NICE National Institute for Health and Care Excellence

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505)

Lead team presentation

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ERG: Warwick Evidence
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Company: Takeda

CDF review committee meeting 15 December 2021

Key issues for consideration

Issue	Summary	Company base case	ERG base case	Impact	Slide
Issue 1	The company's Weibull models for adjusted OS appear almost indistinguishable from the generalised gamma.	Generalised gamma to extrapolate OS	Weibull to extrapolate OS		18 to 19
Issue 2	There is uncertainty surrounding the pre-progression and post-progression life year gains in the adjusted OS modelling.	Adjusted OS to remove non-UK/NHS treatments	As per company	 	14 to 17
Issue 3	The sustained effect of treatment where patients are not receiving the study treatments.	No treatment waning	As per company		20 to 22

Key:
 Model driver;  Unknown impact;  Small/moderate impact

OS: Overall survival

Disease background

Multiple myeloma (MM) is a neoplastic condition that arises from plasma cells in the bone marrow. Myeloma cells suppress the development of normal blood cells that are responsible for fighting infection, carrying oxygen around the body and blood clotting.

People with MM can experience:

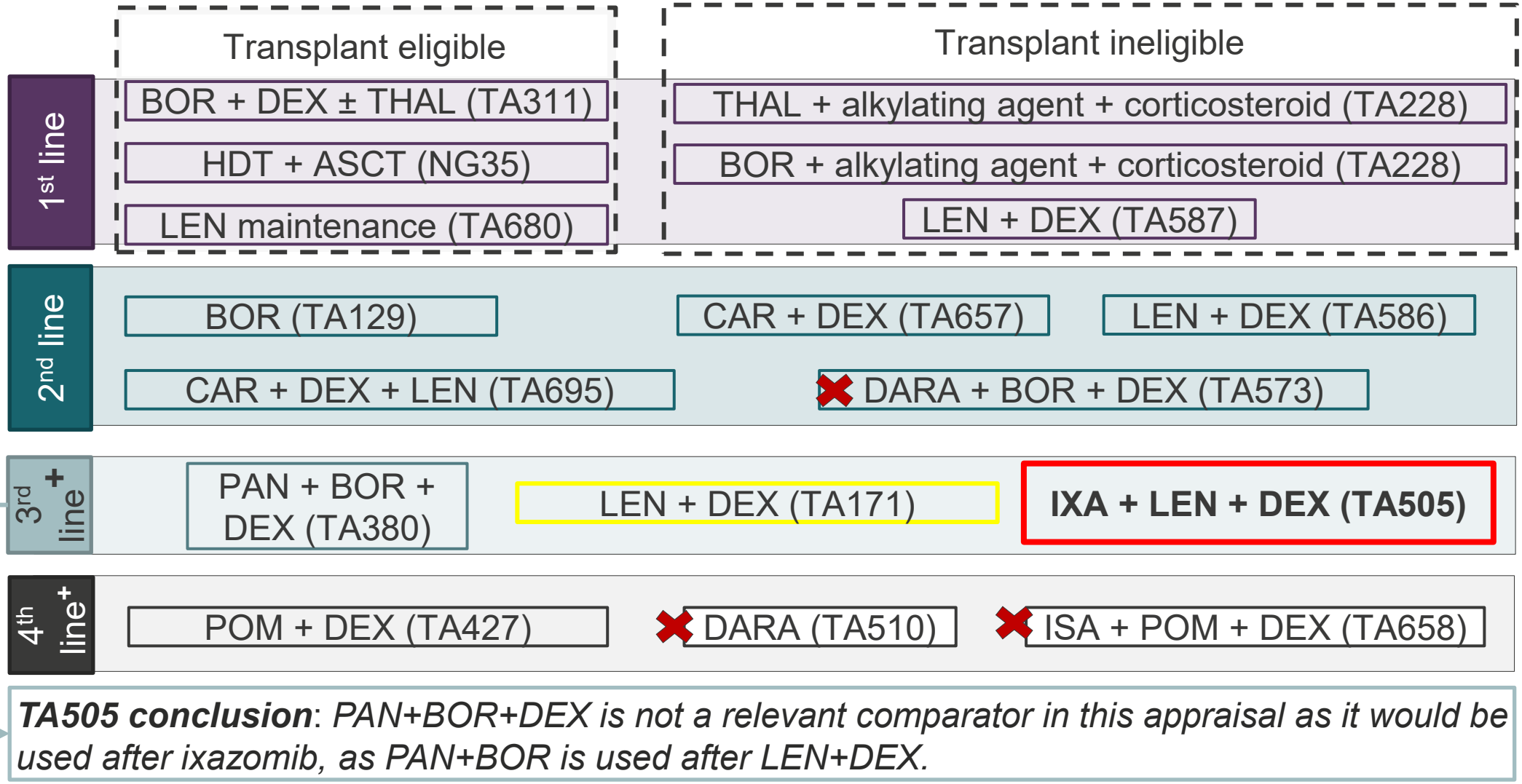
- Bone pain and bone fractures
- Tiredness (as a result of anaemia)
- Infections
- Hypercalcaemia (too much calcium in the blood)
- Kidney problems.

