Public handout

Chair's presentation

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

2nd Appraisal Committee meeting

Committee D

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ERG: Warwick Evidence

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Company: Takeda

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Ixazomib (Ninlaro, Takeda)

Conditional marketing authorisation (Nov 2016)	NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy
Mechanism of action	Proteasome inhibitor
Administration	Oral tablet, given until disease progression/toxicity

Context for the 2nd appraisal committee meeting:

- Ixazomib likely to be used only for people who have had **2 or 3 previous therapies** (displacing lenalidomide plus dexamethasone)
  - *Supported by clinical experts at the first meeting*
  - *Company seek recommendation for use in this population only*
- May seek recommendation in 1 prior therapy group when uncertainty about comparators resolves

ACD: preliminary recommendation

Ixazomib, with lenalidomide and dexamethasone, is not recommended within its marketing authorisation for treating multiple myeloma in adults who have already had at least 1 therapy

- Main clinical trial ongoing (TMM1)
- Data available from first & second interim analyses (IA1 & IA2)
- Survival data immature (median OS not reached)
- Benefit on PFS & other outcomes appeared to reduce at IA2 (for ITT population)
- ICER after 2 or 3 therapies: £138,000–£176,000/QALY gained compared with lenalidomide plus dexamethasone
- Neither of the end of life criterion was met
- Not suitable for CDF

Committee's considerations (1)

Management of myeloma after 2 or 3 therapies	• Lenalidomide used after 2 or 3 therapies • Panobinostat used after 3 or 4 therapies (would have preferred a comparison with panobinostat) • Panobinostat used only after lenalidomide
Effectiveness of ixazomib	• Clinical benefit uncertain based on current data • Ixazomib may be more effective after 3 previous therapies than after 2 previous • Analyses after 3 previous therapies uncertain (breaks randomisation)
Model: clinical inputs	• Model should use most recent trial results (IA2) • Appropriate to use data after 2 or 3 previous tx
Model: treatment costs	• Extrapolating ToT underestimates treatments costs (model overestimates difference between ToT & PFS compared with the trial and practice) • people treated for 65% (IXA) or 75% (LEN) of time spent progression-free vs. 95–100% in trial • Post-progression treatment should be costed weekly

Committee's considerations (2)

Model: HRQoL	• Unreasonable to assume:
	  • better QoL for progressed disease (0.654) than for stable disease (0.653)
	  • stable QoL from progression until 3 months before death
	• PFS utilities overestimated
	  • based on best overall response in trial rather than response at time that QoL assessed
	• All utilities uncertain: not adjusted for age or prior tx

Results	Preferred to see results in people who had only 2 previous treatments to ensure ICERs across both subgroups (2–3 previous treatments) represent ICERs within subgroups
EoL crtieria not met	OS with LEN = 3.6 years OS benefit of IXA uncertain
Unsuitable for CDF	Unlikely that reducing clinical uncertainty would sufficiently reduce ICERs; data will be collected as part of MA

ACD consultation responses

- Consultee comments from:
  - Takeda (including additional evidence)
  - Myeloma UK
  - UK Myeloma Forum (UKMF)

- Web comments from:
  - 2 NHS professionals
    - 1 professor of clinical haematology
    - 1 consultant haematologist
  - 1 patient

Company consultation comments

Comparators	Panobinostat not relevant – it is used only **after** LEN+DEX (therefore would be used **after** ixazomib)*
Effectiveness with longer follow-up	• PFS benefit reduced at second analysis (IA2) only for ITT; remains statistically significant in 2–3 prior tx group • TTP, ORR, ≥VGPR and CR statistically significant at IA2
Effectiveness in subgroups: after 3 prior tx versus after 2 prior tx	• Not biologically plausible for IXA to be more effective after 3 prior than 2 prior therapies** • Difference between subgroups explained by imbalance of prognostic factors between unstratified groups** • Results for people with 3 prior therapies are biased because small sample size (26% of 2–3 prior tx group) • Analyses not appropriate or statistically valid because randomisation/stratification broken**

