NICE National Institute for Health and Care Excellence

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Contains no ACIC data

Lenalidomide for the maintenance treatment of multiple myeloma after autologous stem cell transplant [ID475]

2nd committee meeting

Lead team: Mark Glover, Rhiannon Owen, Tony Wootton

Chair: Sanjeev Patel

Evidence Review Group (ERG): Peninsula Technology Assessment Group (PenTAG)

Technical team: Hannah Nicholas, Carl Prescott, Nicole Elliott

Company: Celgene

12th November 2020 (virtual meeting)

Key issues

- Company conducted new analyses to adjust CALGB (longer term supportive trial) to match Myeloma XI (MXI, main trial) – are methods appropriate?
- For survival extrapolations in the model, what is the most appropriate:
  - source of data? i.e. MXI, CALGB, or MXI followed by CALGB?
  - distribution? i.e. generalised gamma etc
- Is the treatment effect of lenalidomide likely to wane over time? If so, at what timepoint should the treatment effect wane in the model?
- What are the most realistic model assumptions about treatments given after lenalidomide maintenance?
  - N.B. Cancer Drugs Fund treatments are given in practice, but cannot be included in model (as per NICE position statement)
- Should the company's or the ERG's estimate of relative dose intensity be used in the model?
- Is the company's representation of a 28-day dosing regimen appropriate?

