*projector slides*

# Lead team presentation

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

1st Appraisal Committee meeting, 29 March 2017

Cost Effectiveness

Committee D

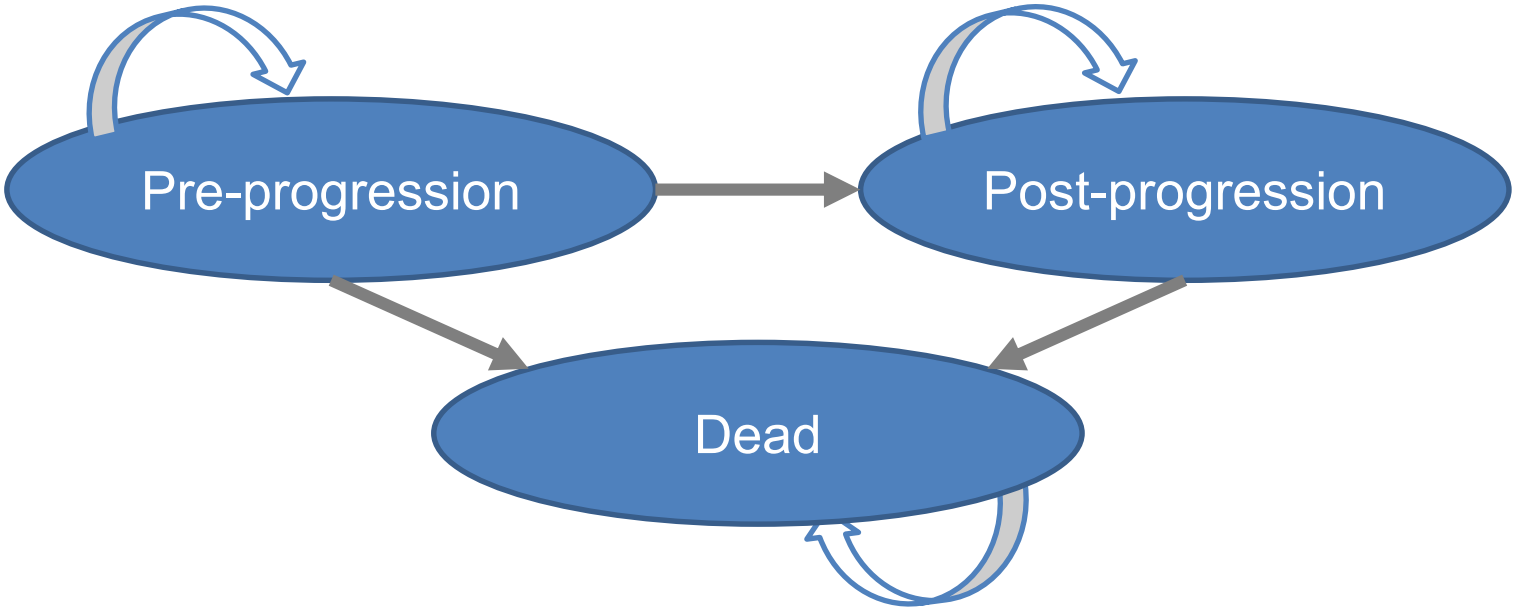
Lead team: David Bowen

ERG: Warwick Evidence

NICE technical team: Sophie Cooper, Raisa Sidhu

Company: Takeda

# Company model: 3-state partitioned survival model




- 25 year time-horizon, because majority of patients aged 66 years and over at baseline
- Weekly cycle (with half cycle correction)
- Utilities and costs discounted at 3.5%
- NHS and personal and social services (PSS) perspective

# Clinical outcomes in the model: interim analyses of TMM1

## Company approach

- Base case model used data from first interim analysis of TMM1
- Scenario analysis using second data cut ↑ ICER by ~20% in 1 prior therapy group and ↓ ICER by ~10% in 2-3 prior therapies

## ERG comments

- Base case should use second interim analysis of TMM1
- Unable to fully critique model accompanying scenario analysis, but several immediate concerns about its validity:
  - company extrapolated OS and ToT using different models (log logistic and log normal), which typically have long and clinically implausible tails
  - company incorporated second data cut for 2 prior therapies but did not update NMA informing ICERs for 1 prior therapy group
  - company did not update HRQoL regression analysis using second interim analysis, which is a key driver of the model