- **6,377** newly diagnosed cases of multiple myeloma in the UK in 2020
- **43%** of people are aged 75 years and over
- Multiple myeloma is more common in men than in women and the incidence is also reported to be higher in people of African family origin.

- **Refractory MM:** disease that is nonresponsive to treatment, or progresses within 60 days of last therapy.
- **Relapsed MM:** previously treated MM that progresses and requires initiation of next line of therapy but does not meet criteria for refractory MM.

Multiple myeloma is an incurable disease. The 5-year survival rate for adults with multiple myeloma in England and Wales is about 50%.

Treatment pathway



✖ Not routinely commissioned, available via the Cancer Drugs Fund only

Comparator in TA505 and current CDF review

ASCT: autologous stem cell transplantation; BOR: Bortezomib; CAR: Carfilzomib; DARA: Daratumumab; DEX: Dexamethasone: HDT: High dose therapy: ISA: Isatuximab; IXA: Ixazomib; LEN: Lenalidomide; PAN: Panobinostat; POM: Pomalidomide; THAL: Thalidomide

Ixazomib (Ninlaro, Takeda)

Marketing authorisation	Ixazomib in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
Mechanism of action	Proteasome inhibitor
Administration	• Oral, recommended starting dose 4mg (1 capsule) once a week on days 1, 8 and 15 of each 28-day treatment cycle • Treatment continued until disease progression or unacceptable toxicity • Other drugs in combination also given orally
Cost	• Average cost of course (i.e. cycle): ○ Total: £10,708 per cycle (list prices) ▪ Ixazomib list price: £6,336 per cycle (has a simple discount PAS) ▪ Lenalidomide list price: £4,368 per cycle (has a confidential discount) ▪ Dexamethasone list price: £4.43 per cycle (has a confidential discount)

PAS: Patient access scheme

Summary of original appraisal TA505 (1)

TA505 recommendation (published Feb 2018):
Ixazomib, with lenalidomide and dexamethasone, is recommended in the Cancer Drugs Fund (CDF) as an option for **treating multiple myeloma** in adults**,** only if they have had 2 or 3 lines of therapy and the conditions in the managed access agreement for ixazomib are followed.

	Decision problem (same scope for TA505 and current CDF review)	Committee preference
Population	• People with relapsed or refractory multiple myeloma (RRMM) who have had at least 1 therapy.	• Population was restricted to people with RRMM who have already had 2 or 3 lines of previous therapy.

Comparators*	• People who have had ≥2 therapies:
	  • LEN+DEX
	  • PAN+BOR+DEX.
		• PAN+BOR+DEX was not a relevant comparator as it would be used after ixazomib, as PAN+BOR is used after LEN+DEX.

Outcomes	• Progression-free survival (PFS) • Overall survival (OS) • Response rates • Time to next treatment • Adverse effects of treatment • Health-related quality of life.	• Company required to collect updated OS and time on treatment (ToT) data from the TMM1 trial and other sources, including the SACT dataset.

*Scope also included comparators for people who had 1 prior therapy (bortezomib with or without dexamethasone, bortezomib retreatment with or without dexamethasone, lenalidomide with dexamethasone) – not relevant because of change to population.
CDF: Cancer Drugs Fund; OS: Overall survival; PFS: Progression-free survival; RRMM: Relapsed or refractory multiple myeloma; SACT: Systematic anti-cancer therapy; TMM1: TOURMALINE-MM1; ToT: Time on treatment

Summary of original appraisal TA505 (2)

Uncertainties in TA505		Committee preference
Extrapolation of trial outcomes	ERG was concerned that the choice of curve for extrapolating trial outcomes produced clinically implausible results.	Alongside TMM1 data, data from the SACT dataset would provide evidence to address the uncertainties in the clinical evidence.
Continued treatment effect	Assumed that the relative survival benefit was maintained at the same level after treatment stopped, for the rest of a person's life.	Mature data from TMM1 could reduce the uncertainty regarding the proportional hazards assumption.
Subsequent therapies	The total cost of treatments taken after progression was the same in the ixazomib arm as in the LEN+DEX arm.	The company should explore the most appropriate subsequent treatments costs to be included in the model for both arms based on the more mature TMM1 trial data.
Utilities	The utility for progressed disease was higher than the UK population norms for this age group.	Mature data from TMM1 could reduce the uncertainty.

