in last 10 years** **Study types: RCTs, Controlled studies, Prospective cohort studies, case series**
Exclusion Criteria	**Non-English language studies**

11. Search Strategy

1. EMBASE; WALDENSTROEM DISEASE/ OR WALDENSTROEM MACROGLOBULIN/ OR WALDENSTROEM MACROGLOBULINAEMIA/ OR WALDENSTROEM MACROGLOBULINEMIA/ OR WALDENSTROEM'S DISEASE/ OR WALDENSTROEM'S MACROGLOBULINAEMIA/ OR WALDENSTROEM'S MACROGLOBULINEMIA/ OR WALDENSTROM DISEASE/ OR WALDENSTROM MACROGLOBULIN/; 8314 results
2. EMBASE; BORTEZOMIB/; 21311 results
3. EMBASE; relapse.ti,ab,af; 178267 results
4. EMBASE; 1 AND 2 AND 3; 146 results
5. Medline; WALDENSTROM MACROGLOBULINEMIA/; 4955 results
6. Medline; BORTEZOMIB/; 4150 results
7. Medline; 1 AND 2; 53 results

NB: Lymphoplasmacytic lymphoma maps to EMTREE thesaurus term WALDENSTROEM MACROGLOBULINEMIA/.

12. Evidence selection

- Total number of publications reviewed: 146
- Total number of publications considered relevant: 24
- Total number of publications selected for inclusion in this briefing: 5

13. References

AGATHOCLEOUS, A., ROHATINER, A., RULE, S., HUNTER, H., KERR, J. P., NEESON, S. M., MATTHEWS, J., STRAUSS, S., MONTOTO, S., JOHNSON, P., RADFORD, J. & LISTER, A. 2010. Weekly versus twice weekly bortezomib given in conjunction with rituximab, in patients with recurrent follicular lymphoma, mantle cell lymphoma and Waldenstrom macroglobulinaemia. *Br J Haematol,* 151**,** 346-53.

CHEN, C. I., KOUROUKIS, C. T., WHITE, D., VORALIA, M., STADTMAUER, E., STEWART, A. K., WRIGHT, J. J., POWERS, J., WALSH, W., EISENHAUER, E. & NATIONAL CANCER INSTITUTE OF CANADA CLINICAL TRIALS, G. 2007. Bortezomib is active in patients with untreated or relapsed Waldenstrom's macroglobulinemia: a phase II study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol,* 25**,** 1570-5.

GHOBRIAL, I. M., HONG, F., PADMANABHAN, S, BADROS, A., ROURKE, M., LEDUC, R., CHUMA, S., KUNSMAN, J., WARREN, D., HARRIS, B., SAM, A., ANDERSON, K. C., RICHARDSON, P. G., TREON, S. P., WELLER, E., MATOUS, J. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia. *Clin Oncol,* 28(8),1422-8.

KIMBY, E., TREON, S. P., ANAGNOSTOPOULOS, A., DIMOPOULOS, M., GARCIA-SANZ, R., GERTZ, M. A., JOHNSON, S., LEBLOND, V., FERMAND, J. P., MALONEY, D. G., MERLINI, G., MOREL, P., MORRA, E., NICHOLS, G., OCIO, E. M., OWEN, R., STONE, M. & BLADE, J. 2006. Update on recommendations for assessing response from the Third International Workshop on Waldenstrom's Macroglobulinemia. *Clin Lymphoma Myeloma,* 6**,** 380-3.

LEBLOND, V., KASTRITIS, E., ADVANI, R., ANSELL, S. M., BUSKE, C., CASTILLO, J. J., GARCIA-SANZ, R., GERTZ, M., KIMBY, E., KYRIAKOU, C., MERLINI, G., MINNEMA, M. C., MOREL, P., MORRA, E., RUMMEL, M., WECHALEKAR, A., PATTERSON, C. J., TREON, S. P. & DIMOPOULOS, M. A. 2016. Treatment recommendations for Waldenstrom macroglobulinemia from the Eighth International Workshop on WM. *Blood*.

MOOSMANN, P., HEIZMANN, M., KOTRUBCZIK, N., WERNLI, M. & BARGETZI, M. 2010. Weekly treatment with a combination of bortezomib and bendamustine in relapsed or refractory indolent non-Hodgkin lymphoma. *Leuk Lymphoma,* 51**,** 149-52.

ORPHANET Waldenström macroglobulinemia. Last update March 2016. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=33226. Accessed 09/09/2016.

OWEN, R. G., PRATT, G., AUER, R. L., FLATLEY, R., KYRIAKOU, C., LUNN, M. P., MATTHEY, F., MCCARTHY, H., MCNICHOLL, F. P., RASSAM, S. M., WAGNER, S. D., STREETLY, M., D'SA, S. & BRITISH COMMITTEE FOR STANDARDS IN, H. 2014. Guidelines on the diagnosis and management of Waldenstrom macroglobulinaemia. *Br J Haematol,* 165**,** 316-33.

PHEKOO, K. J., JACK, R. H., DAVIES, E., MOLLER, H., SCHEY, S. A. & SOUTH THAMES HAEMATOLOGY SPECIALIST, C. 2008. The incidence and survival of Waldenstrom's Macroglobulinaemia in South East England. *Leuk Res,* 32**,** 55-9.

TREON, S. P., HUNTER, Z. R., MATOUS, J., JOYCE, R. M., MANNION, B., ADVANI, R., COOK, D., SONGER, J., HILL, J., KADEN, B. R., SHARON, D., STEISS, R., LELEU, X., BRANAGAN, A. R. & BADROS, A. 2007. Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: results of WMCTG Trial 03-248. *Clin Cancer Res,* 13**,** 3320-5.

WEBER, D., TREON, S. P., EMMANOUILIDES, C., BRANAGAN, A. R., BYRD, J. C., BLADE, J. & KIMBY, E. 2003. Uniform response criteria in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol,* 30**,** 127-31.

14. Appendix

Definitions of disease response from the Second and Third International Workshops on Waldenstrom's Macroglobulinaemia (IWWM-2 & IWWM-3).

Outcome	IWWM-2 (Weber et al., 2003)	IWWM-3 (Kimby et al., 2006)
Complete response	• disappearance of monoclonal IgM from serum and urine by immunofixation • resolution of adenopathy/organomegaly • no signs or symptoms of WM, • absence of malignant cells from bone marrow histologic evaluation reconfirmation at least 6 weeks later	
Partial response	• ≥50% reduction of serum monoclonal IgM by protein electrophoresis • ≥50% improvement in bulky adenopathy/organomegaly on CT scan • no new signs, symptoms or other evidence of disease	
Minor response	N/A	• ≥25% but <50% reduction in serum monoclonal IgM determined by protein electrophoresis • no new signs or symptoms of active disease
Stable disease	N/A	• < 25% change in serum monoclonal IgM determined by electrophoresis • no progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms caused by disease and/or signs of WM
Progressive disease	• >25% increase in serum monoclonal IgM from lowest attained level by protein electrophoresis • confirmation by at least one other investigation or clinically significant disease-related symptom	• ≥25% increase in serum monoclonal IgM by protein electrophoresis, confirmed by: ○ a second measurement, or ○ progression of clinically significant findings caused by disease (e.g. anemia thrombocytopenia, leukopenia, bulky adenopathy/ organomegaly), or ○ symptoms attributable to WM (e.g. unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% weight loss, hyperviscosity, neuropathy, symptomatic cryoglobulinaemia)