*comments from UKMF and an NHS professional support this statement
**comments from NHS professional supports this statement

Company consultation comments

Utilities	Experts suggest QoL does not decline significantly after progression; biggest decrease is 3 months before death*

Modelling treatment costs: PFS vs ToT	• In trials & practice, ToT<PFS (remission after tx stopped)**
	• Plausible ToT:PFS ratio to be lower for IXA than for LEN
	  • deeper clinical response with IXA triplet leads to prolonged remission after stopping treatment**
	• Should use ToT to model costs
	  • using PFS extrapolation overestimates costs because assumes tx until progression

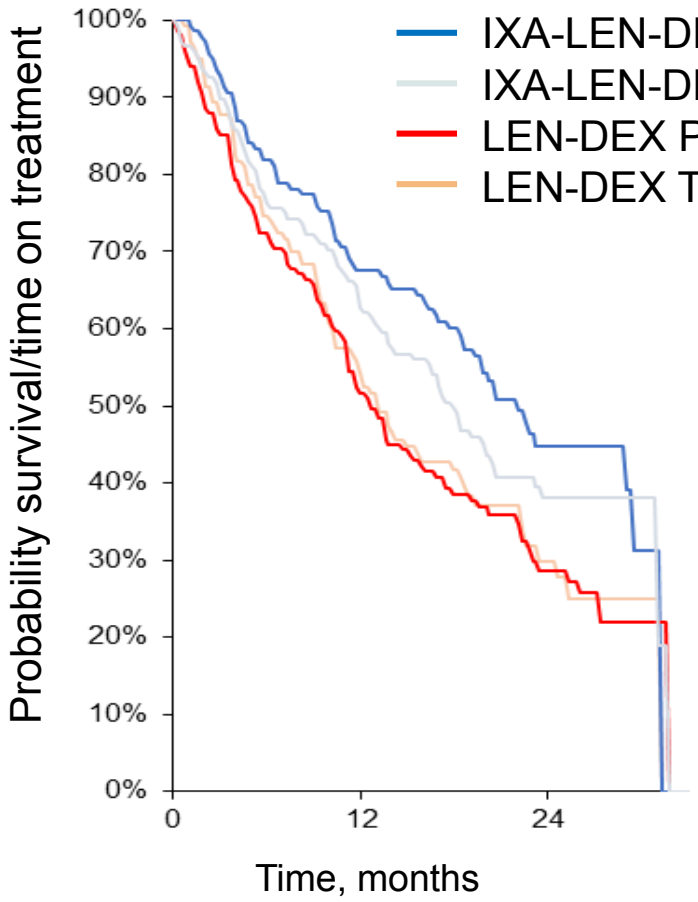
End of life (EoL)	Should apply the qualification used for pertuzumab (ID523): • life expectancy MORE THAN 24 months • combined with existing tx (both licensed until progression) • sufficient evidence to indicate extension to life, normally ≥3 months