# Relative efficacy: 1 prior therapy

## Company approach

- Relative efficacy compared with BORT+DEX based on NMA
- NMA used proxy data from TMM1: people who had received ≥1 prior therapy (ITT population)

## ERG comments

- The company underestimated benefits of BORT+DEX:
  - Company NMA underestimated OS with BORT+DEX
  - Issues with distribution of best overall response (BoR) for BORT+DEX (% of people in the VGPR+, PR and SD health states)
    - used a trial of BORT monotherapy
    - erroneously used BoR for DEX instead of BORT+DEX
- Proxy data not ideal but ERG preferred company methods to its exploratory analyses in people with only 1 prior therapy

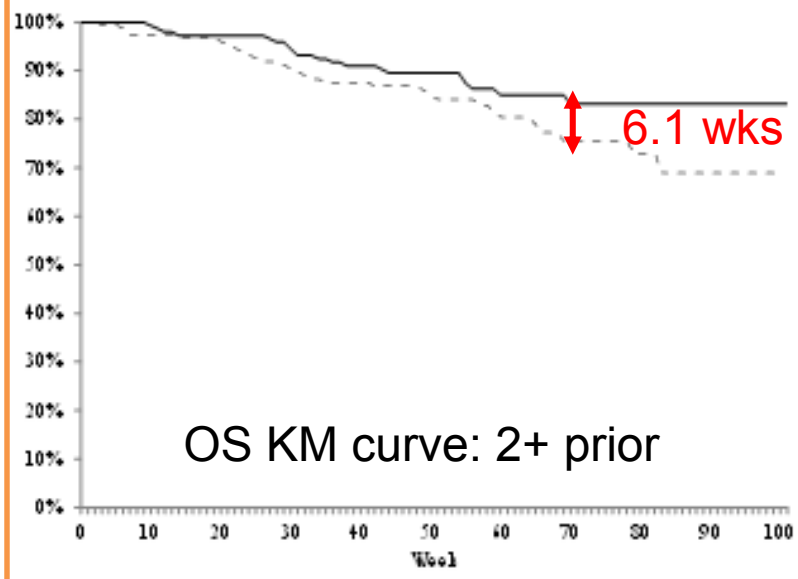
# Relative efficacy: 2 prior therapies

## Company approach

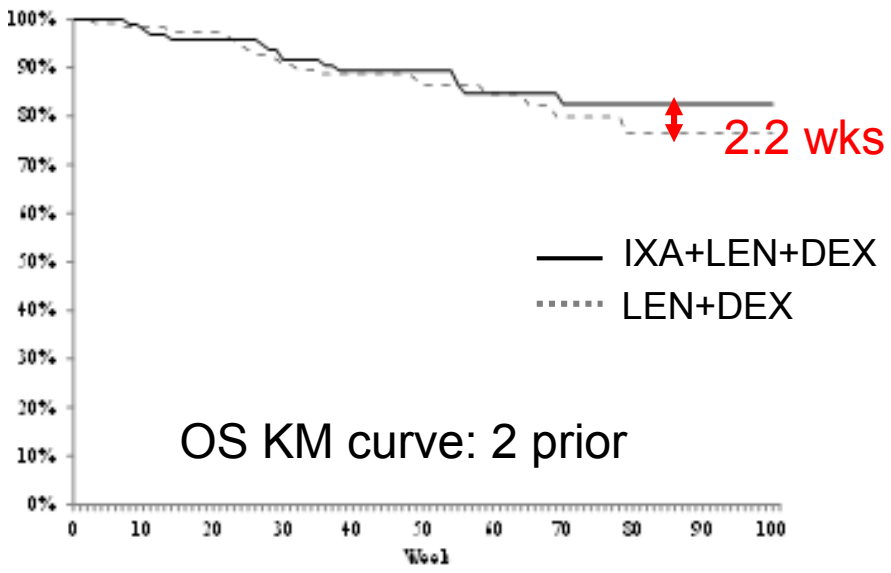
- Relative efficacy compared with LEN+DEX based on TMM1 directly
- Model used proxy data from TMM1: people who had received 2–3 prior therapies (pre-specified subgroup & stratification factor)

