Erratum for

Title: Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma

Produced by: Warwick Evidence

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The authors have no conflicts of interest.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors: Xavier Armoiry (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and co-ordinated the project; Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence; Martin Connock (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and undertook additional analyses; Alexander Tsertsvadze (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and the NMA; G.J. Melendez-Torres (Assistant Professor) conducted the critique of clinical effectiveness evidence and the NMA; Rachel Court (Information specialist) and Pam Royle (Research Fellow) conducted the critique of the company searches; Karoline Munro conducted the critique of the background section and decision problem and contributed to the reporting of clinical effectiveness data; and Aileen Clarke (Professor of Public Health and Health Services Research) co-ordinated the project and provided comments on the report.

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Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

years in 2012 to 2014.[16] If one choses to express the value of a life year in monetary value, if one agreed with $150,000, and if one assumed that the average life expectancy is 85 years for 75 year old patients, the total value of life years lost would be $1,500,000. This calculation can be called into question at any point.

The company argues that high-risk subgroups should be identified according to NICE guidelines (CS, 48; NG35[17]), and states that IXA+LEN+DEX have demonstrated a consistently good performance in pre-specified subgroups, including amongst other things, patients with high-risk cytogenetic abnormalities (CS, 49). The CHMP however disagrees and states that "[i]t is not possible to identify a higher-risk subgroup that could benefit from treatment with ixazomib, especially based on post-hoc analysis and in view of non-compelling overall results. In addition, the results for the primary analysis and for sub-groups worsen from the first interim analysis to the second interim analysis and where the better results seen in high-risk patients appeared to be driven by patients with del(17) in the first interim analysis, but seemed driven by those with t(4;14) in the second interim analysis". [18] The CHMP states that no benefit can be observed for high-risk patients. This conclusion has not been revoked in the final decision by the EMA in November, in which they agree to grant marketing authorisation on the basis of the good toxicity profile but in expectation of more clinical data to support a positive benefit-risk balance.

2.2 Critique of company's overview of current service provision

The CS presents a treatment pathway for MM on page 56 and corresponding text on pages 56-57. The treatment pathway for first line is presented depending on patients are eligible or not for ASCT, and this is in line with current standards. In the pathway suggested by company, the importance of bortezomib for first line is highlighted and in text the company states that bortezomib retreatement is not recommended for second line. This apparently contradicts the postioning by the company of bortezomib-dexamethasone for second line. By definition, the use of bortezomib-dexamethasone for second line should only pertain to patients who did not receive bortezomib at first line. The ERG considers that the pathway should have better differentiated first line treatment depending on whether patients received bortezomib.

ixazomib must be combined with lenalidomide and dexamethasone. Therefore, we believe that, if ixazomib was to be recommended, the drug would be implicitly used in the situations where lenalidomide-dexamethasone is already used within the UK. Assuming bortezomib-dexamethasone to be the most relevant comparator for second line, a lenalidomide-dexamethasone based combination (used alone or with ixazomib) would have some advantages over bortezomib in terms in ease of use or better acceptance, but these would rely on the lenalidomide-dexamethasone based regimen, with or without ixazomib, which means that the advantages of an oral treatement advocated by the company do not come from ixazomib itself but from lenalidomide-dexamethasone.

3 Critique of company's definition of decision problem

3.2 Population

The population in the decision problem, and subsequent clinical evidence matches the population described in the final scope. The population of relevance includes patients with relapsed or refractory multiple myeloma (RRMM) who have had at least one prior therapy.

Our understanding is that the company has proposed the positioning of ixazomib as a second and third line treatment, which would exclude subsequent lines. Despite the exclusion of subsequent lines, the company has conducted clinical and cost-effectiveness analyses considering RRMM patients with at least one prior treatment. Although these analyses match the population described in the final scope, it does not exactly correspond to the population targeted by the company to benefit from ixazomib (i.e. second and third line).

Since we assume that the proposed positioning of ixazomib by the company is relevant to the current practice, we believe that the company would have better stated that the population in the decision problem is restricted to RRMM patients at second and third line. This would have been consistent to the choice of comparators in the decision problem where the company better differentiated between patients who have had 1 prior therapy to those who had 2 prior therapies.