*comments from an NHS professional support this statement

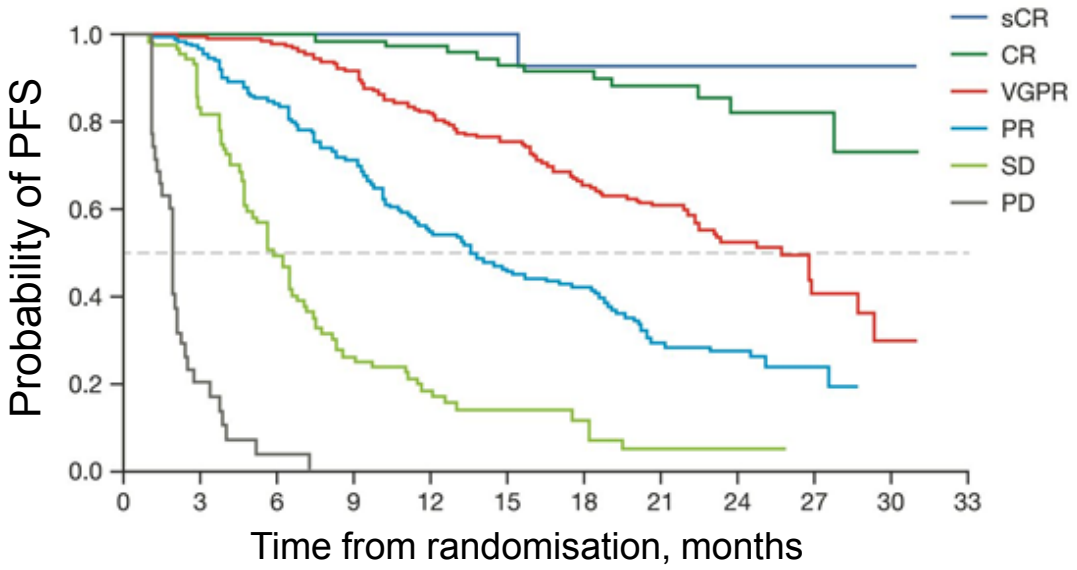
**comments from Myeloma UK, UKMF & NHS professional support this statement

Plausible for ratio of ToT:PFS to be lower for ixazomib than for lenalidomide

Ratio of ToT:PFS is lower with IXA than LEN



Depth of response correlates with PFS



Source: Fig. 1 & 2 company response to ACD (2nd interim analysis of TMM1, 2/3 prior therapies subgroup)

Other consultee and web comments

Need new treatment	• Important to have a range of novel agents • Triple therapy is gold standard, at **all** stages of pathway
Expected use of ixazomib	Potential to use later than after 3 previous therapies (after 4+); relevant to people in clinical trials
Clinical effectiveness	• Conclusion that PFS benefit reduces over time is based on non-primary endpoint data - interpret with caution • PFS benefit in TMM1 was clinically meaningful & statistically significant (esp. for people with 2–3 prior tx) • PFS is valued by patients and is a proxy for OS • Real-world experience of ixazomib similar to TMM1
Quality of life benefits	TMM1 shows maintained HRQoL during ixazomib treatment
Innovation	1st oral proteasome inhibitor & 1st all oral triplet regimen
Cost effectiveness	Challenging for combination treatments to be cost effective when the backbone is borderline cost effective

Extracts from interviews with people with multiple myeloma (Myeloma UK)

I have a good quality of life on ixazomib ... I'm able to run the house … Basically, I can do all the things I would normally do and that I enjoy in life.

We rely on drugs to keep us well. When one stops working there has to be another one there.

Ixazomib scores very highly in terms of what I want from a treatment. It is very beneficial that it is an oral treatment.

With ixazomib I feel I am in control… With previous treatments … I was having to go upstairs on all fours. I would say I have had no side-effects at all from ixazomib. I am in a senior position in my company and continue to perform highly

[Ixazomib] has helped us to have a normal life more than any other treatment. Taking Ixazomib means that he can largely forget that he has incurable cancer

New evidence from company

Company new evidence

- Updated economic model:
  - data from second interim analysis (IA2) of TMM1
  - same extrapolations for PFS, OS and ToT as were used for IA1 data in original submission
    - different from extrapolations used in previous scenario analysis using IA2
  - regular (rather than one off) costs for post-progression treatment (tx)
    - # pts with subsequent treatment increases in IA2: 66%
    - different weekly costs of post-progression tx in each arm
  - updated analysis of EQ-5D derived utility data
  - continues to use ToT extrapolation to cost treatments
- Base cases ICERs for 1 subgroup: 2–3 prior therapies
- Scenario analysis for 2 prior therapies only
- Proposed recommendation in the CDF

Not presented in slides; see ERG critique

Updated utility analysis (using IA2)

- Updated regression model included 3 more covariates: age, race, gender
  - plus response status, gr.3/4 AEs, hospitalisation, ≤3 months to death
  - regression used response at time EQ-5D assessed in trial ('contemporaneous response') instead of best overall response