SACT: Systematic anti-cancer thearpy; TMM1: TOURMALINE-MM1

CDF review TA505 – Key clinical evidence

Outcome	TA505		CDF review		
	TMM1 2014/2015	TMM1 2014/2015	TMM1 2020		SACT 2020
	IXA+LEN+DEX (n=148)	LEN+DEX (n=149)	IXA+LEN+DEX (n=148)	LEN+DEX (n=149)	IXA+LEN+DEX (n=2,460)
Median follow-up, months	23		85		15 for OS and 8.3 for ToT
Median OS, months	NE	NE	53.0	43.0	30.0
Hazard ratio (HR) (95% CI)	0.65 (0.41 to 1.02)		0.85 (0.64 to 1.11)		NA
Median PFS, months	22	13	PFS observations were not collected beyond the second interim analysis of TMM1. Therefore, no updates to PFS are available for consideration in this CDF review.		NA
HR (95% CI)	0.62 (0.45 to 0.86)				NA
Median ToT, months (95% CI)	17.7 (14.0 to 20.6)	12.6 (11.1 to 16.8)	18.2 (16.1 to 22.4)	13.4 (11.2 to 17.3)	11.5 (10.5 to 12.2)
HR (95% CI)	0.75 (0.56 to 0.99)		0.76 (0.60 to 0.96)		NA

CDF: Cancer drugs fund; CI: Confidence interval; HR: Hazard ratio; NA: Not available; NE: Not estimable; OS: Overall survival; PFS: Progression-free survival; SACT: Systematic anti-cancer therapy; TMM1: TOURMALINE-MM1; ToT: Time on treatment

CDF review TA505 – Key considerations

	Committee preferred in TA505	Company base case in current CDF review
Data source	Subgroup of people who had 2 or 3 lines of therapy	
Comparator	LEN+DEX	
OS extrapolation	Weibull curve	Generalised gamma
PFS extrapolation	Weibull curve	
ToT	Weibull curve	
Utility values	From TMM1, limitations with data but no alternative utility values	Utility values from final analysis of TMM1, in line with committee expectations from TA505
End of life	The end-of-life criteria were not met	

Use of SACT data:

- Data from the SACT dataset collected to address the uncertainties in the clinical evidence.
- However, the generalisability of the TMM1 data could not be validated or compared to the SACT dataset. Specifically, the people from SACT tended to be older, less fit, and had a poorer prognosis than people in TMM1.

CDF: Cancer drugs fund; OS: Overall survival; PFS: Progression-free survival; SACT: Systematic anti-cancer therapy; TMM1: TOURMALINE-MM1; ToT: Time on treatment

Patient expert perspectives

Responses from: Myeloma UK (patient experts agreed with the Myeloma UK submission)

Myeloma UK surveyed 139 patients who had had ixazomib and provided a full analysis

Experience of the condition

- Multiple myeloma is an incurable relapsing and remitting cancer which becomes resistant to treatment.
- Complications can be significant, debilitating and painful and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system.
- Relapsed patients usually face a greater disease burden, greater adverse side effects, more hospital visits, and greater dependence on carers.
- 94% of carers are emotionally impacted and 25% have been unable to work.

Advantages of ixazomib

- Patient experiences of IXA+LEN+DEX:
  - 81% rated their experience as positive or very positive
  - 87% said their mental health stayed the same or improved
  - Oral administration highly valued
  - Delivers improved efficacy and progression-free survival.

"The uncertainty of not knowing when it will come back but the certainty of knowing it will is particularly difficult"

Clinical expert perspectives

Responses from: Professor Gordon Cook and Professor Graham Jackson

Experience of the condition	• Myeloma is currently incurable and response rates and outcomes beyond 3rd line therapies are very poor. • There is a huge unmet need in this indication. • With each relapse, managing the disease can be more of a challenge for clinicians and people with the disease.
Current treatments	• There is no commissioned pathway in England and no other useful therapy available at the 3rd line setting for people with relapsed refractory multiple myeloma. • CDF usage data demonstrates the how clinicians view the importance of ixazomib.
Advantages of ixazomib	• Ixazomib is a highly active, effective and all oral regime, reducing pressure on hospital out-patient and chemotherapy day units (important during COVID-19 pandemic too). • Ixazomib significantly prolongs PFS and OS without adverse impact on quality of life, tolerance in real world data were better than trial data.
Investment required to introduce ixazomib	• None: removing the technology would require significant investment as it would lead to increased use of intravenous and subcutaneous therapies and put considerable pressure on chemotherapy units.