Recap of clinical evidence and company's model

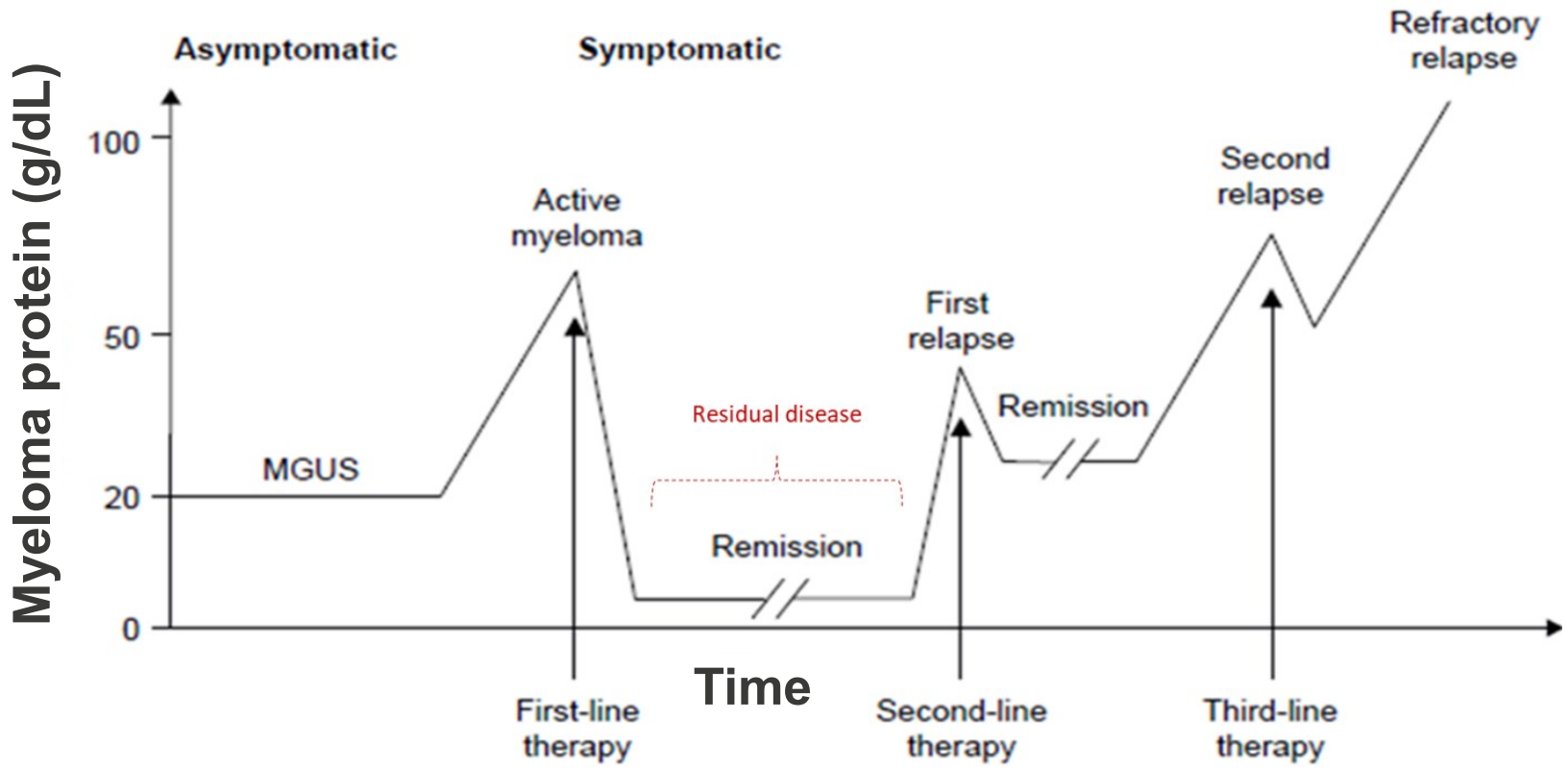
Disease background: multiple myeloma

- Type of blood cancer caused by proliferation of plasma cells (a type of white blood cell) in bone marrow
- Myeloma cells supress development of normal blood cells responsible for:
  - fighting infection (white blood cells)
  - carrying oxygen around body (red blood cells)
  - blood clotting (platelets)
- Symptoms and complications include bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems
- In 2017, 5,034 people were diagnosed with multiple myeloma in England
- More common in older people – median age of diagnosis = 73 years
- More common in men than women
- 5- and 10-year survival rates 52% and 29% respectively

 Sources: ID1475 final scope and company submission document B, page 15.

Disease background: progression

- Characterised by cycles of remission and response
- As number of lines of therapy increases, time in remission decreases
- Therapy aims to prolong disease-free remission by supressing residual disease, prolong survival and maintain quality of life by controlling disease and relieving symptoms



MGUS, monoclonal gammopathy of undetermined significance.
Sources: company document B, page 16 and ID475 final scope.

Management of newly diagnosed multiple myeloma

- Approximately 25–30% of newly diagnosed people receive ASCT in UK
- Eligibility for ASCT assessed by age, performance status, comorbidities – usually people under 65 who have no major underlying medical issues
- Full ASCT process involves:
  - induction with a 3-drug regimen, e.g. bortezomib, thalidomide, dexamethasone (TA311) to try to destroy most myeloma cells
  - healthy stem cell mobilisation and collection
  - high dose therapy – usually melphalan chemotherapy – to try to kill remaining myeloma cells
  - ASCT – infusion of person's healthy stem cells back into body
- Currently, after ASCT, clinicians observe patients but do not offer further active therapies until first relapse occurs
- **Lenalidomide proposed as maintenance therapy to prolong remission after ASCT**

