Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib (part-review of TA171) STA

4th meeting, 5th October 2016

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Evidence Review Group: PenTAG with Matrix

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Chair: Amanda Adler

Key issues for consideration

Comparators and relative effectiveness	Is bortezomib retreatment still a relevant comparator?
	If yes, prefer to estimate effectiveness of bortezomib using: 1) Taverna, 2) Reyal or 3) assume equivalence with dexamethasone?
	Prefer to estimate effectiveness of melphalan using: 1) Petrucci; 2) assume equivalence with dexamethasone?
Subsequent treatments	Should model include company adjustments for subsequent treatment?
Modelling progression-free survival	For dexamethasone, prefer ERG or company approach?
Modelling overall survival	Does company modelling of dexamethasone reflect 2nd line patients?
	Should model assume equal survival after stopping treatment?

Recap

Jun 2009 TA171
Recommended for people who had 2 or more prior therapies; dose-cap PAS after 26 cycles
Treatment after 1 prior therapy not cost effective

Nov 2012 NICE decides to update TA171 for people who had 1 prior therapy with bortezomib
Rationale: treatment pathway changed plus new evidence

Feb 2014
1st meeting
PAS did not apply
ACD: not recommended

June 2014
2nd meeting
PAS did not apply
ACD2: not recommended

Oct 2014
Appraisal suspended pending new evidence

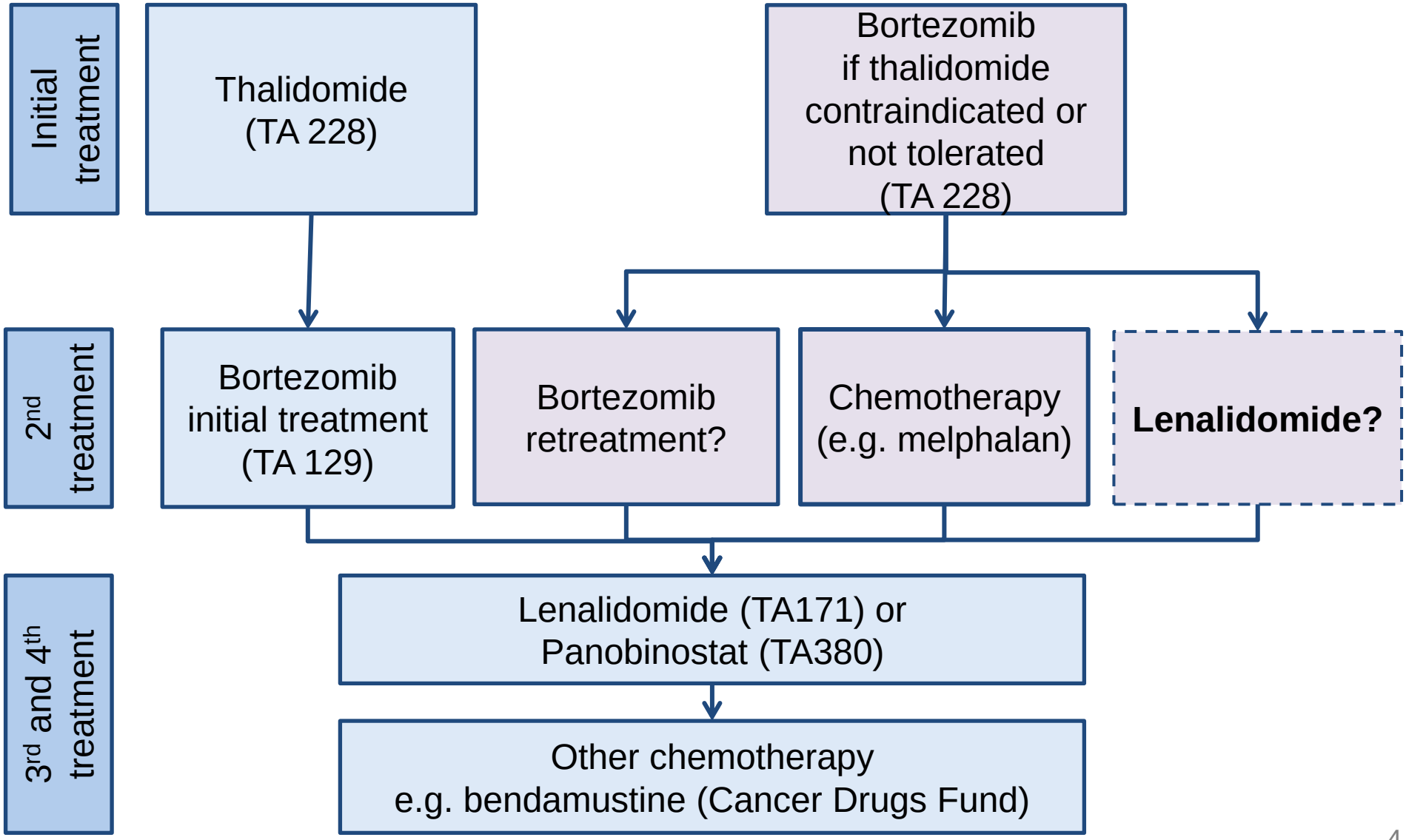
Sept 2015
Existing PAS extended to include treatment after 1 prior therapy
New clinical and cost evidence