"It is especially well tolerated in the older, frailer patient population, an important factor given the median age of presentation with myeloma is 74 in the UK"

CDF: Cancer Drugs Fund; OS: Overall survival; PFS: Progression-free survival

Issues resolved after technical engagement

Issue	Summary	ERG critique
Additional issue 1	• Lack of PFS data in the final analysis of the pivotal trial (TMM1). • PFS from the 2nd data cut-off from TMM1 used in this CDF review.	• PFS observation is shorter than the final cut OS observation leading to different handling of the 2 pivotal inputs for the comparison of clinical effectiveness. • The ERG recognises that data on PFS were not collected beyond the second interim analysis of TMM1.

CDF: Cancer Drugs Fund; OS: Overall survival; PFS: Progression-free survival; TMM1: TOURMALINE-MM1

Key issues for consideration

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OS: Overall survival

Issue 2: Pre-progression and post-progression LYs (1)

Background of the two-stage adjustment

- Treatments not routinely used in the NHS (including those recommended in the CDF) should not be considered as comparators or subsequent treatments in NICE appraisals.

Non-UK/NHS subsequent therapies	Treatment arm	
	LEN+DEX	IXA+LEN+DEX
DARA	31/149 = **21%**	19/148 = **13%**
ELOT	7/149 = **5%**	3/148 = **2%**
aSCT	9/149 = **6%**	1/148 = **0.7%**

- Company used the two-stage method with recensoring to remove the impact of non-UK/NHS based treatments, which were presumed to be effective and improve survival.

Company approach	ERG critique
• Listed covariates to satisfy the 'no unmeasured confounders' assumption.	• Company justified their choice of covariates on the basis that it is consistent with clinical opinion. ERG could not verify this information.

aSCT: allogeneic stem cell transplant; CDF: Cancer Drugs Fund; ELOT: Elotuzumab; LY: Life year

Issue 2: Pre-progression and post-progression LYs (2)

Background of the two-stage adjustment

- This resulted in decreased OS for both arms (by approximately 0.13 years = 1.5 months), yielding a similar median OS gain between unadjusted and adjusted analyses.
- After adjustment, modelled post-progression life expectancy reduces to a greater extent in the LEN+DEX arm compared with the IXA+LEN+DEX arm.

	Post prog LYs		Median OS (years)		
	LEN+DEX	IXA+LEN +DEX	LEN+DEX	IXA+LEN+ DEX	HR (95% CI)
Unadjusted	2.59	2.65	3.58	4.42	0.85 (0.64 to 1.11)
Adjusted	2.29	2.62	3.46	4.28	0.71 (0.54 to 0.95)
Incr.	-0.3	-0.03	-0.12	-0.14	-

CI: Confidence interval; HR: Hazard ratio; LY: Life year; OS: Overall survival

Issue 2: Pre-progression and post-progression LYs (3)

ERG critique	Company comment
• Only small differences in non-UK/NHS subsequent therapies between arms.	• Differences in subsequent therapies received in the 2 arms means more people in the LEN+DEX arm had therapies that extend survival.
• Modelled post-progression LY gain after adjustment represents 30.5% of total LY gain, which is considerable. • Modelled post-progression LY gain before adjustment represents 7.4% of total LY gain. • Results depart from clinical plausibility in terms of LY gains.	• People in the LEN+DEX arm had a median of 3 lines of subsequent therapy vs 2 in the IXA+LEN+DEX arm, so statistical adjustment to remove this confounding would likely have a greater impact in the LEN+DEX arm. • The difference in survival for people having novel subsequent therapies vs those who don't is smaller in the IXA+LEN+DEX arm and the curves move closer together at the end of follow-up. • Difference in reduction in LYs in treatment arms is clinically plausible according to UK advisory board.

Is the adjustment to OS reasonable?