4.4 Identified Studies

The main trial of the CS is the Tourmaline MM-1 study (1 publication from the main trial, [26] 1 publication from the China study,[29] plus unpublished data from the 2nd data cut IA2 (12th July 2015). The company also included this trial in their NMA (for discussion of the NMA see relevant section). The trial was funded by the Millennium Pharmaceuticals subsidiary of Takeda Pharmaceuticals.

The details of the trial were summarised and discussed in the CS on pp.81-110. The trial design was reported on p.81f. of the CS. The trial was an international, Phase III, randomised, double blind trial comparing IXA+LEN+DEX (4mg IXA on days 1, 8, 15 plus 25mg LEN on days 1-21, plus 40 DEX on days 1, 8, 15, 22) with LEN+DEX (placebo plus 25mg LEN on days 1-21, plus 40 DEX on days 1, 8, 15, 22) in 28 days cycles. 360 patients were randomly assigned to the IXA+LEN+DEX group, and 362 to the Placebo +LEN+DEX group. Randomisation was stratified by number of prior therapies (1 vs. 2 or 3), previous proteasome inhibitor treatment (naïve vs. exposed), and International Staging System disease stage (ISS I or II vs. III). Treatment continued until disease progression or unacceptable toxicity. Permitted concomitant medications were thromboprophylaxis according to American Society of Clinical Oncology (ASCO) guidelines, aspirin (81-325mg orally once daily), low-molecular weight heparin, prophylactic antiviral therapy as clinically indicated, myeloid growth factors, erythropoietin, red blood cells and platelet transfusions, standard anti-emetics as clinically indicated and prophylactic, topical, intravenous or oral antihistamines or steroids, bisphosphonates, CYP1A2 inhibitors. Strong CYP3A inducers were to be avoided and radiation therapy or anti-neoplastic treatment was not permitted (CS, 85).

Eligibility criteria were reported on p.82f. and in table 30 on p.83. The trial was designed to select patients with RRMM based on standard criteria and with measurable disease and an Eastern Cooperative oncology Group (ECOG) performance status between 0-2 (on a scale from 0-5), whilst excluding patients who were refractory to lenalidomide or proteasome inhibitor-based therapy. The trial included male and female patients who had 1-3 prior therapies and relapsed after previous treatment, both refractory and not refractory, and who had never responded to previous treatment. Patients were recruited in 147 centres in 26 countries, including 9 centres in the UK, which included 21 patients (CS, 84, table 31).

The median age of patients in both the IXA+LEN+DEX and the placebo group was 66 years, (38-91 in the IXA group and 30-89 in the placebo group). 53% of patients in the IXA group and 51% in the placebo group were over 65 years old. For both groups, the time since diagnosis was similar (median 44.2 months IXA vs. 42.2 months placebo). The number of

Overall, the company concludes a survival trend in favour of IXA+LEN+DEX for both ITT and the high-risk population. However, the CHMP did not agree with the company's conclusion for both ITT and for the high-risk population. On the contrary, the CHMP argues that the evidence the company provided is not substantial enough to draw conclusions for high-risk groups (EMA, 124).

4.10.1.3 Time to progression

In the 1st interim analysis, the median TTP for the IXA+LEN+DEX group is 21.4 months, for the LEN+DEX group 15.7 (HR 0.71, 95%CI 0.56-0.91;p=0.007). The 2nd interim analysis the results for IXA+LEN+DEX was 22.4 months and 17.6 months (Table 1). The ERG regrets that the company presented the HR for progression (0.79) without its 95%CI.

These results indicate that, like for PFS, the benefit of IXA on the risk of progression is reduced between the first and second interim analysis. The comparable HR for TTP and PFS, from both first and second interim analysis, confirm our statement that TTP can be considered as a good proxy for PFS (see section on NMA critique).