Apr 2016
3rd meeting
No ACD/FAD.
Requested additional evidence from company

TODAY

Multiple myeloma treatment pathway

(for people unsuitable for stem cell transplantation)



Lenalidomide (Revlimid)

- Marketing authorisation: combined with dexamethasone for adults who had at least 1 prior therapy
  - 25 mg orally once daily on days 1-21 of repeated 28-day cycle
- Treat until disease progresses
- If neutropenia or thrombocytopenia occur, reduce dose
- Related to thalidomide; teratogenic; must fulfill conditions of Pregnancy Prevention Programme
- Complex patient access scheme (dose capping)

Decision problem

	NICE scope	Company decision problem
Pop.	Adults with myeloma contraindicated to thalidomide whose disease progressed after bortezomib (and not eligible for stem cell transplantation)	
Comp.	1. Chemotherapy: melphalan, vincristine, cyclophosphamide, doxorubicin 2. Bortezomib • Monotherapy • + dexamethasone 3. Bendamustine	1. Melphalan 2. Previous modelling included bendamustine & bortezomib, current analyses focus on comparison with melphalan
Outcomes	• Progression-free survival • Response rates • Time to next treatment • Mortality • Adverse effects of treatment • Health-related quality of life	Did not provide time to next treatment (not reported in main trial)
Subgroups	None	

Summary of committee conclusions – comparators

Bendamustine

- Bendamustine not comparator – used later, as 4th or 5th treatment

Bortezomib retreatment

- TA129 recommends bortezomib after 1 prior therapy
  - does not specify which previous treatments, key trial enrolled patients who had not had bortezomib
- Bortezomib retreatment removed Cancer Drugs Fund Jan 2015
- April 2016 meeting: heard not funded for some people, but clinicians considered it a comparator

Committee conclusions 3rd meeting

- If disease suitable for bortezomib retreatment: comparators bortezomib retreatment and chemotherapy
- If bortezomib retreatment not suitable or not available: comparator is chemotherapy

Comparators

- Email from NHS England to NICE, March 2016: NHS England does not commission bortezomib retreatment for patients relevant to this appraisal

<u>Company comments June 2016</u>

- Bortezomib retreatment not funded, not a comparator
- Provided supporting email from NHS England pharmacist to NHS clinician

⊙ *Is bortezomib retreatment still a relevant comparator?*

Sources of clinical evidence

No trials comparing lenalidomide with comparators

Lenalidomide

Pooled analysis of 2 RCTs: MM009 and MM010

- Lenalidomide + dexamethasone vs. placebo + dexamethasone

Response rates for lenalidomide given after bortezomib (VISTA)

Bortezomib

- 6 retrospective observational studies, company selected Taverna et al. (2012) - 14 patients of 42 died
- Response rates for bortezomib retreatment (VISTA)
- Small observational study in Korean patients (Ahn et al. 2014)
- Reyal et al (2016) small UK observational study

Chemotherapy

- 2 small observational studies

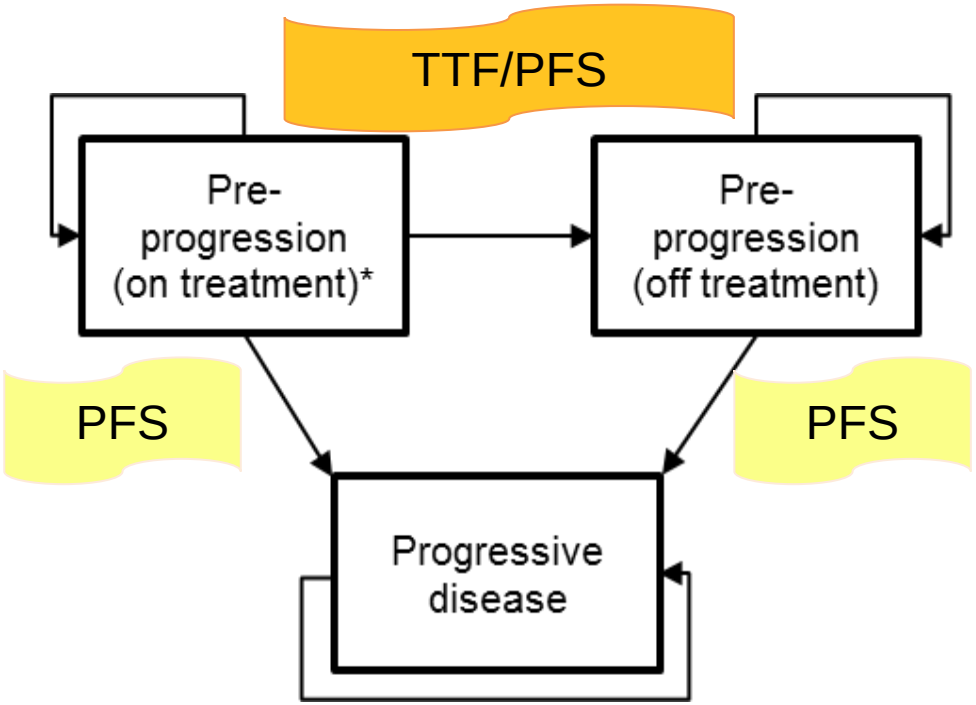
Key:

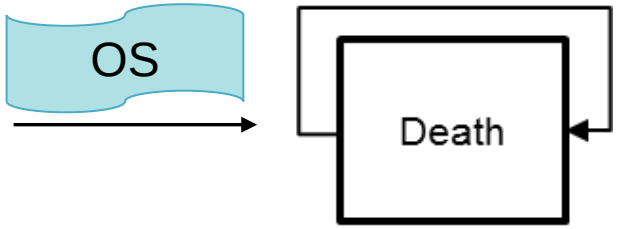
Additional evidence for this meeting

Committee conclusions at meetings 1-3

CLINICAL EFFECTIVENESS
MM009 and MM010 trials: • Populations did not match appraisal population, but clinical expert stated differences unlikely to affect outcomes • Irrelevant comparator for NHS (dexamethasone) • Lenalidomide more effective than placebo plus dexamethasone
Lenalidomide compared with **bortezomib retreatment**: • Evidence from small observational studies and mixed treatment comparison • High risk of confounding • Study populations not directly relevant to appraisal • Significant uncertainty about relative effectiveness
Lenalidomide compared with **chemotherapy**: • Simple comparison of observational studies suggests longer survival with lenalidomide; clinical experts agreed • High risk of confounding • Lenalidomide likely to be more effective

Company's Markov model





- TTF: time to treatment failure (stop before progression, e.g. adverse events)
- PFS: progression-free survival
- OS: overall survival

- Population: patients previously treated with bortezomib
- Comparator: chemotherapy (ERG analyses also include bortezomib retreatment)

Committee conclusions at meeting 1-3

COST EFFECTIVENESS
Significant uncertainty in hazard ratios for lenalidomide compared with bortezomib retreatment
Hazard ratios calculated using medians – assumptions hold only when used with exponential distribution
Subsequent treatments - prefer to include both costs and effectiveness, and should be same in both arms of model
For bortezomib retreatment, prefer to take estimates of treatment duration and efficacy from the same source (Taverna – mean 3.8 cycles – in latest ERG analyses)
Assume bortezomib complex PAS equates to 15% discount (in latest ERG analyses, not a key driver)
End of life criteria **not** met – life expectancy >24 months

New evidence

Committee request after 3rd meeting	**New evidence for discussion today**
Unclear how subsequent treatments included in model	Company analyses include subsequent treatments; ERG analyses exclude
Data from new Reyal (2016) study of bortezomib retreatment	Used in ERG scenario
Concerned model lacks face validity	New analyses assuming melphalan and dexamethasone equally effective
Concerned about survival benefit after stopping treatment	New scenarios with no treatment effect after stopping treatment or progression

Comparator adjustments for subsequent treatment

Recap: in company Feb 2016 base case all bortezomib and melphalan patients have lenalidomide 3rd line.
Committee: impact of adjustment difficult to understand – adding 3rd line lenalidomide after bortezomib modestly increases survival but substantially increases costs. Asked company to explain.

- Company:
  - Agree 'spurious results' when adjusting bortezomib arm to include 3rd line lenalidomide – but think bortezomib not a comparator
  - Suggest this problem does not exist for melphalan arm
- ERG:
  - Company adjustment for subsequent treatments not plausible
  - ERG analyses do not include costs and benefits of subsequent treatments, increases ICER vs company base case
- Company: ERG scenario does not reflect treatment pathway