LY: Life year; OS: Overall survival

Issue 2: Pre-progression and post-progression LYs (4)

Additional ERG analyses

ERG

- **Aim**: To examine the consistency of the OS results, and to verify the impact of adjustment on a larger sample size and number of events.
- **Rationale**: Publication of the final results from the trial places the submission in its context, the final TMM1 results show no survival advantage for IXA+LEN+DEX relative to LEN+DEX.
- **Methodology**: ERG reviewed the final OS analyses of TMM1 beyond the scope of the CDF review, i.e., including the intention to treat (ITT) TMM1 population (relapsed or refractory multiple myeloma with 1+ prior therapy).
  - Adjustments for subsequent therapies after people discontinued study treatment, using MSMs and IPCW.
- **Results (IXA+LEN+DEX vs placebo+LEN+DEX):**
  - Based on the ITT population – OS HR: 0.94 95% CI [0.78,1.13]
  - MSMs – OS HR: 0.68 95% CI [0.46, 1.00]
  - ICPW – OS HR: 0.70 95% CI [0.48, 1.03].
- **Conclusion:** Although the use of subsequent therapies may have confounded the analyses the ERG believes that the question of whether ixazomib improves OS in the 2+ prior population is yet to be determined.

Company: These analyses are outside the scope of a CDF review and are based on a broader population than this review.

CDF: Cancer drugs fund; CI: Confidence interval; HR: Hazard ratio; IPCW: Inverse probability of censoring weighting; ITT: Intention to treat; LY: Life year; MSM: Marginal structural models; OS: Overall survival; TMM1: TOURMALINE-MM1

Issue 1: Modelling of the adjusted OS (1)

Background

- Company suggested the **generalised gamma** curves provided a reasonable estimation of OS with LEN+DEX and IXA+LEN+DEX.
- ERG considers **Weibull curve** to be as valid on the grounds of clinical plausibility as the generalised gamma curve.
- TA505: *"a Weibull curve should be used to extrapolate all 3 outcomes in the model".*

Company

- The generalised gamma curve was selected by myeloma clinical experts at an advisory board, as reflecting expected outcomes for IXA+LEN+DEX and outcomes observed in clinical practice for LEN+DEX in the 2+ prior lines population.

ERG

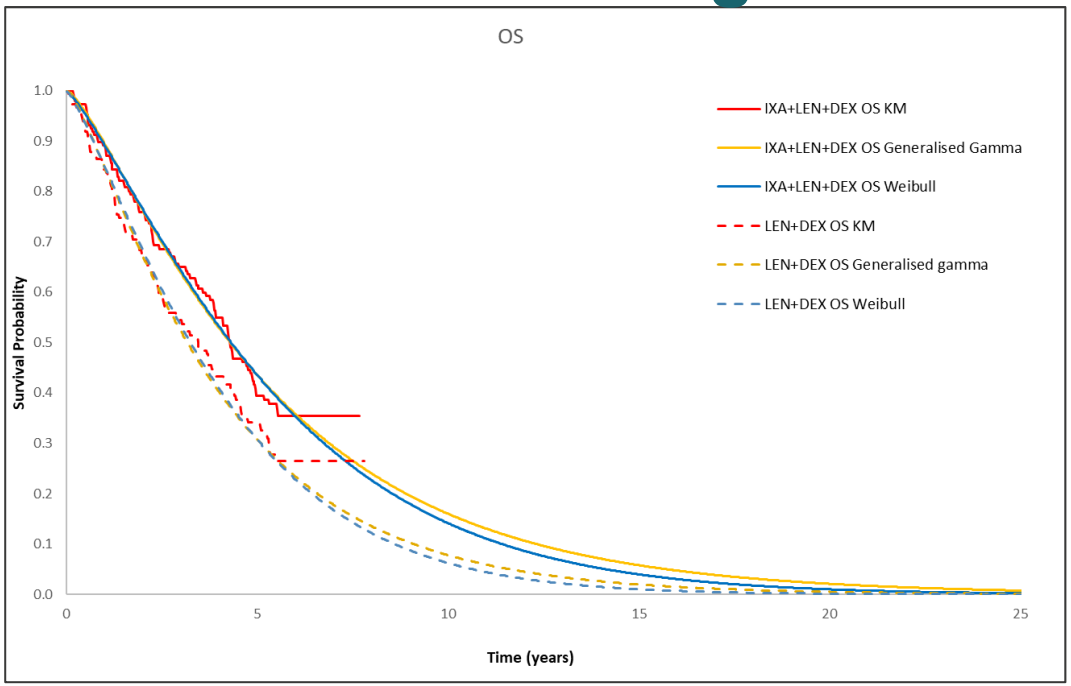
- The company's Weibull models for adjusted OS appear almost indistinguishable from the generalised gamma.
- The ERG cannot verify the independence of the advisory board or their conflicts of interest.
  - No uncertainty or range was attached for this estimate of the clinicians' deliberations.
  - Minimal information provided on the conduct of the meeting to elicit clinical opinion.
- There is uncertainty associated with the OS modelling, exemplified by differences produced using different methods of adjustment.
- The ERG notes that there is great sensitivity in the economic model even with small changes in modelling of OS.