≥Very good partial response (VGPR+)	0.689
Partial response (PR)	0.690
Stable disease (SD)	0.678
Progressed disease (PD)	0.650

0.028 decrease from SD to PD (declines again 3 months before death)

- As in original submission:
  - PFS health-state utility obtained using distribution of best overall response (BoR)
  - treatment-specific response distributions result in treatment-specific PFS health state utility values

Updated company results (with PAS)

Deterministic base case (people who have had 2–3 therapies)

Treatment	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER/QALY
LEN+DEX	£132,369	2.73			
IXA+LEN+DEX	£255,289	3.71	£122,920	0.98	£125,277

PSA: ICER of £124,428 /QALY (Δ cost £122,578; Δ QALY 0.99)

- Biggest driver in one-way sensitivity analyses: treatment effect coefficient for OS extrapolation
  - reflects wide CI (0.48 to 1.00) and immature data
  - ICER ranges from £60k to £5mn/QALY
- Scenario analyses: ICERs mostly between £120k and £140k/QALY

ERG critique

ERG critique: population, comparators & QoL

- Analyses in 2 prior subgroup no longer relevant
  - agree with company that imbalances in prognostic characteristics drive differences in efficacy between subgroups (2 prior vs 3 prior)
- No data to allow comparison with panobinostat in the relevant subgroup
- Utility analysis
  - overestimates PFS health state utility because of mixing contemporaneous response data with BoR data
  - adjustment for age is small & suggests slower age-related QoL decline than in UK population norms
  - no adjustment for prior or subsequent treatments

ERG critique: costs

- As before, model underestimates treatment costs by overestimating difference between ToT and PFS
  - Model: people treated for 62% (IXA) or 69% (LEN) of time spent progression-free
  - Trial: people treated for 92% (IXA) or 97% (LEN) of time spent progression-free (i.e. some divergence acceptable)
  - Divergence has increased with IA2 data (due to different extrapolation curves)
- Misleading for company to state weekly costs for post-progression tx
  - When multiplied by time spent in PPS, the arm-specific weekly costs equate to the same one off cost for both arms (£78,607)
  - Unstated company assumption is that post-progression tx is unaffected by duration of PPS (which is 26 weeks longer for IXA)
    - This was an issue in the original company model
    - ERG consider that increased PPS → increased # of tx

ERG critique: extrapolations

OS (Weibull)

- Agree with Weibull, but poor fit to observed data (overestimates benefit)
- Benefit maintained for model duration but should diminish over time
- ***One third*** of IXA's net OS gain occurs post-progression – not plausible?
  - % of OS gains occurring in PPS reduces when a diminishing treatment effect is applied (which increases the ICER)

PFS (gamma)

- Poor fit to KM curve and implausible extrapolation: more un-progressed patients alive than total patients alive
  - company fix is implausible: company make PFS and OS curves identical from cross over, implying no-one survives after progression
- Weibull better fit and more plausible BUT increases proportion of OS gain achieved post-progression (to ***nearly half***)
  - mitigate by amending OS extrapolation *(ERG exploratory analyses)*

ToT (exponential) - applying Weibull to PFS and ToT reduces divergence

ERG amended base case

- 2 alternative base cases: using PFS or ToT for treatment costs
- Accepted company survival extrapolations for PFS, OS and ToT
  - Scenario analyses explore different extrapolations
    - *gamma, lognormal and loglogistic extrapolations of OS are not presented in the slides because they predict implausible number of patients alive at end of time horizon (long tails)*
  - Scenario analyses apply diminishing treatment effect to address balance of survival gains occurring pre-progression/post-progression
- Updated utilities to avoid mixing BoR and contemporaneous data: applied BoR distribution (from IA2) to BoR regression data (from IA1)
  - Ideally ERG would use BoR regression from IA2, but not available
  - ERG included adjustment for age in regression
- Applied weekly post-progression survival costs for people not receiving treatment to people who are between treatment
  - minimal effect on ICER