⊙ *Should model include company adjustments for subsequent treatment?*

Only relevant if bortezomib is a comparator

New evidence for bortezomib

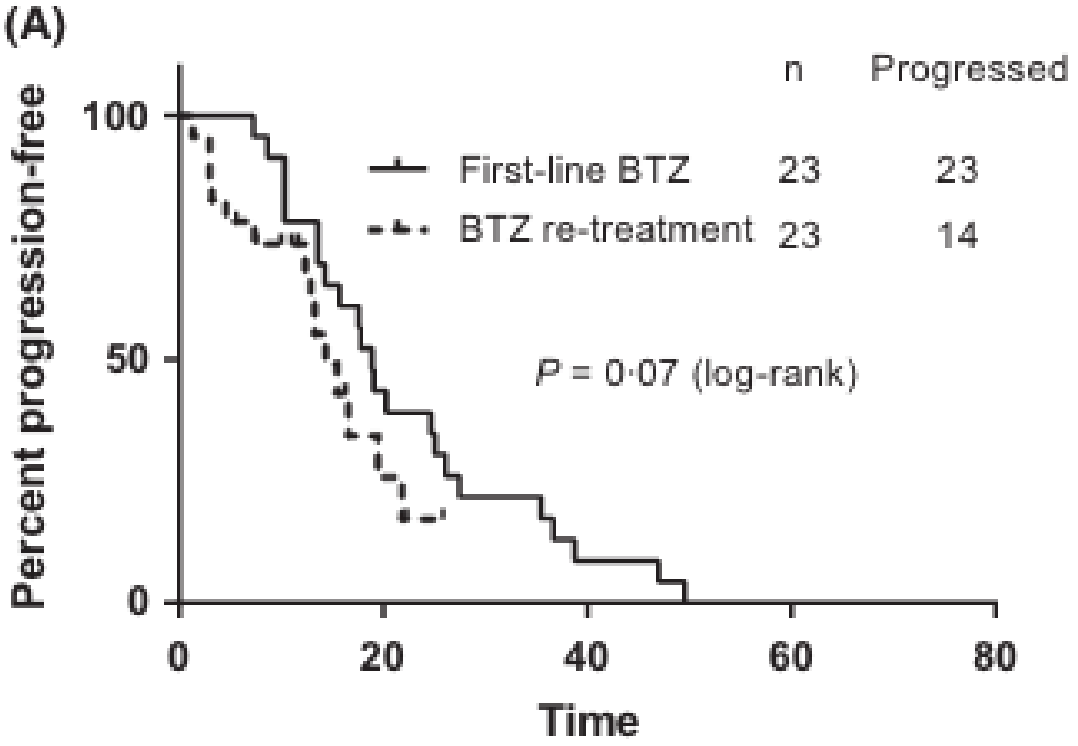
Study design

	Taverna 2012 (in Feb 2016 base case)	Reyal 2016 (ERG Sept 2016 scenario)
Design	Retrospective survey	Retrospective record review (single centre)
Pop.	42 patients in Switzerland; responded to initial bortezomib therapy but subsequently progressed or relapsed	23 patients in UK, at first relapse, had at least partial response and treatment-free interval ≥60 days after 1st line bortezomib
Treat-ment	All patients had bortezomib retreatment, although not necessarily 2nd line	Bortezomib 2nd line
Comp.	None – all patients treated with above	None – all patients treated with above
Out-comes	Median overall survival	Median progression-free survival

Only relevant if bortezomib is a comparator

New evidence for bortezomib

Reyal letter to British Journal of Haematology



"Our data indicate that bortezomib re-treatment at first relapse can produce durable responses in a high proportion of patients, with acceptable toxicity."

Only relevant if bortezomib is a comparator

New evidence for bortezomib

Results

Outcome	Company Feb 2016 base case	Taverna (2012)	Reyal (2016)
Bortezomib treatment cycles	Mean 6.6	Mean 3.8	Median 5
Median progression-free survival (months)	10.1	NR	14.4

- Company:
  - Bortezomib not a comparator
  - Reyal carried out in transplant eligible population (not in scope)
- ERG: Reyal limited as only 23 participants, but they were from NHS
- New ERG scenario using Reyal:
  - Reduce mean duration of bortezomib from 6.6 to 5 cycles
  - Longer progression-free survival (versus Taverna 2012)
  - Overall survival unchanged
  - Company's base case ICER increased from £20,000 to £46,000

⊙ *Prefer to estimate effectiveness of bortezomib using: A) Taverna; B) Reyal; C) assume equivalence with dexamethasone – later slides*

Predicted survival times for comparators

Recap: model survival benefit vs. chemotherapy or bortezomib greater than was observed in trial vs dexamethasone – implausible
Asked for model predicted outcomes for comparators (naive indirect comparisons) and dexamethasone (direct trial data), **not adjusted** crossover.

Model predictions for	**Undiscounted life years**
Lenalidomide + dexamethasone	5.87
Dexamethasone (48% had len 3rd line)	3.97
Melphalan + prednisolone (100% had len 3rd line)	3.15
Bortezomib retreatment (100% had len 3rd line)	3.69

- Model predicts longer survival with dexamethasone alone than bortezomib or chemotherapy
- Company and ERG agree this is a problem

⊙ *Is this model based on naive indirect comparison suitable for decision making?*

Predicted survival times for comparators

- Company solution: **assume melphalan and dexamethasone equally effective**
  - Use dexamethasone arm of MM trials to model melphalan
  - Large, randomised data set, 48% had lenalidomide 3rd line
  - Assumption supported by Facon: 122 patients in melphalan arm & 127 in dexamethasone arm – no difference in overall survival

ERG response

- Facon showed longer progression-free survival with melphalan than with dexamethasone and Facon patients not representative of population for appraisal
- Nonetheless, assuming equivalence is ERG's preferred approach

- ⊙ *Appropriate to assume **melphalan** equivalent to dexamethasone (preferred by company and ERG)?*
- ⊙ *Appropriate to assume **bortezomib** equivalent to dexamethasone (ERG believes worst-case scenario for bortezomib, gives lower bound ICER)?*

Only relevant if assuming melphalan and dexamethasone equally effective

New scenarios assuming melphalan and dexamethasone equally effective: ERG critique