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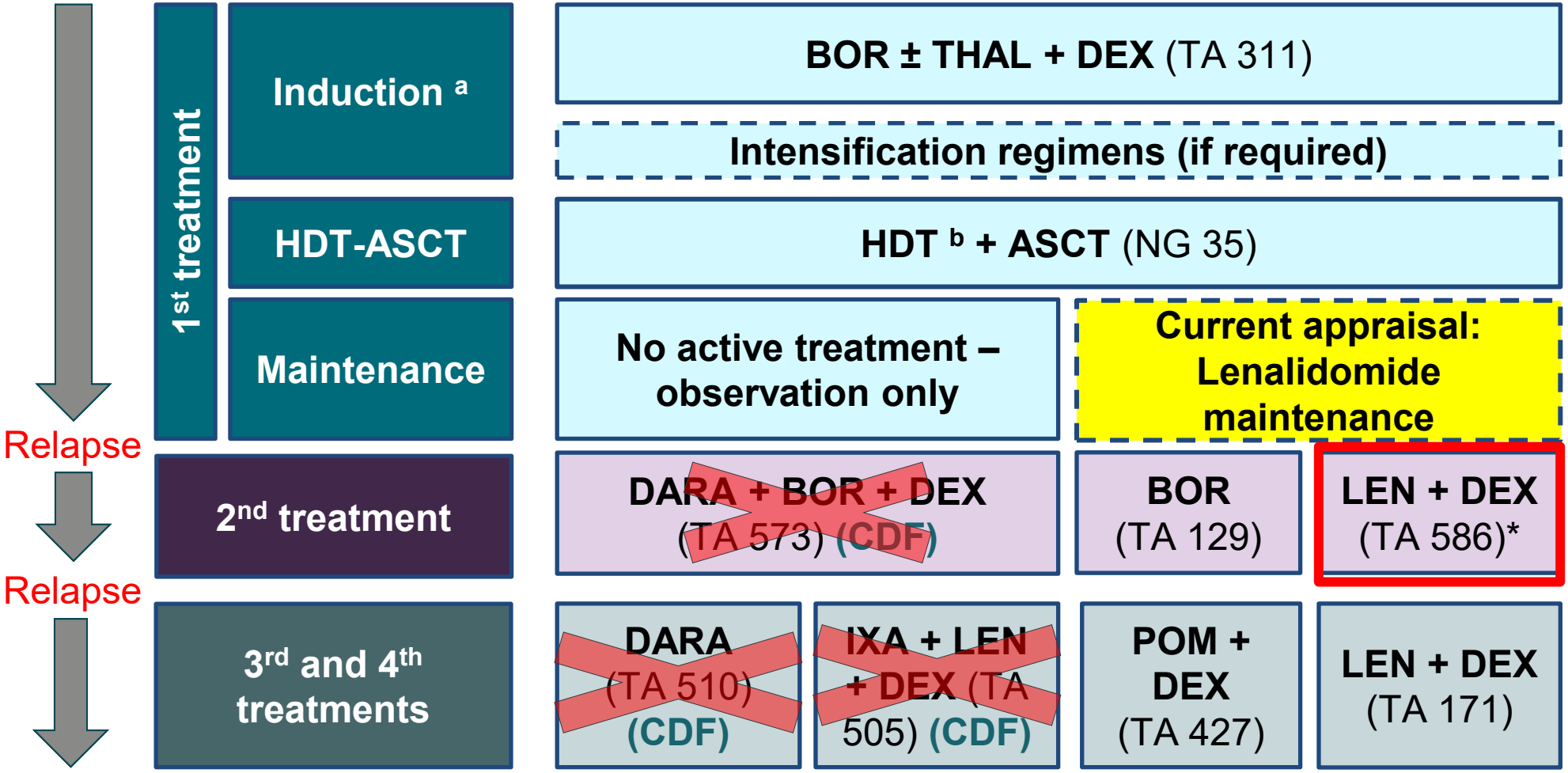
ASCT, autologous stem cell transplant
Post-ASCT consolidation therapy not currently recommended in UK, and was not used in Myeloma XI trial or company submission / model.

What does the *ASCT eligible* NICE treatment pathway look like without CDF treatments?



*TA586 states "the relevant population is people who cannot have a stem cell transplant or first-line thalidomide, and who have already had bortezomib". Note: more than 1 ASCT may be offered in NHS practice.

Only includes NICE-recommended therapies. [a] Induction therapies in Myeloma XI trial differed vs NICE recommendations; [b] NHS treatment algorithm recommends high dose melphalan. ASCT, autologous stem cell transplant; BOR, bortezomib; CDF, cancer drugs fund; DARA, daratumumab; DEX, dexamethasone; HDT, high-dose therapy; IXA, ixazomib; POM, pomalidomide; THAL, thalidomide.

Lenalidomide (Revlimid, Celgene)

Marketing authorisation	*"Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation"* (EMA license granted in 2017)
Administration and licensed dose [a]	• Oral treatment (capsules) • **Licence**: 10mg once daily continuously (on days **1 to 28** of repeated 28-day cycles) • Increased to 15mg orally if tolerated after 3 cycles • Stopping rule: disease progression or intolerance • **Trial and company expectation of clinical practice: 10mg** once daily on days **1 to 21** of repeated 28-day cycles
Mechanism of action	• Oral immunomodulatory imide drug (IMiD) based on thalidomide • Inhibits proliferation of certain haematopoietic tumour cells and production of proinflammatory cytokines, and enhances T cell- and Natural Killer cell-mediated immunity
List price [b]	Price per 21-tablet pack: **10 mg = £3780.00**; 15 mg = £3969.00 Note: patient access scheme discount available
Tests	Pregnancy tests at initiation and every 4 weeks during treatment [c]

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[a] Model used Myeloma XI trial dosing (10 mg/day given on days 1–21 of a 28-day cycle) to align with anticipated clinical practice; [b] Price in model is lower as it includes patient access scheme discount; [c] Modelled population have an average baseline age of 59 and are predominantly male so costs of pregnancy tests were excluded.