ERG amended base case results (PAS)

Using ToT for treatment costs (deterministic)

Treatment	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER/QALY
LEN+DEX	£132,786	2.37			
IXA+LEN+DEX	£256,296	3.25	£123,510	0.88	£140k

PSA: ICER of £145k/QALY (Δ cost £137k; Δ QALY 0.88)

Using PFS for treatment costs (deterministic)

Treatment	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER/QALY
LEN+DEX	£136,858	2.37			
IXA+LEN+DEX	£314,097	3.25	£177,239	0.88	£202k

PSA: ICER of £201k/QALY (Δ cost £177k; Δ QALY 0.88)

Company base case ICER: £125,277/QALY

Exploring extrapolations (PAS)

	Costing	LY	% LY in PPS	Δ QALY	Δ cost	ICER
ERG base case (OS Weibull, PFS gamma, ToT exponential)						
OS Weibull	ToT	1.562	32%	0.88	£124k	£140k
	PFS				£177k	£202k
Scenarios: retaining base case PFS & ToT curves, and varying OS curves						
OS exponential	ToT	2.522	52%	1.24	£124k	£100k
	PFS				£189k	£153k
OS gompertz	ToT	0.992	15%	0.61	£122k	£200k
	PFS				£159k	£262k
Scenarios: applying Weibull to PFS and ToT and varying OS curves						
OS exponential	ToT	2.522	67%	1.22	£124k	£102k
	PFS				£139k	£114k
OS Weibull	ToT	1.562	47%	0.87	£121k	£140k
	PFS				£136k	£157k
OS gompertz	ToT	0.992	19%	0.60	£120k	£199k
	PFS				£136k	£225k

- AIC and BIC similar for OS exponential, Weibull and gompertz
- Gompertz most pessimistic OS gain but may have most plausible %LY in PPS
- If Weibull is retained for OS, may be more reasonable to accept company curves for PFS and ToT than to apply Weibulls

ERG exploratory analyses (PAS)

	Δ QALYs	Δ costs		ICER/QALY	
		ToT costing	PFS costing	ToT costing	PFS costing
ERG base case	0.88	£124k	£177k	**£140k**	**£202k**
Tx effect lasts for					
23 mths	0.30	£110k	£158k	**£374k**	**£537k**
32 mths	0.39	£114k	£163k	**£293k**	**£417k**
32 mths, 1 to 5 yrs waning	0.45 to 0.62	£116k to £120k	£165k to £170k	**£258k to £194k**	**£366k to £274k**
32 mths,10 yrs waning	0.73	£122k	£173k	**£167k**	**£238k**
One-off cost of post-prog tx higher with IXA versus LEN	0.88	£137k	£191k	**£156k**	**£217k**
Apply trial ToT:PFS ratio	0.88	N/A	£165k	**N/A**	**£188k**