1. Substantial error in cost of acquisition of melphalan (changed in ERG base case)

NB: Company agrees with ERG correction

2. Error in calculating overall survival with melphalan (changed in ERG base case, company disagrees)

⊙ *Does committee think ERG correction to overall survival is necessary?*

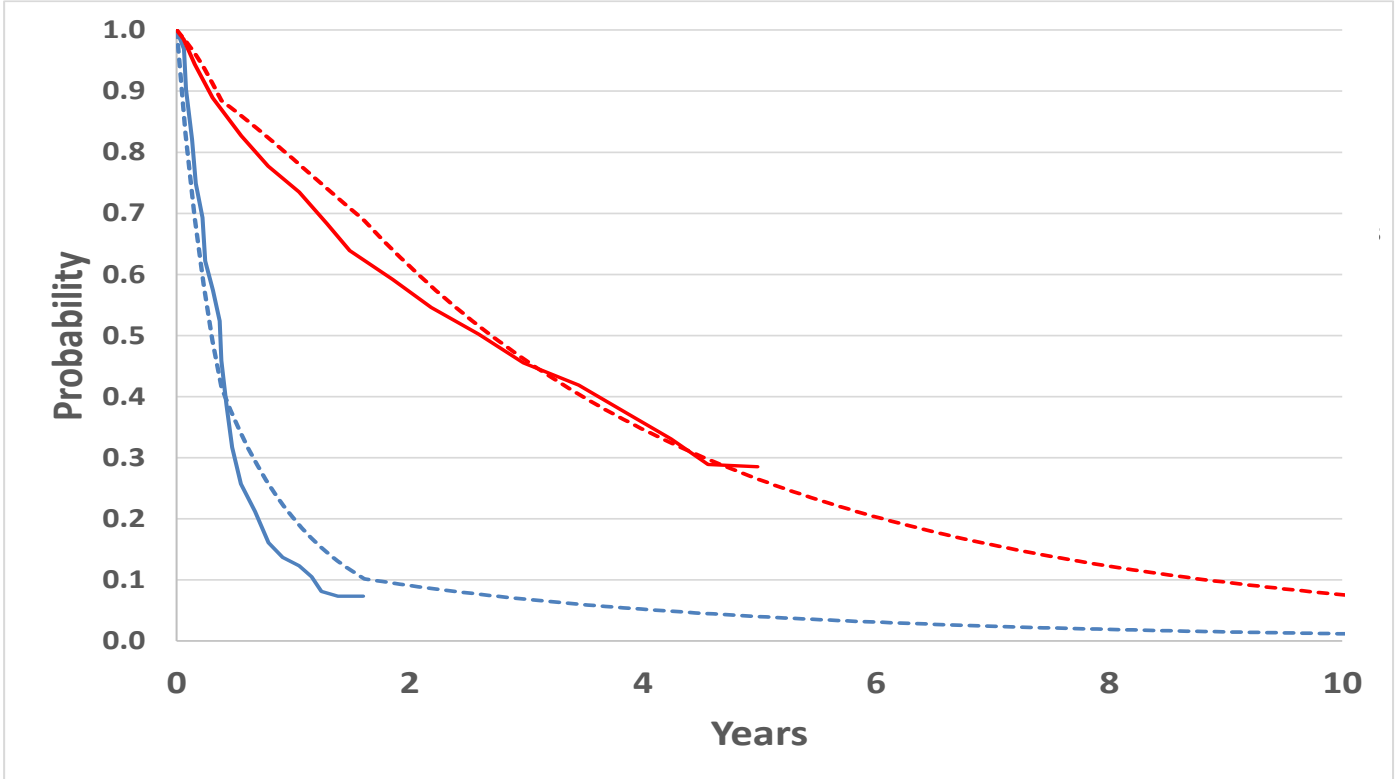
3. Implausibly long 'tail' to progression-free survival curve for dexamethasone (changed in ERG base case, company disagrees)

4. Model used data from all dexamethasone patients, not just 2nd line (changed in ERG scenario, company disagrees)

Only relevant if assuming melphalan and dexamethasone equally effective

Progression-free survival with dexamethasone

- Company modelling (focus on blue lines)
- ERG: progression-free survival tail implausibly long



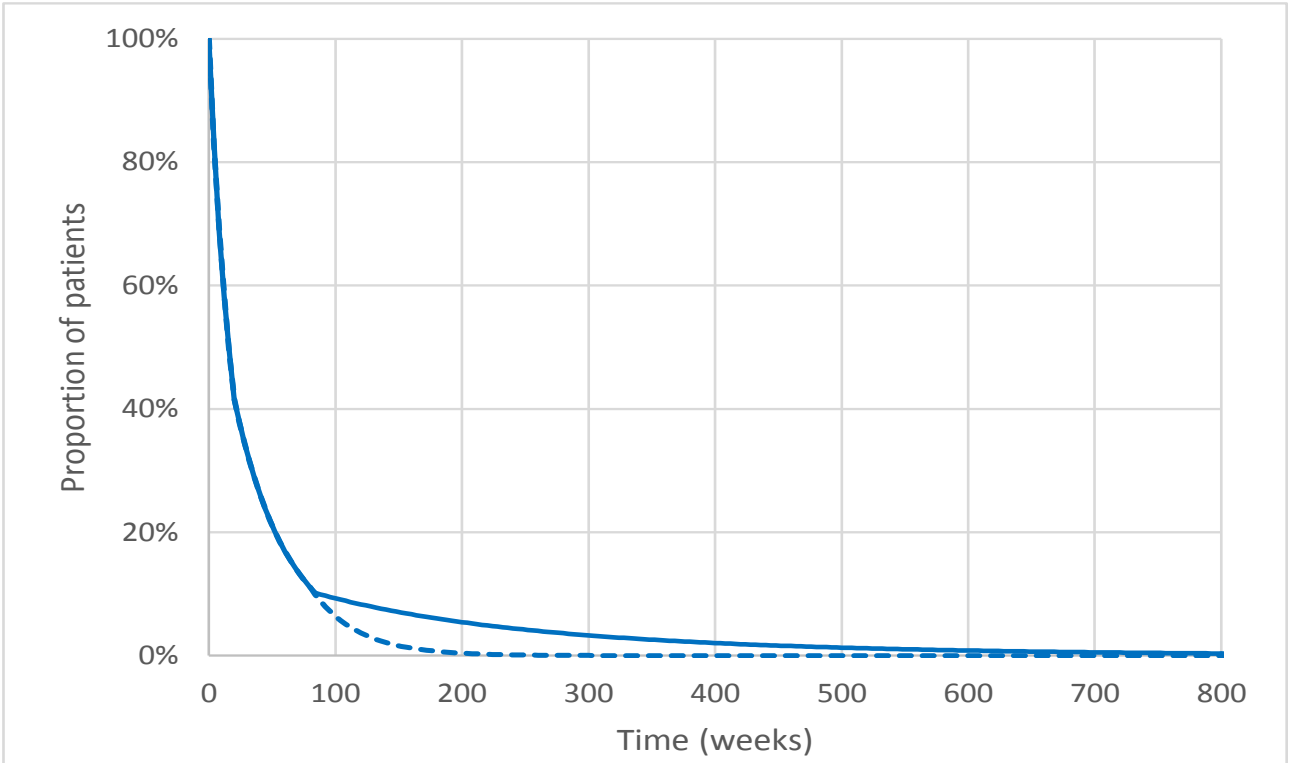
company progression free survival
company overall survival
progression free survival from RCTs
overall survival from RCTs