Table 1: Tourmaline entire ITT population Time to progression results (HR <1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	360	362
1st interim analysis (median FUP 15 months)		
Number of progressions	114	145
Median TTP (months)	21.4	15.7
HR for progression (95%CI)	0.71 (0.56, 0.91)	
P value	0.007	
2nd interim analysis (median FUP 23 months)		
Number of progression	158	180
Median TTP (months)	22.4	17.6
HR for progression (95%CI)	0.79 (0.64, 0.98)	
P value	*	

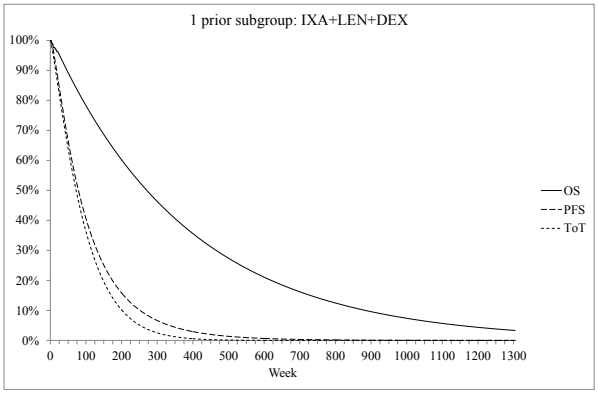
* P value not reported in the main CS

Table 2: Tourmaline 1 prior therapy Response rates (OR >1 favours IXA+LEN+DEX)

	IXA+LEN+DEX	LEN+DEX
Number of patients	212	213
1st interim analysis (median FUP 15 months)		
Overall response rate, n (%)	163 (76.9)	159 (74.6)
OR for OR rate (95%CI)	1.13 (0.72, 1.77)	
P value	NR	
very good response and complete response, n (%)	95 (44.8)	(43.7)
OR for VGPR + CR (95%CI)	1.05 (0.71, 1.54)	
P value	NR	
Complete response or better,n (%)	19 (9.0)	17 (8.0)
OR for CR or better (95% CI)	1.13 (0.57, 2.25)	
P value	NR	
2nd interim analysis (median FUP 23 months)		
Overall response rate, n (%)	164 (77.4)	166 (77.9)
OR for OR rate (95%CI)	0.97 (0.61, 1.53)	
P value	NR	
Very good response and complete response, n (%)	105 (49.5)	105 (49.3)
OR for VGPR + CR (95%CI)	-	
P value	NR	
Complete response or better,n (%)	26 (12.3)	27 (12.7)
OR for CR better (95% CI)	-	
P value	NR	

The results of the main trial do not show any benefit of IXA-LEN-DEX over LEN-DEX in terms of response rates. Initial insignificant benefits in PFS, TTP and OS seem to decrease from first to second interim analysis. It may even be argued that the triplet performs worse than the doublet.

Overall, the similarity between the IXA-LEN-DEX and LEN-DEX groups with 1 prior therapy supports the company's request to prioritise consideration of IXA-LEN-DEX for 3rd line positioning within the UK. The company did however provide a cost-effectiveness analysis of IXA-LEN-DEX vs. bortezomib plus dexamethasone in the 1 prior therapy group (i.e. at 2nd line) and requests that this positioning be considered as a secondary priority.



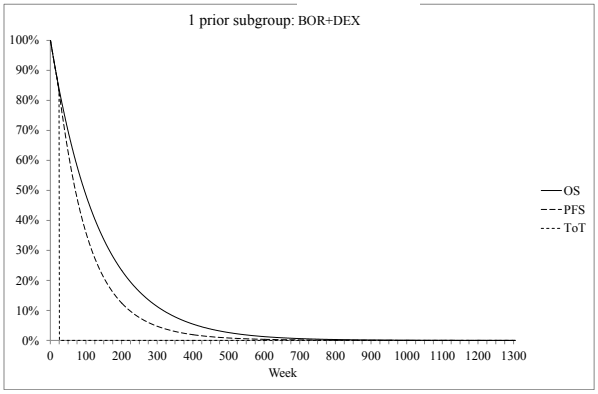


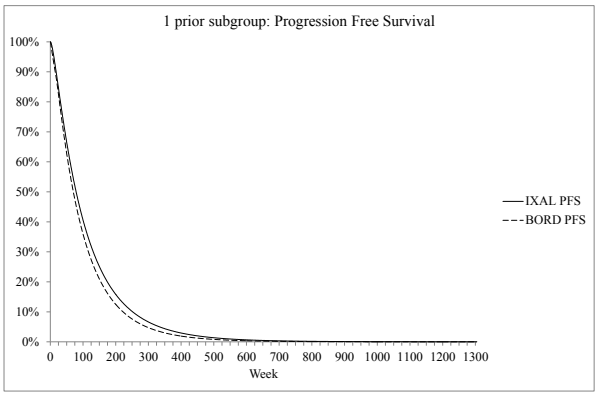
Figure 1: 1 Prior: Company base case curves

Immediately apparent from the above is the difference in terms of time on initial therapy, with IXA+LEN+DEX being much as per the PFS curve but BORT+DEX being restricted to 9 three week cycles to yield 27 weeks of treatment.