Summary of lenalidomide maintenance trials

	Myeloma XI	CALGB	GIMEMA	IFM 2005-02 [a]
Countries	UK	USA	Italy, Israel	France, Belgium, Switzerland
N	XXXXX	460	273	614
Comparator	Placebo	Placebo	Placebo	Placebo
Dosing (days per 28-day cycle)	1–21	1–28	1–21	1–28
Used for EMA regulatory approval?	No	Yes	No	Yes
Presented as clinical evidence? [b]	Yes	No	No	No
Used in model?	Yes	Yes / No [c]	No	No

Cells highlighted green to show alignment with UK practice, or to highlight positive attributes for appraisal. [a] IFM 2005-02 is not relevant to this appraisal because limited applicability to UK practice; [b] In its submission the company only presents Myeloma XI data as clinical evidence (discussed in later slides); [c] CALGB trial data used in company's base case but not ERG's base case – to be discussed as an issue. EMA, European Medicines Agency.

Summary of clinical effectiveness results

	Myeloma XI (decision problem cohort) [a]	CALGB 100104 [b]
Country	UK	USA
N	XXXXX	460
Median follow-up	31 months	91 months
Primary outcome: progression-free survival		
Hazard ratio (95% CI)	XXXX XXXXXXXXXXXXX	0.53 (0.42 to 0.72)
Primary outcome: overall survival		
Hazard ratio (95% CI)	XXXX XXXXXXXXXXXXX	0.47 (0.35 to 0.62)

Comparisons limited due to differences in trials, e.g. different doses and durations

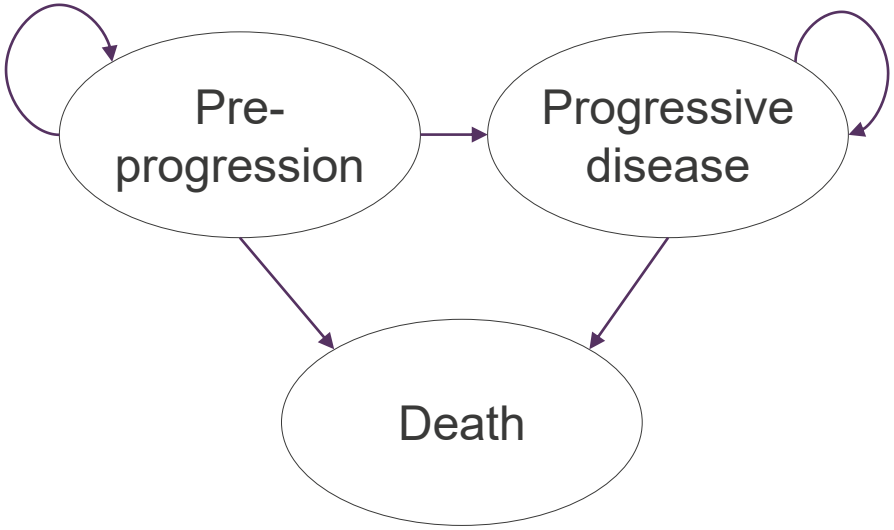
Committee concluded that lenalidomide is an effective maintenance treatment post ASCT

N.B. GIMEMA results not presented as trial data not used in model.

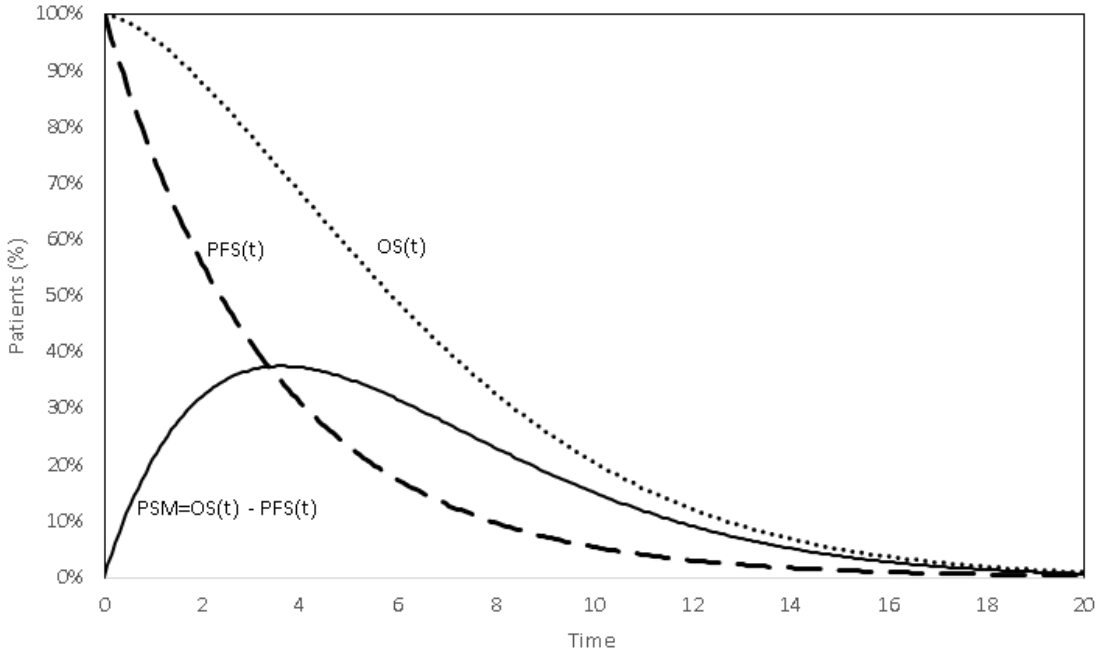
[a] From company submission document B, Table 15; [b] From Table 9 of ERG report (adjusted values).