Only relevant if assuming melphalan and dexamethasone equally effective

Progression-free survival with dexamethasone

- ERG base case: same as company to 1.5 years, then exponential distribution
- Impact: shorter treatment with melphalan, higher ICER

ICER



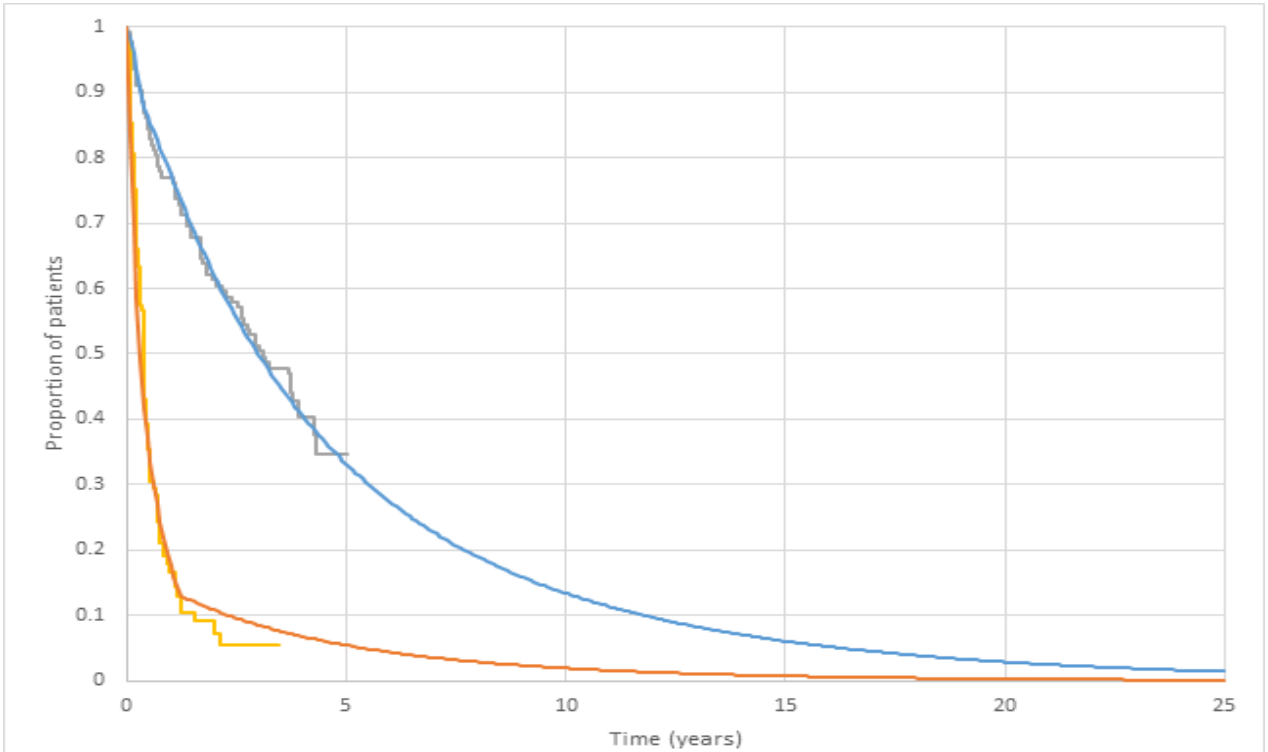
company progression-free survival for dexamethasone

ERG progression-free survival for dexamethasone

Only relevant if assuming melphalan and dexamethasone equally effective

Progression-free survival with dexamethasone

- Company response: ERG curves showed interim analyses, fit is adequate looking at more recent data from 2008



company overall survival
overall survival from RCTs (2008)
company progression free survival
progression free survival from RCTs (2008)

⊙ *Prefer ERG or company approach?*

Only relevant if assuming melphalan and dexamethasone equally effective

Overall survival with dexamethasone

ERG critique and scenario

- Lenalidomide arm of model reflects 2nd line patients (survival is better than for patients at later lines)
- ERG think **dexamethasone arm reflects all patients in trials** (company disagree, think model predicts 2nd line only)
- ERG content to use data from all patients for PFS
- ERG unsure whether to extend overall survival times to reflect possible better outcomes for 2nd line patients
- ERG scenario:
  - For lenalidomide, calculate ratio of survival times 2nd line vs all patients
  - Extend mean survival with dexamethasone using this ratio
  - Impact: company ICER for lenalidomide vs. melphalan increases from £20,000 to £35,000

⊙ *Does company model reflect 2nd line patients? If not, use ERG scenario with longer overall survival with dexamethasone?*

Survival after stopping treatment

Committee: no evidence of an ongoing survival benefit, so asked for scenario analysis using hazard ratio of 1 after stopping treatment.