## ERG comments

- Proxy data overestimates benefits of IXA+LEN+DEX at third line: **OS**




OS KM curve: 2+ prior

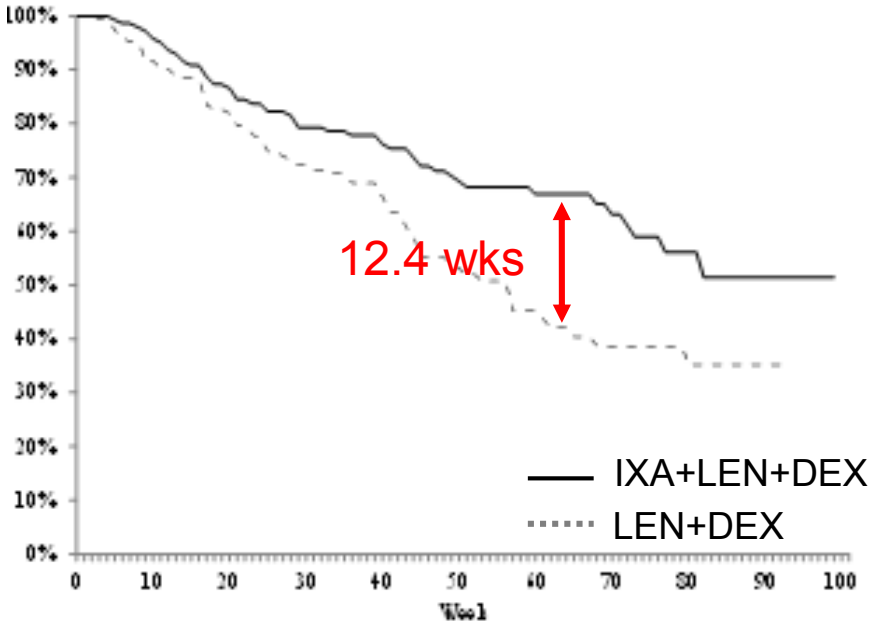



OS KM curve: 2 prior

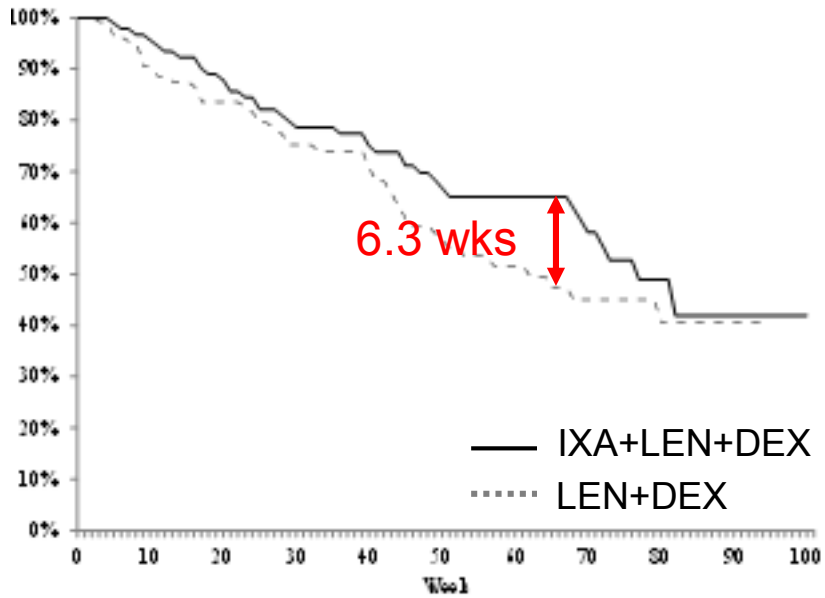
# Relative efficacy: 2 prior therapies cont.

ERG comments

- Proxy data overestimates benefits of IXA+LEN+DEX at third line: **PFS**




PFS KM curve: 2+ prior




PFS KM curve: 2 prior

*Sources: figs 48 (OS) & 49 (PFS) ERG report*

# Utility estimates

## Company approach

- EQ-5D data from TMM1 (based on best overall response; not response observed at time of EQ-5D assessment)
- Decrement of 0.025 to patients receiving subcutaneous bortezomib

## ERG comments

- Disutility for subcutaneous BORT overestimated by applying it for entire 3-week duration of each BORT+DEX cycle
- Assuming utility for progressed disease is greater than utility for stable disease (0.654 vs. 0.653) contradicts published literature and expert opinion
- No exploration of HRQoL decline with lines of therapy or age
- No adjustment for baseline EQ-5D despite potential association between baseline EQ-5D and best overall response
- Utility in PFS state may be overestimated because it is based on best overall response (not response at time of EQ-5D assessment)