Clinical expert

- The generalised gamma provided the most reasonable outcome estimation.

OS: Overall survival

Issue 1: Modelling of the adjusted OS (2)



Source		PP LY*	% alive	
			5-years	10-years
G. Gamma *company*	LEN+DEX	2.29	30.74%	7.80%
	IXA+LEN+DEX	2.62	43.60%	16.01%
Weibull *ERG*	LEN+DEX	2.21	30.77%	6.24%
	IXA+LEN+DEX	2.45	43.57%	14.15%

ERG also explored other extrapolations of OS:

Source		PP LYs*	5-years	10-years
Exponential	LEN+DEX	2.44	32.77%	10.74%
	IXA+LEN+DEX	2.87	44.67%	19.96%
Log-normal	LEN+DEX	2.97	32.55%	14.69%
	IXA+LEN+DEX	3.57	44.20%	22.86%
Log-logistic	LEN+DEX	2.95	31.48%	13.52%
	IXA+LEN+DEX	3.48	43.88%	21.02%
Gompertz	LEN+DEX	2.08	31.25%	3.40%
	IXA+LEN+DEX	2.17	43.99%	9.18%

What is the most appropriate method for extrapolating OS data?

*Pre-progression life years are almost identical for each extrapolation (1.5 for LEN+DEX and 2.25 for IXA+LEN+DEX).

LY: Life year; OS: Overall survival; PP: Post progression

Issue 3: Treatment waning effect (1)

Background:

- TA505: Committee agreed that although it was biologically plausible for the relative treatment benefit of ixazomib to continue after stopping treatment, it might not be maintained at that level for the rest of a person's life.