⊙ *There are different ways to implement this scenario, is this issue still relevant if assume equivalence with dexamethasone? Does the committee want to discuss further?*

Company

- Could not apply hazard ratio of 1 within model structure; instead explored equal post-progression survival across all arms, by using lenalidomide + dexamethasone data for comparator
- But not a valid comparison – trial data shows post progression survival benefit for lenalidomide compared with dexamethasone, when dexamethasone arm is adjusted for crossover

Survival after stopping treatment – company response

Progression-free survival for comparator	Post-progression survival for comparator	3rd line LEN costs in comparator arm	ICER vs. bortezomib	ICER vs. melphalan
Feb 2016 base case: from Taverna/Petrucci	From Taverna/ Petrucci	Included	£20,000	£24,000
From Taverna/ Petrucci	= LEN + DEX	Included	£31,048	£22,172
From Taverna/ Petrucci	= LEN + DEX	Excluded	£71,449	£35,830
June 2016: = DEX	= DEX	Included	Not reported	£20,000
= DEX	= LEN + DEX	Included	Not reported	£23,152
= DEX	= LEN + DEX	Excluded	Not reported	£38,267

DEX, dexamethasone; LEN, lenalidomide.

New scenario assuming no survival benefit after treatment stopped: ERG critique

- ERG approach #1: survival after stopping treatment:
  - Start with 'old' model based on naive indirect comparisons
  - Assume same proportion alive when stop treatment
  - Assume PFS = time on treatment (company: artificially extends treatment time and cost)
  - Only include costs and QALYs up to time of stopping treatment
- ERG approach #2: survival after progression (similar to company)

	ICER vs. bortezomib	ICER vs. melphalan
Company Feb 2016 base case (at ACM 3)	£20,000	£24,000
ERG scenario #1: model up to treatment stopping	£45,000	£59,000
ERG scenario #2: equal survival after progression	£68,000	£36,000

⊙ *Should model assume equal survival after stopping treatment? If yes, prefer company approach or ERG #1 or ERG #2?*

Lenalidomide vs melphalan

Assume melphalan equal to dexamethasone?

No

Old approach based on naive indirect comparison with Petrucci (1989)

Include costs and benefits subsequent treatments?
Company: include, ICER £24,000
ERG: exclude, ICER £26,000

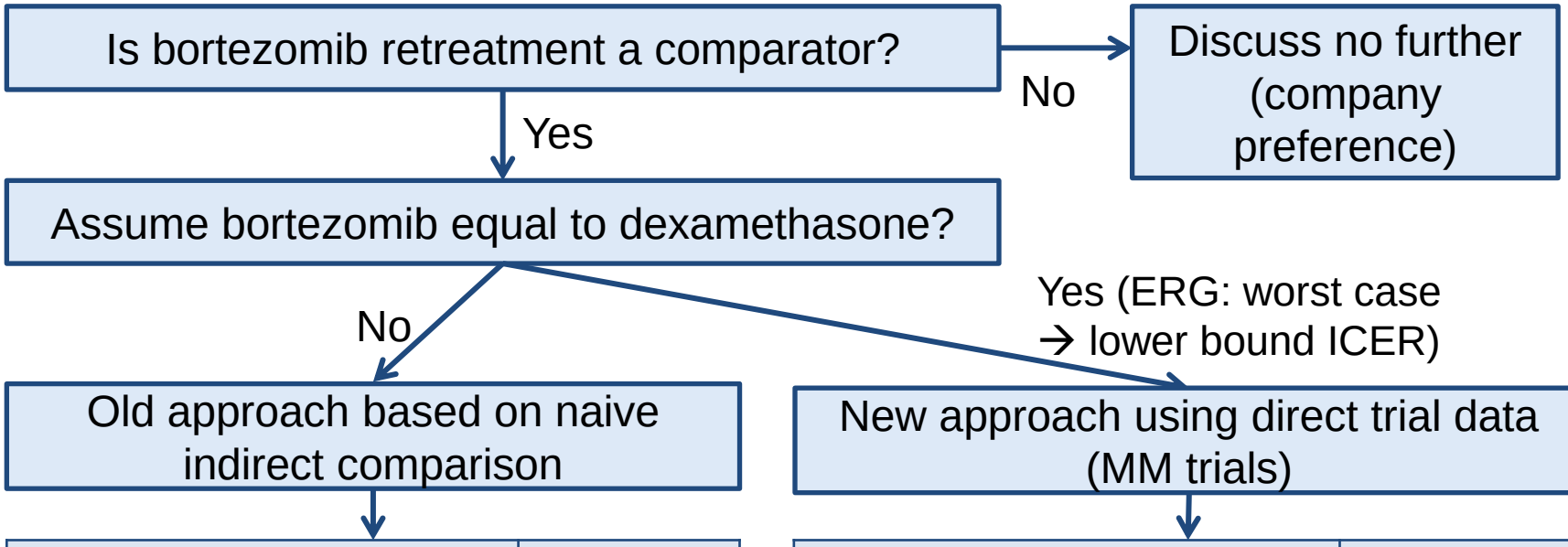
For both approaches, there are scenarios assuming equal survival after stopping treatment – slides 24 and 25