# Utility estimates (cont.)

ERG comments

- Different distributions of best overall response (BoR) result in different treatment-specific PFS utility values
- Applied for entire duration that patients remain in PFS

| | | 1 prior subgroup | | | | 2 prior subgroup | |
|---|---|---|---|---|---|---|---|
| | | IXA | | LEN | BORT | IXA | LEN |
| | Utility | NMA | Trial | Trial | NMA | Trial | Trial |
| VGPR+ | 0.712 | 47% | 48% | 46% | 3% | 59% | 38% |
| PR | 0.674 | 33% | 34% | 32% | 86% | 31% | 41% |
| SD | 0.653 | 15% | 14% | 16% | 10% | 10% | 21% |
| PFS | - | 0.690 | 0.690 | 0.689 | 0.674 | 0.694 | 0.684 |

Company chose trial distribution; ERG consider this reasonable and consistent with using trial data for survival extrapolation

Lower utilities because small % in VGPR+, which is incorrect for BORT+DEX

# Costs

## Company approach

- Included drug acquisition and administration costs (incl. concomitant treatment), resource use & end-of-life
- Included patient access scheme (PAS) for comparators

## ERG comments

BORT+DEX costs overestimated because company assumed:

- BORT+DEX treatment stops at progression and PAS applied only if disease progressed within 4 cycles, whereas TA129 includes a stopping rule and PAS based on failure to achieve at least a partial response at 4 cycles
  - resulted in no BORT+DEX costs being refunded as per the PAS, because no patients progressed before the 4$^{th}$ cycle
- maximum of 9 cycles, even in people with complete response (SmPC specifies max 8 cycles and only 2 after complete response)
- same ToT for BORT+DEX and LEN+DEX; should have used HR for PFS compared with LEN+DEX (1.06)

# Costs (cont.)

## Company approach

- One-off cost applied for subsequent treatment (distribution of treatment from TMM1, assumed 24.4% patients receive treatment)
- Included LEN+DEX PAS in intervention arm for both populations
- Assumed dose intensities based on trial data for IXA+LEN+DEX (93.10%) and LEN+DEX (94.90%)
- Assumed dose intensity of 100% for BORT+DEX (no trial data)

## ERG comments

- Cost of subsequent therapy underestimated
  - proportion of patients with subsequent treatment underestimated
  - one-off cost cancels out between arms; more reasonable to apply ongoing weekly cost
- LEN+DEX PAS not applicable in 1 prior therapy group
- More consistent to assume 100% dose intensity for all treatments

# Costs (cont.)

## Company approach

- Costs were determined by time on treatment (ToT) curves

## ERG comments

PFS curve more appropriate for modelling treatment costs than ToT

- Using ToT to model costs may underestimate treatment costs because ToT curves were consistently below PFS curves
  - Why? Patients lost to follow-up censored for PFS but counted as event for ToT → patients lost to follow up without disease progression retained treatment benefits but without incurring costs
- Treatment discontinuation before disease progression was high

| | 1 prior therapy | 2-3 prior therapies | |
|---|---|---|---|
| | IXA+LEN+DEX | IXA+LEN+DEX | LEN+DEX |
| Area under curve: ToT curve as a % of PFS curve | 82% | 65% | 75% |
| Treatment holidays accounted for separately in model (dose intensity) | | | |

# Extrapolating OS, PFS and ToT

## Company approach

| | 1 prior therapy | 2-3 prior therapies |
|---|---|---|
| **PFS** | Generalised gamma | Generalised gamma |
| **OS** | Delayed exponential (from month 5; KM HRs observed in TMM1 applied for the first 5 months) | Weibull |
| **ToT** | Weibull | Exponential |

## ERG comments

- OS (1 prior therapy): Weibull more clinically plausible: close to zero patients alive at end of time horizon (delayed exponential predicted 3% IXA+LEN+DEX arm and 5% LEN+DEX arm still alive)
- PFS (1 prior therapy): Weibull has lowest AIC & BIC. Negligible impact on ICER in company & ERG analyses; would impact ICER if PFS used for costs
- ToT (2 prior therapies): expect same distribution to be appropriate for ToT and PFS