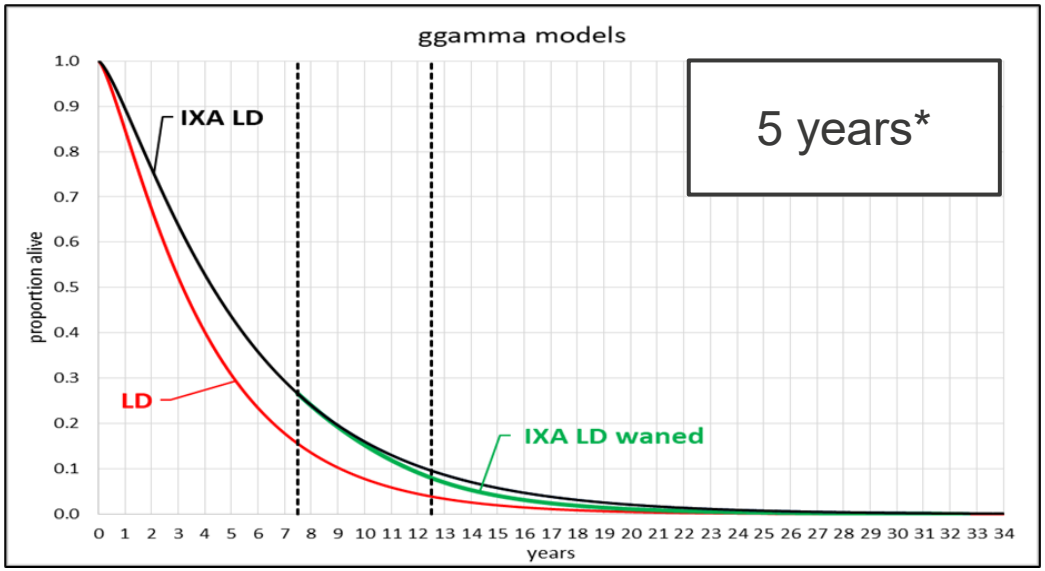
ERG

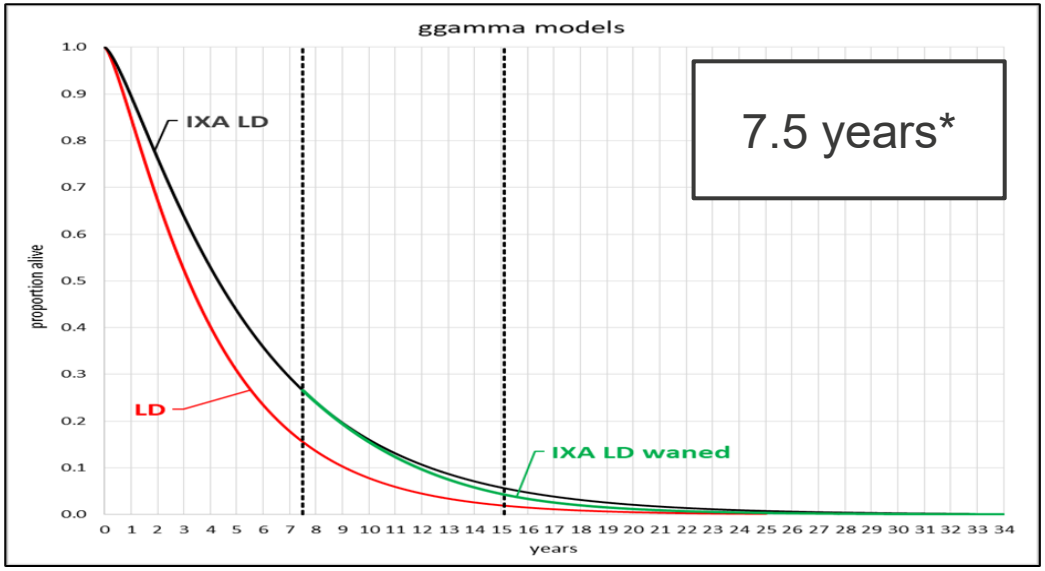
- Accept that waning/discontinuation of treatment almost completely been captured within the observed time of the trial, but this is separate to waning of treatment effect.
- Over 90% of people were only observed for approximately 2 years following discontinuation of ixazomib, which is insufficient to capture any waning of treatment effect.
  - Approximately 95% of people had completed treatment by year 5 while at year 8 approximately 35% people still alive in IXA+LEN+DEX arm.
  - Company model assumes that the treatment effect of ixazomib is fully maintained for a further 18 years.
  - Waning of the ixazomib treatment effect after treatment has stopped will likely occur before 18 years have expired.
- Conducted scenarios to explore potential impact of treatment waning.

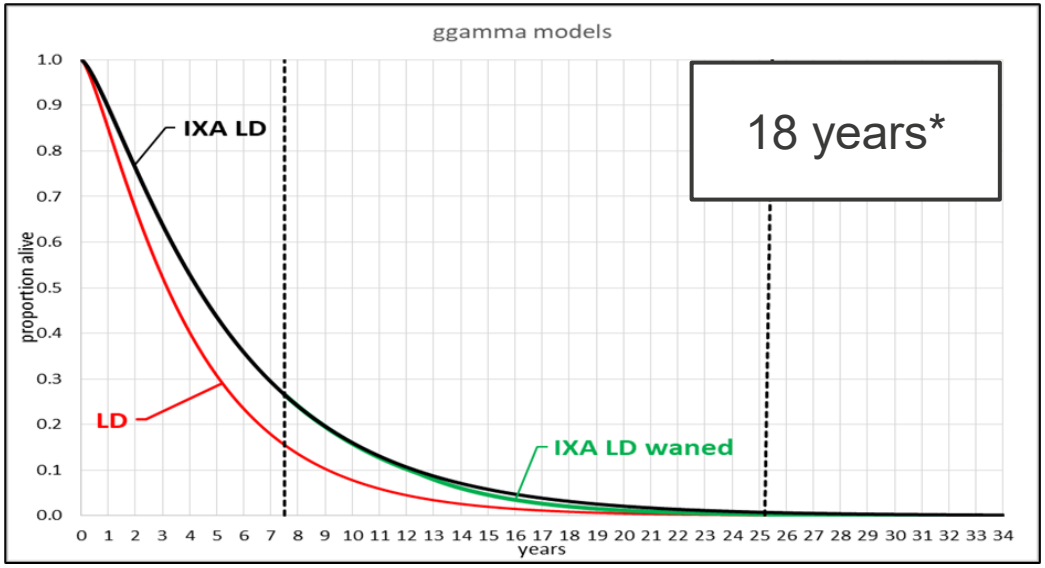
Issue 3: Treatment waning effect (2)

ERG treatment waning scenario method:

- Treatment waning applied gradually to hazards, by using a weighted hazard produced at each model cycle.
  - Avoids step changes in hazards.
- Generated an adjusted overall survival estimate for people randomised to IXA.







*Dotted lines = the starting point where waning of ixazomib treatment effect on the generalised gamma model commences and ends.

Issue 3: Treatment waning effect (3)

Company

- Do not assume a sustained effect of ixazomib.
  - Use the treatment effect estimated across the whole trial follow-up, including the effect of ixazomib and subsequent therapies relevant to UK clinical practice.
  - All waning (except for approximately 5% of the IXA population) has already been captured within the 8-year observation period.
- Median follow-up of over 7-years from the TMM1 clinical trial.
  - A window of 5.6 years (IXA+LEN+DEX) and 6.0 years (LEN+DEX) where people are not having the study treatments.
- For overall survival, the hazard ratio or treatment effect in the IXA+LEN+DEX arm is no longer the isolated effect of treatment with IXA+LEN+DEX, but a composite measure reflecting a pathway of treatments.