Company's model structure

- Partitioned survival analysis model comprised of 3 health states: pre-progression, progressive disease, and death
- Cycle length: 28 days
- Time horizon: lifetime (40 years)



Determining transitions between health states



Committee's conclusion:

- Company's model structure had limitations
- Uncertainty around the cost-effectiveness estimate because assumptions about effects of subsequent therapies on survival could not be fully explored

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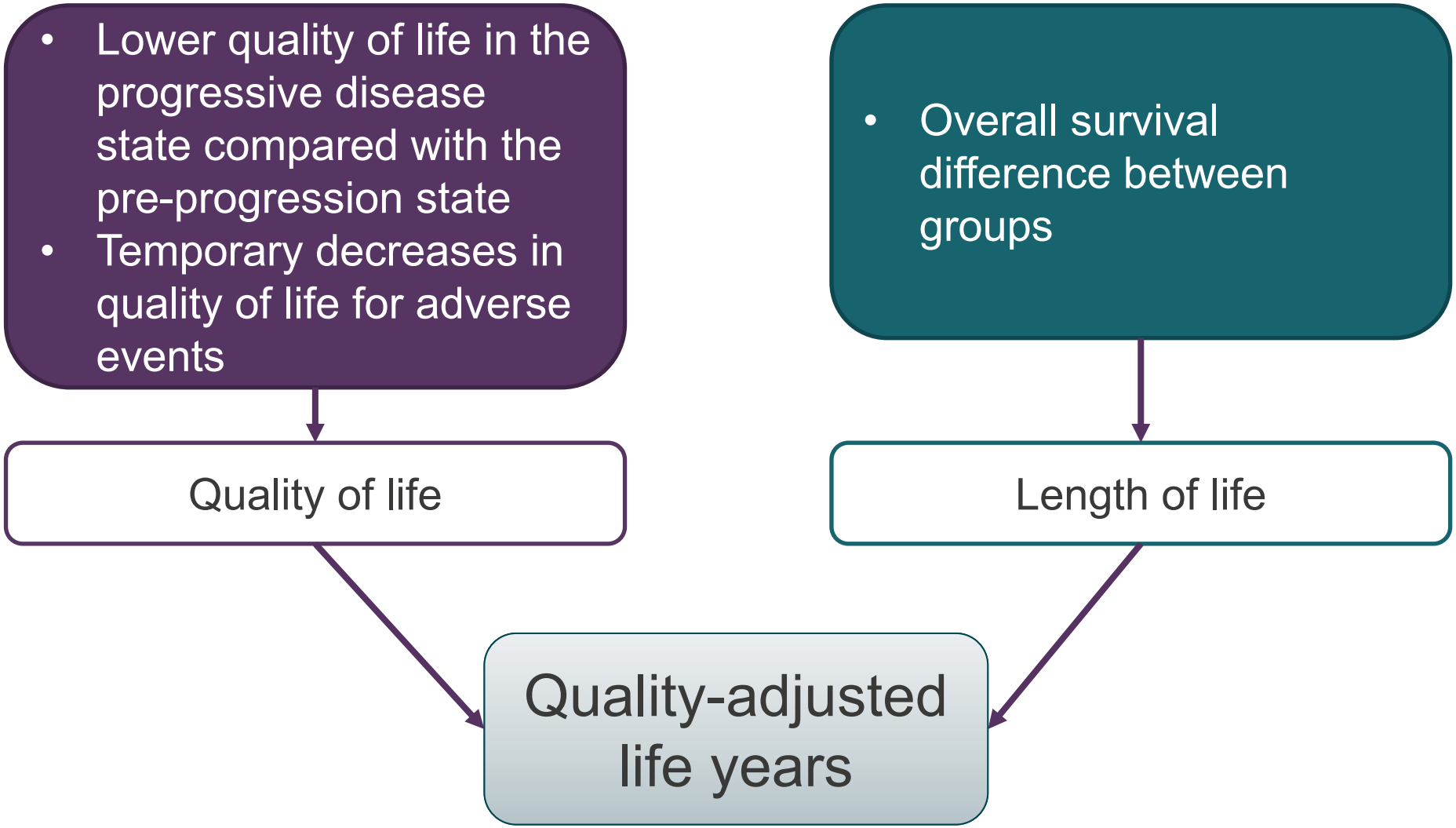
OS, overall survival; PFS, progression-free survival; PSM, progressive state membership; t, time. Source: company document B, pages 64 and 65.