# Summary of ERG critique (1)

| ERG comment | Addressed in exploratory analyses? |
|---|---|
| **1 prior therapy** | |
| Underestimated benefits of BORT+DEX because: | |
| NMA underestimated OS (because of an error in hazard ratios plus other methodological issues) | Yes: ERG base case |
| Error in estimation of best overall response | Yes: ERG base case |
| Overestimated BORT+DEX cost because: | |
| Maximum 9 cycles (rather than 8) | Yes: ERG base case |
| Same ToT as LEN+DEX | Yes: ERG base case |
| Treatment discontinued at progression (TA129 stopping rule not included) and no PAS refunds given | No |
| People with complete response receive max # of cycles | No |
| Patients completed every treatment cycle that they start | No |
| Lenalidomide PAS not applicable for 1 prior therapy group | Yes: ERG base case |
| *ERG alternative base case for 1 prior therapy labelled as 'ERG analysis 4' in ERG report* | |

# Summary of ERG critique (2)

| ERG comment | Addressed in exploratory analyses? |
|---|---|
| **2 prior therapies** | |
| Clinical data from people with 2–3 prior therapies used as proxy for 2 prior therapies subgroup | Yes: ERG analysis 5 |
| **Both populations** | |
| Should have used second interim analysis of TMM1 | No |
| PFS better than ToT for modelling costs | Yes: SA08 |
| Inappropriate extrapolation of OS, ToT and PFS | Yes: SA01-SA03 |
| Cost of subsequent therapy underestimated | Yes: SA09 |
| Concerns with utilities: | |
| disutility for sc injection overestimated | Yes: ERG base case |
| progressed disease utility > stable disease utility | Yes: SA06 |
| no adjustment for baseline EQ-5D or declining QoL | No |
| HRQoL in PFS state may be overestimated | Partially: SA06 |
| *ERG alternative base case for 2 prior therapies is labelled as 'ERG analysis 2' in ERG report* | |

# Company base case model results
*(including all patient access schemes)*

**For people who have had 1 prior therapy**

| Treatment | Total costs | Total QALYs | Inc. costs | Inc. QALYs | ICER/QALY |
|---|---|---|---|---|---|
| BORT+DEX | £40,612 | 1.74 | | | |
| IXA+LEN+DEX | £201,274 | 3.93 | £160,662 | 2.19 | £73,333 |

When the ERG corrected the error in NMA and removed the LEN+DEX PAS from the intervention arm: **BORT+DEX dominated IXA+LEN+DEX**, with incremental costs for IXA+LEN+DEX of £169,000 and incremental QALYs of −0.382.

**For people who have had 2-3 prior therapies**

| Treatment | Total costs | Total QALYs | Inc. costs | Inc. QALYs | ICER/QALY |
|---|---|---|---|---|---|
| LEN+DEX | £91,428 | 2.204 | | | |
| IXA+LEN+DEX | £222,532 | 3.174 | £131,104 | 0.9694 | £135,237 |

# ERG alternative base case (incl. PAS)

**For people who have had 1 prior therapy** *('ERG analysis 4')*

| Treatment | Total costs | Total QALYs | Inc. costs | Inc. QALYs | ICER/QALY |
|---|---|---|---|---|---|
| BORT+DEX | £69,872 | 4.356 | | | |
| IXA+LEN+DEX | £238,733 | 3.932 | £168,861 | −0.424 | Dominated |

**For people who have had 2-3 prior therapies** *('ERG analysis 2')*

| Treatment | Total costs | Total QALYs | Inc. costs | Inc. QALYs | ICER/QALY |
|---|---|---|---|---|---|
| LEN+DEX | £97,655 | 2.204 | | | |
| IXA+LEN+DEX | £231,377 | 3.174 | £133,722 | 0.969 | £138,000 |

**For people who have had 2 prior therapies only** *('ERG analysis 5')*
*Using data from post-hoc analysis of people who had received 2 prior therapies only (instead of people with 2–3 prior therapies) increased ICER*

| Treatment | Total costs | Total QALYs | Inc. costs | Inc. QALYs | ICER/QALY |
|---|---|---|---|---|---|
| LEN+DEX | £115,334 | 3.592 | | | |
| IXA+LEN+DEX | £232,973 | 4.222 | £117,639 | 0.631 | £186,000 |

# ERG sensitivity analyses

- SA01: Varying the OS curves functional forms
- SA02: Varying the PFS curves functional forms
- SA03: Varying the ToT curves functional forms
- SA06: Applying the utility values from TA171 and TA338
- SA07: Assuming a 5 week cycle for BORT+DEX
- SA08: Costing treatments using PFS curve rather than ToT curve
- SA09: Increasing the cost of post-progression treatment by:
  - increasing the proportion of patients receiving subsequent treatment after progression from 24% to 41%
  - applying ongoing weekly cost of £1,561 (instead of a one off cost)