Should treatment waning be captured in the model beyond the observation period?

Key modelling assumptions

Assumption	Company base case	ERG base case
Data source	Subgroup of people who had 2 or 3 lines of therapy	
Comparator	LEN+DEX	
OS extrapolation	Generalised gamma	Weibull curve
PFS extrapolation	Weibull curve	
ToT	Weibull curve	
Utility values	Utility values from final analysis of TMM1, in line with committee expectations from TA505	
Treatment waning	Not used in base case	

Company and ERG base cases identical apart from choice of OS extrapolation curve

OS: Overall survival; PFS: Progression-free survival; ToT: Time on treatment; TMM1: TOURMALINE-MM1

Base case cost-effectiveness results

Ixazomib PAS price and assumed generic price for lenalidomide

Company deterministic results (PAS price for ixazomib and assumed generic price for lenalidomide [redacted])

	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
LEN+DEX	[redacted]	2.47	-	-	-
IXA+LEN+DEX	[redacted]	3.18	[redacted]	0.71	**£37,519**

ERG deterministic results (PAS price for ixazomib and assumed generic price for lenalidomide*)

	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
LEN+DEX	[redacted]	2.43	-	-	-
IXA+LEN+DEX	[redacted]	3.08	[redacted]	0.65	**£40,440**

Cost effectiveness results with confidential commercial arrangement for comparators will be considered in part 2. Accounting for this changes the cost-effectiveness estimates

*Using assumed generic price for lenalidomide throughout the modelling. Assumed generic price is used for illustrative purposes only. Committee will base its decision making on cost-effectiveness results generated using a price confirmed by NHS England.

ICER: Incremental cost-effectiveness ratio; PAS: Patient access scheme; QALY: Quality-adjusted life year

ERG scenario analysis: treatment waning

Deterministic results of waning treatment effect, as seen on slide 21 (PAS price for ixazomib and assumed generic price for lenalidomide)

Scenario	ICER (£/QALY)
Implemented in company base case (generalised gamma model for OS and no treatment waning)	**£37,519 (base case)**
Post treatment waning of effect takes 5 years to complete	£40,476
Post treatment waning of effect takes 7.5 years to complete	£39,706
Post treatment waning of effect takes 18 years to complete	£39,076
Weibull model for OS (no treatment waning)	**£40,558**
Post-treatment waning of effect takes 5 years to complete	£43,180
Post-treatment waning of effect takes 7.5 years to complete	£42,396
Post-treatment waning of effect takes 18 years to complete	£41,349

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ICER: Incremental cost-effectiveness ratio; PAS: Patient access scheme; OS: Overall survival; QALY: Quality-adjusted life year

ERG scenario analysis: OS extrapolation

Deterministic results (PAS price for ixazomib and assumed generic price for lenalidomide)

OS options for both arms	ICER (£/QALY)	LEN+DEX 5-year OS	IXA+LEN+DEX 5-year OS
Generalised gamma*	**£37,519**	30.74%	43.60%
Weibull†	**£40,558**	30.77%	43.57%
Exponential	**£34,459**	32.77%	44.67%
Log-normal	**£31,100**	32.55%	44.20%
Log-logistic	**£32,984**	31.48%	43.88%
Gompertz	**£47,477**	31.25%	43.99%

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*Company base case, †ERG preferred method of extrapolation.
ICER: Incremental cost-effectiveness ratio; OS: Overall survival; PAS: Patient access scheme; QALY: Quality-adjusted life year

Innovation and equality

Innovation:

- During technical engagement clinical experts highlighted the following:
  - The importance of an all-oral regime to people is unlikely to be captured in a QALY calculation*.
    - This has reduced time in hospital and on chemotherapy day units.
    - Reduces hospital associated infections and anxiety around the pandemic.
  - People with high-risk disease would be particularly disadvantaged if the technology was not available.

Equality:

- During technical engagement clinical experts highlighted the following:
  - Myeloma is twice as common in people of Afro-Caribbean family origin.

- **Is ixazomib an innovative treatment for relapsed or refractory multiple myeloma after 2 or 3 lines of therapy?**
- **Are there any additional benefits of ixazomib that have not been captured adequately in the economic model?**
- **Are there any equality issues relevant to this appraisal?**

*Comparator is also an all-oral regime.
QALY: Quality-adjusted life year

Key issues for consideration

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OS: Overall survival