There is also only limited additional PPS survival subsequent to PFS survival for BORT+DEX but a great deal of additional PPS survival subsequent to PFS for IXA+LEN+DEX.

IXA+LEN+DEX appears to have altered the course of the disease subsequent to progression compared to BORT+DEX.

The OS and the PFS curves modelled for each comparator can also be presented alongside one another.



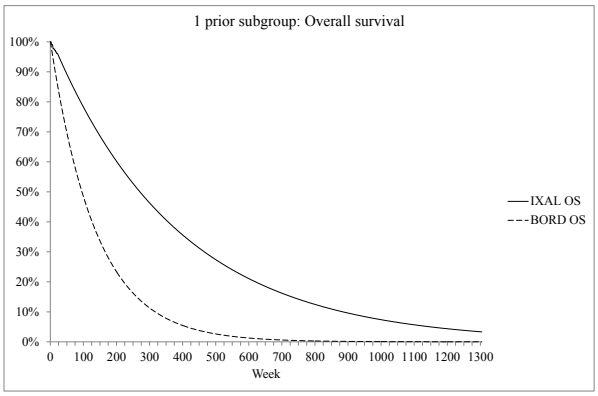


Figure 2: 1 Prior: Company base case OS and PFS curves[1]

[1] Within the tables and figures of the economics, in order to economise on space IXA+LEN+DEX is abbreviated to IXAL, LEN+DEX is abbreviated to LEND and BORT+DEX is abbreviated to BORD.

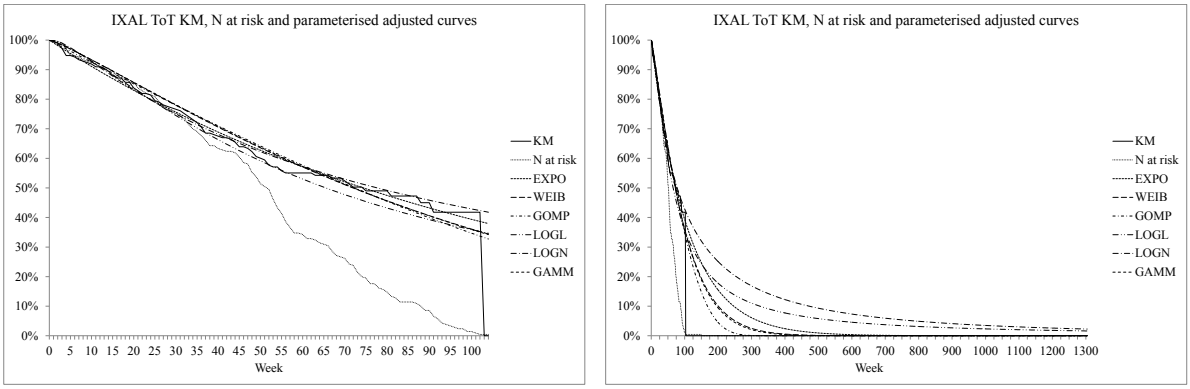
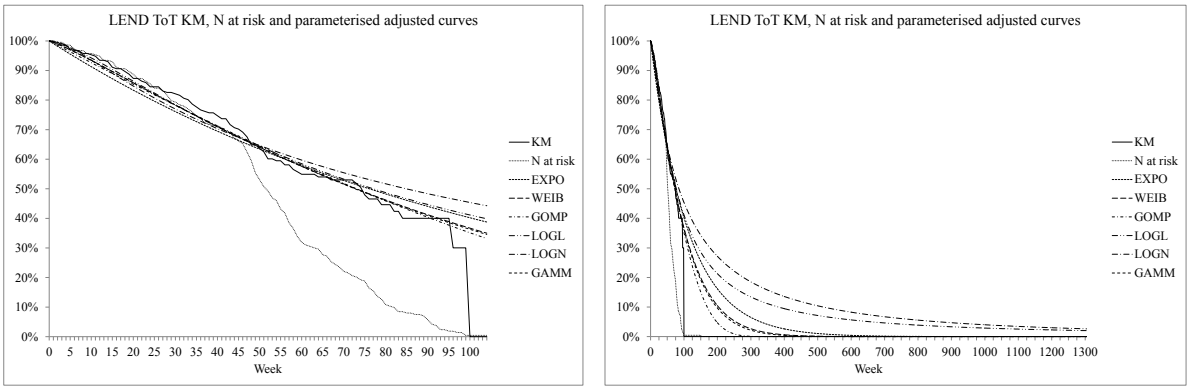