*Note that this does not include the cost of pomalidomide, which is now NICE-recommended and could affect the ICER*

# ERG sensitivity analyses (incl. PAS)

| | ICER for IXA+LEN+DEX (£/QALY) | |
|---|---|---|
| | **1 prior therapy (vs. BORT+DEX)** | **2 prior therapies (vs. LEN+DEX)** |
| ERG base case | IXA+LEN+DEX is dominated by BORT+DEX | £138,000–£186,000 |
| SA01: OS curves | | £93,024–£290,000 |
| SA02: PFS curves | | £138,000–195,000 |
| SA03: ToT curves | | £138,000–£336,000 |
| SA06a: TA171 utilities | | £127,000–£173,000 |
| SA06b: TA338 utilities | | £134,000–£180,000 |
| SA07: 5 wk BORT cycle | | N/A |
| SA08: PFS instead of ToT | | £176,000–£265,000 |
| SA09: post progression costs | | £151,000–£202,000 |
| The range of ICERs in the 2 prior therapies group reflects results using proxy data from people with 2–3 prior therapies (lower estimate) and post-hoc data from people with 2 prior therapies only (upper estimate) | | |

# End-of-life criteria

- Company state that, based on current data, the ixazomib regimen does not meet all end-of-life criteria
- Median OS not reached in either treatment arm of TMM1 trial; data were 35% mature
- Further follow up is warranted to determine final benefit
  - third interim OS analysis expected in Q2 2017
  - final OS analysis expected in Q3 2019
- Company did not comment on the life expectancy of people with relapsed multiple myeloma
  - Note: end-of-life criteria specifies a short life expectancy of less than 24 months, and evidence of extension to life of at least 3 months

# Company comments on innovation

- IXA+LEN+DEX is an all oral treatment regimen
  - First oral proteasome inhibitor
  - Lower toxicity than other treatments *(Note: the ERG suggest that this claim is not supported by clinical data)*
  - Convenient administration; reduced travel is important because bone degradation, fractures and fatigue are common symptoms of the disease *(Note: LEN+DEX is also an all-oral regimen)*
- Triple combination: benefits of a proteasome inhibitor, immunomodulatory agent and steroid
- There are benefits not captured by the QALY calculations:
  - Unmet need in 2nd and 3rd line
  - Convenient all-oral treatment taken at home *(Note: company base-case model includes disutility for subcutaneous treatment; the ERG removed this disutility from exploratory analyses)*
  - Reduced carer burden
  - Benefits for people still in employment

# Equalities

- No equalities issues were identified in evidence submissions from consultees

# Key cost-effectiveness issues (1)

- Is using data from the 1st, rather than 2nd, interim analyses of TMM1 sufficiently robust?
- When modelling 3rd line (2 prior therapies) positioning of IXA+LEN+DEX, is it more appropriate to use data from the pre-specified subgroup of people who had 2–3 prior therapies in TMM1 as a proxy, or data specific to people with 2 prior therapies (a post-hoc analysis)?
- The SmPC for LEN+DEX and IXA+LEN+DEX state that treatment should be continued until disease progression or unacceptable toxicity. Time on treatment (ToT) might therefore be shorter than PFS
  - How many people stop treatment before disease progression? Did the model overestimate this? In practice, would the ToT to PFS ratio for IXA+LEN+DEX be similar or different than for LEN+DEX?
  - More appropriate to use the ToT curve or the PFS curve to model treatment costs?
- Which is the most plausible method to extrapolate OS in the 1 prior therapy group? (company base case uses delayed exponential and the ERG are in favour of the Weibull). And for PFS - Weibull or generalised gamma?

# Key cost-effectiveness issues (2)

- Did the company overestimate the cost of BORT in its base case model?
  - Are the restrictions in the SmPC applied in practice? That is, a maximum of 8 cycles, with only 2 cycles given after a complete response?
  - Is the stopping rule in TA129 applied in practice (treatment stops in people who do not have a complete or partial response after 4 cycles)?
  - Do patients complete every treatment cycle that they start?
- Quality of life
  - Was it appropriate for the company to assume a higher utility for progressed disease than stable disease?
  - How do subcutaneous injections affect HRQoL? Does the model accurately reflect this?
  - Is there an association between baseline HRQoL and response? Does HRQoL decline with each relapse and age?
- Should post-progression treatments be modelled as a one-off or ongoing cost?
- CDF: does IXA+LEN+DEX have plausible potential to be cost-effective at the current price?