Yes (preferred by company and ERG)

New approach using direct trial data (MM trials)

Company	**£20,000***
Company correct melphalan cost	£46,000
ERG corrections	£32,000
ERG corrections + shorter PFS for dex	£34,000
ERG corrections, shorter PFS for dex + longer survival with dex to reflect 2nd line	£90,000
ERG base case £34,000 to £90,000	
*Company reported £24,000, ERG believe should be £20,000	

Lenalidomide vs bortezomib retreatment



Company (Taverna)	£20,000
ERG: mean 3.8 cycles bortezomib, **Taverna**	£44,000
ERG: mean 5 cycles bortezomib, **Reyal**	£76,000
ERG analyses: exclude subsequent treatments, full bortezomib PAS	

For both approaches, see scenarios assuming equal survival after stopping treatment – slides 24 + 25

Company	NR
ERG base case minimum	>£31,000
ERG base case maximum (longer survival with dex to reflect 2nd line)	>£83,000
ERG believe ICER exceeds either £31,000 or £83,000 ERG analyses: include corrections, shorter PFS for dex, mean 3.8 cycles bortezomib	

ICERs for lenalidomide vs. melphalan

(old approach based on naive indirect comparison)

Recap – ERG state that all ICERs highly uncertain:

- Underlying clinical data not randomised
- Quality of clinical data used to inform outcomes for comparators is extremely low
- Nature of subsequent treatments is uncertain

	ICER vs. melphalan
Company base case at ACM3	**£24,000**
1. ERG no subsequent treatment costs	£37,000
2. ERG remove extension to overall survival to reflect 3rd line lenalidomide after melphalan	£19,000
3. ERG equal mortality between treatment arms after progression	£36,000
1 & 2 (ERG base case at ACM 3)	**£26,000**

ICERs for lenalidomide vs. melphalan

(new approach assuming equivalence with dexamethasone)

	ICER vs. melphalan
Company current analysis at ACM4	£24,000
Company current analysis at ACM4 (ERG corrected)	**£20,000**
1. ERG correct error in melphalan acquisition cost	£46,000
2. ERG correct error in overall survival for melphalan	£15,000
3. ERG shorten dexamethasone progression free survival tail	£23,000
1 & 2 & 3 (ERG base case minimum at ACM 4)	**£34,000**
4. ERG extend dexamethasone overall survival tail to reflect 2nd line patients	£35,000
1 & 2 & 3 & 4 (ERG base case maximum at ACM 4)	**£90,000**
5. Equal mortality between treatment arms after progression	£22,000

ERG unable to give precise value because unsure of overall survival for dexamethasone 2nd-line

ICERs for lenalidomide vs. bortezomib

(old approach based on naive indirect comparison)

	ICER vs. bortezomib
Company base case at ACM3	**£20,000**
1. ERG no subsequent treatment costs	£36,000
2. ERG reduce mean duration bortezomib from 6.6 to 3.8 cycles	£29,000
3. ERG remove extension to overall survival to reflect 3rd line lenalidomide after bortezomib	£20,000
1 & 2 & 3 (ERG base case at ACM3)	**£44,000**
4. ERG implement full bortezomib PAS discount	£21,000
1 & 2 & 3 & 4	**£44,000**
5. Equal mortality between treatment arms after progression	£68,000
6. Reduce mean duration of bortezomib from 6.6 to 5 cycles, extend PFS (based on Reyal 2016)	£46,000
1 & 3 & 4 & 6	**£76,000**

ICERs for lenalidomide vs. bortezomib

(new approach assuming equivalence with dexamethasone)

	ICER vs. bortezomib
Company current analysis at ACM4	Not modelled
ERG amendments to model bortezomib arm	>£35,000
1. Correct error overall survival with dexamethasone	>£25,000
2. Shorten dexamethasone progression free survival tail	>£32,000
3. Reduce mean duration of bortezomib from 6.6 to 3.8 cycles	>£48,000
1 & 2 & 3 (ERG base case minimum at ACM 4)	**>£31,000**
4. Extend dexamethasone overall survival tail to reflect 2nd line patients	>£65,000
1 & 2 & 3 & 4 (ERG base case maximum at ACM 4)	**>£83,000**
5. Equal mortality between treatment arms after progression	>£30,000

ERG unable to give a precise value because unsure of overall survival for dexamethasone 2nd-line

Key issues for consideration

Comparators and relative effectiveness	Is bortezomib retreatment still a relevant comparator?
	If yes, prefer to estimate effectiveness of bortezomib using: 1) Taverna, 2) Reyal or 3) assume equivalence with dexamethasone?
	Prefer to estimate effectiveness of melphalan using: 1) Petrucci; 2) assume equivalence with dexamethasone?
Subsequent treatments	Should model include company adjustments for subsequent treatment?
Modelling progression-free survival	For dexamethasone, prefer ERG or company approach?
Modelling overall survival	Does company modelling of dexamethasone reflect 2nd line patients?
	Should model assume equal survival after stopping treatment? If yes: company approach, ERG 1 or ERG 2?