End of Life

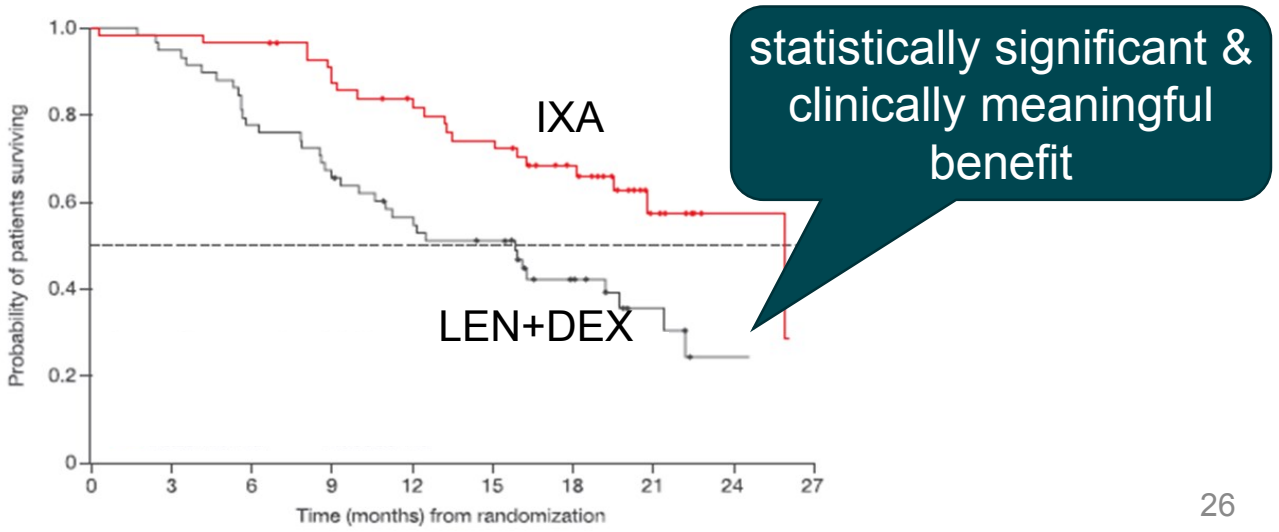
End of life (CDF process addendum)

- The Appraisal Committee will satisfy itself that all of the following criteria have been met:
  - the treatment is indicated for patients with a short life expectancy, **normally** less than 24 months
  - there is **sufficient** evidence to indicate that the treatment has the **prospect of offering an extension to life**, **normally** of a mean value of at least an additional 3 months, compared with current NHS treatment.
- In addition, the Appraisal Committees will need to be satisfied that:
  - the estimates of the extension to life are **sufficiently robust** and can be **shown or reasonably inferred from either progression-free survival or overall survival** (taking account of trials in which crossover has occurred and been accounted for)
  - the assumptions used in the reference case economic modelling are **plausible, objective and robust**.

	IXA	LEN+DEX	HR (95% CI)
TMM1: median OS, months			
≥1 prior (ITT)	NE	NE	1.11 (0.74, 1.66)
2-3 prior (stratified)	NE	NE	0.65 (0.41, 1.02)
TMM1: median PFS, months			
2-3 prior (stratified)	22.0	13.0	0.62 (0.45, 0.86)
China continuation study: median OS, months			
≥1 prior (ITT) n=115	25.8	15.8	0.42 (0.24 to 0.73) p=0.001
2 prior (not stratified) n=44	19.4	10.9	0.39 (0.17 to 0.87)
3 prior (not stratified) n=20	NE	11.7	0.34 (0.08 to 1.42)

China continuation study final OS analysis (ITT)

Fig. 4 company response to ACD



Modelled survival: using updated models (post-consultation)

	IXA+LEN+DEX	LEN+DEX	Incremental
QALYs gained			
Company updated base case	3.71	2.73	0.98 QALYs
ERG updated base case	3.25	2.37	0.88 QALYs
Undiscounted life years gained			
Company updated base case	5.48	3.91	1.56 years
ERG base case	5.48	3.91	1.56 years

ERG note: the majority of the survival gain in the model occurs during extrapolation

- 94% after the median 23 month follow up of IA2
- 88% after the 32 months longest duration of follow up

Key issues for discussion

- Is panobinostat a relevant comparator?
- Is OS benefit maintained after stopping treatment or would it diminish?
  - What is the most plausible assumption about diminishing effect?
- Balancing survival gains between PFS and PPS
  - Does committee accept company extrapolations of OS, PFS & ToT?
  - *32% of OS gain is realised in post-progression health state;*
    % of OS gains in PPS reduce if assume diminishing treatment effect
- Modelling treatment costs: should ToT or PFS extrapolations be used?
- Utilities: does committee accept the ERG base case?
- Are # of post-progression treatments influenced by duration of post-progression survival? That is, more costly with ixazomib?
  - *Scenario overestimates ICER – no cap on # of post-progression tx*
- Does ixazomib meet EoL criteria? Suitable CDF candidate?