# Key clinical issues

- Does the company's placement of ixazomib (restricted to 2nd and 3rd line) reflect its anticipated use in clinical practice?
- Have all relevant comparators been included?
  - Is panobinostat used 3rd line?
  - What are the current established treatment options in England for people who have received 1st-line BORT (either as induction before ASCT, or in people ineligible for ASCT)?
- Does IXA+LEN+DEX improve clinical outcomes — including PFS, OS and response rates — compared with LEN+DEX?
  - Are these benefits maintained long-term?
  - Are there any subgroups in whom IXA+LEN+DEX is more effective? For example, based on number of prior therapies
- In the network meta-analysis, is it appropriate to:
  - use the Montefusco study? (as in the company NMA)
  - use TTP as a proxy for PFS? (as in the ERG exploratory NMA)
- Does IXA+LEN+DEX improve clinical outcomes compared with BORT+DEX?

# Back up slides

# Adverse events in TMM1

| **Adverse events, n (%)** | **IXA+LEN+DEX (n=361)** | **LEN+DEX (n=359)** |
|---|---|---|
| Any AE | 355 (98) | 357 (99) |
| Any grade ≥3 AE | 267 (74) | 247 (69) |
| Any serious AE | 168 (47) | 177 (49) |
| AE resulting in dose reduction of any drug in the regimen | 203 (56) | 181 (50) |
| AE resulting in discontinuation of any drug in the regimen | 91 (25) | 73 (20) |
| AE resulting in discontinuation of full drug regimen | 60 (17) | 50 (14) |
| On-study death | 15 (4) | 23 (6) |
| **Most common AEs** | | |
| Neutropenia | 118 (33) | 111 (31) |
| **Thrombocytopenia** | **112 (31)** | **57 (16)** |
| **Diarrhoea** | **164 (45)** | **139 (39)** |
| **Rash** | **131 (36)** | **82 (23)** |
| **Peripheral neuropathy** | **97 (27)** | **78 (22)** |
| **Red bold denotes differences of ≥5% between the 2 treatments** | | |

# Common adverse events in TMM1 (second interim analysis)

| | IXA+LEN+DEX (n=361) | | | LEN+DEX (n=359) | | |
|---|---|---|---|---|---|---|
| | **Any grade** | **Grade 3** | **Grade 4** | **Any grade** | **Grade 3** | **Grade 4** |
| **Common haematologic AEs of any cause, n (%)** | | | | | | |
| Neutropenia | 118 (33) | 64 (18) | 17 (5) | 111 (31) | 63 (18) | 22 (6) |
| **Thrombocytopenia** | **112 (31)** | **43 (12)** | **26 (7)** | 57 (16) | 19 (5) | 13 (4) |
| Anaemia | 103 (29) | 34 (9) | 0 | 98 (27) | 48 (13) | 0 |
| **Common non-haematologic AEs of any cause, n (%)** | | | | | | |
| **Diarrhoea** | **164 (45)** | 23 (6) | 0 | 139 (39) | 9 (3) | 0 |
| **Rash SMQ** | **131 (36)** | **18 (5)** | 0 | 82 (23) | 6 (2) | 0 |
| **Rash HLT** | **72 (20)** | 9 (2) | 0 | 45 (13) | 6 (2) | 0 |
| **Constipation** | **126 (35)** | 1 (<1) | 0 | 94 (26) | 1 (<1) | 0 |
| Fatigue | 106 (29) | 13 (4) | 0 | 102 (28) | 10 (3) | 0 |
| **Nausea** | **104 (29)** | 6 (2) | 0 | 79 (22) | 0 | 0 |
| **Red denotes differences of ≥5% between the 2 treatments** | | | | | | |