Figure 3: 1 Prior: IXA+LEN+DEX ToT KM, N at risk and adjusted parameterised curves

The graphs of the adjusted curves for LEN+DEX are as below.

Figure 4: 1 Prior: LEN+DEX ToT KM, N at risk and adjusted parameterised curves



The gompertz is the lowest curve for both IXA+LEN+DEX and LEN+DEX. The Weibull and the gamma are the pair of curves lying above this, and are little different from one another.

The BORT+DEX arm is assumed to have the same ToT curve as the LEN+DEX arm despite being estimated to have an inferior PFS curve to the LEN+DEX arm. In the absence of alternative data the more natural assumption might have been to apply the PFS hazard of 1.059 to the LEN+DEX ToT curve. BOR+ DEX is only administered for 8 three week cycles, which curtails its ToT curve to 24 weeks[2]. Note that the Weibull for IXA+LEN+DEX lies slightly below that for LEN+DEX.

[2] Or rather 25 weeks in the model given half cycle correction.

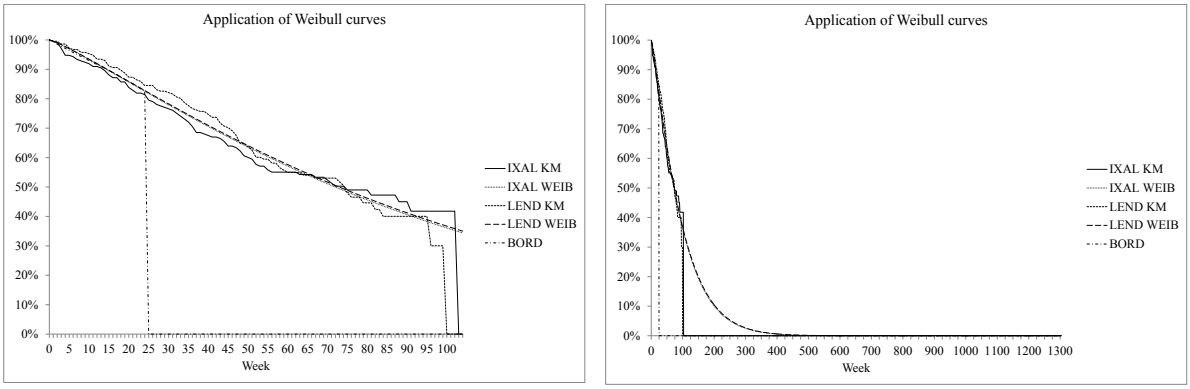


Figure 5: 1 Prior: Company base case ToT curves: Weibulls

5.2.6.10 Time on treatment (ToT): 2+ Prior subgroup

The economic model provides the following unadjusted and adjusted curves for the 1 prior subgroup, with the AIC and BIC values being taken from appendix 11 of the company submission and the company response to the ERG clarification questions.

Table 3: 2+ Prior: Unadjusted parameterised ToT curves

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.312	0.323	-0.308	0.368	0.393	0.349
Constant	-4.476	4.497	-4.377	4.113	4.153	4.407
Gamma		-0.044	-0.003			
Sigma				0.108	0.506	0.211
Kappa						0.680
AIC	1542.37	1544.05	1543.66	1543.55	1547.47	1545.33
BIC	1549.75	1555.13	1554.74	1554.64	1558.55	1560.11

Table 4: 2+ Prior: Adjusted parameterised ToT curves