# Common adverse events in TMM1 (second interim analysis)

| | IXA+LEN+DEX (n=361) | | | LEN+DEX (n=359) | | |
|---|---|---|---|---|---|---|
| | **Any grade** | **Grade 3** | **Grade 4** | **Any grade** | **Grade 3** | **Grade 4** |
| **Common non-haematologic AEs of any cause, n (%)** | | | | | | |
| **Peripheral oedema** | **101 (28)** | **8 (2)** | 0 | 73 (20) | 4 (1) | 0 |
| **Peripheral neuropathy** | **97 (27)** | **9 (2)** | 0 | 78 (22) | 6 (2) | 0 |
| **Back pain** | **87 (24)** | **3 (<1)** | 0 | 62 (17) | 9 (3) | 0 |
| **Vomiting** | **84 (23)** | 4 (1) | 0 | 42 (12) | 2 (<1) | 0 |
| Upper respiratory tract infection | 83 (23) | 2 (<1) | 0 | 70 (19) | 3 (<1) | 0 |
| Nasopharyngitis | 81 (22) | 0 | 0 | 73 (20) | 0 | 0 |
| **Insomnia** | 73 (20) | 7 (2) | 0 | **98 (27)** | 11 (3) | 0 |
| **Muscle spasms** | 66 (18) | 0 | 0 | **95 (26)** | 2 (<1) | 0 |

**Red denotes differences of ≥5% between the 2 treatments**

# ERG alternative base case: summary of changes

| | |
|---|---|
| Updated BORT+DEX costs | • Removed assumption that duration of BORT+DEX treatments is the same as LEN+DEX (by applying the HR for PFS to the LEN+DEX ToT curve)<br>• Limited to 8 cycles (as per SmPC)<br>• Added outpatient cost for administration |
| Updated BORT+DEX benefits | • Applied ERG NMA<br>• Updated distribution of best overall response<br>• Removed 0.025 disutility for sc administration |
| Updated IXA+LEN+DEX costs | • Removed lenalidomide PAS from intervention arm in 1 prior therapy group |
| Other | • Applied costs for iv administration of concomitant treatments<br>• Assumed 100% dosing intensity |

# End-of-life criteria: conclusions of other appraisals in multiple myeloma

| Appraisal | EoL? | Life expectancy <24 months | OS benefit >3 months |
|---|---|---|---|
| **2-3 prior therapies (3rd and 4th line)** | | | |
| TA427 pomalidomide (4th line) | Yes | Yes (model predicted 13, 9 & 6 months OS with panobinostat, bendamustine & chemo) | Yes (vs. chemo or bendamustine) |
| TA380 panobinostat (3rd line) | No | No (expert statement: OS with LEN+DEX = 30 months) | No |
| TA171 lenalidomide (3rd line) | Yes | Yes (~9 months with DEX according to clinical trials & MRC data) | Yes |
| Carfilzomib (3rd line); preliminary guidance | No | No (HMRN data shows 1.3 years OS with 3rd line LEN+DEX, model predicted 5 years but too uncertain) | Yes |
| **1 prior therapies (2nd line)** | | | |
| ID934 carfilzomib; preliminary guidance | No | No; didn't meet for 3rd line so would not meet at 2nd line | Yes |
| ID667 lenalidomide; preliminary guidance | No | No; model predicted OS >24 months with chemo | Not discussed |
| TA129 bortezomib | N/A: appraisal conducted before EoL criteria introduced | | |

# End-of-life criteria: comparison of trial and model outcomes for mean OS

| | Mean OS, months | | |
|---|---|---|---|
| | **IXA+LEN+DEX** | **Comparator** | **Incremental** |
| **1 prior therapy** | | | |
| Clinical trial result | 21.0 | N/A | - |
| Company base case model (contains error in NMA) | 20.9 | 16.6 | 4.3 |
| ERG base case model (analysis 4) | 21.5 | 20.9 | −0.6 |
| **2-3 prior therapies** | | | |
| Clinical trial result | 20.9 | 19.3 | 1.56 |
| Company base case model | 21.1 | 19.8 | 1.4 |
| ERG base case model (analysis 2) | 21.1 | 19.8 | 1.4 |
| ERG scenario in 2 prior therapies only (analysis 5) | 20.9 | 20.3 | 0.5 |

# End-of-life criteria: undiscounted life-year gains in the model

| | Undiscounted life years gained | | |
|---|---|---|---|
| | **IXA+LEN+DEX** | **Comparator** | **Incremental** |
| **1 prior therapy** | | | |
| Company base case model (contains error in NMA) | 7.2 | 2.6 | 4.5 |
| ERG base case model (analysis 4) | 7.2 | 8.1 | −0.9 |
| **2-3 prior therapies** | | | |
| Company base case model | 5.3 | 3.6 | 1.7 |
| ERG base case model (analysis 2) | 5.3 | 3.6 | 1.7 |
| ERG scenario in 2 prior therapies only (analysis 5) | 7.7 | 6.5 | 1.3 |