Overview: how quality-adjusted life years accrue



Appraisal consultation document (ACD) conclusions + uncertainties (1)

	Committee conclusion	Requires discussion?	ACD section
Treatment pathway	• Lenalidomide is only potential option for maintenance treatment after ASCT	No	3.1
2nd ASCT	• ~5% to 10% of people currently get 2nd ASCT • Numbers likely to fall as alternative options become available	No	3.2
Dosing schedule	• Dosing schedule that would be used in clinical practice (days 1–21 per 28-day cycle) different to the marketing authorisation (days 1–28 per 28-day cycle)	Yes [a]	3.3
Clinical effectiveness	• Lenalidomide an effective maintenance treatment vs observation alone for people who have had an ASCT	No	3.4

[a]Committee satisfied 21-day dose given in practice, but must take into account licensed dose.
ASCT, autologous stem cell transplant; OS, overall survival; PFS, progression-free survival.

Appraisal consultation document (ACD) conclusions + uncertainties (2)

	Committee conclusion	Requires discussion?	ACD section
Other trials of lenalidomide maintenance	• Company should have presented evidence from other trials of lenalidomide maintenance treatment	Yes	3.5
Safety profile	• Safety profile of lenalidomide as a maintenance treatment compared with monitoring alone likely to be acceptable	No	3.6
Model structure	• Company's model structure does not allow assumptions about subsequent treatments to be explored • Structure has limitations	No	3.7
Company's methods	• Company's methods and rationale for pooling Myeloma XI and CALGB data, and adjusting for treatment switching, unclear	Yes	3.8
Survival extrapolations	• Survival extrapolations should use Myeloma XI data as the main source of evidence but could be supplemented with CALGB data	Yes	3.9

Appraisal consultation document (ACD) conclusions + uncertainties (3)

	Committee conclusion	Requires discussion?	ACD section
Treatment effect waning	• Treatment effect may wane over time • Should have been included in model	Yes	3.10
Subsequent treatment costs	• Costs of subsequent treatments are highly uncertain so scenarios should be presented	Yes	3.11
Dose adjustments and wastage	• Myeloma XI trial data should be used to estimate relative dose intensity	Yes	3.12
Cost-effectiveness estimate	• No analyses reflect the committee's preferred assumptions	Yes	3.13
Other	• No evidence of additional benefits not captured by QALY • No equalities issues	No	3.14

First appraisal committee meeting outcome

- **Cost-effectiveness estimate**
  - Uncertain because company methods not provided in enough detail to be adequately scrutinised
  - None of the company's nor the ERG's analyses reflected the committee's preferred assumptions

- **Recommendations**
  - Lenalidomide is not recommended, within its marketing authorisation, as maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma in adults

Summary of appraisal consultation document (ACD) responses

Consultation responses

Responses received from:

- Celgene (company)
- Myeloma UK
- Public comments - web

Patients + patient organisations: comment themes

- **Significant unmet need**
  - “clear and significant unmet need for lenalidomide maintenance”
  - “the only alternative to the patient is to die faster”
- **Lenalidomide is an effective treatment option**
  - “an incredibly effective, life-extending, safe treatment”
  - “longer quality of life, which is so important to us”
- **Benefits of an oral treatment**
  - “administered orally which, in the current COVID-19 environment, delivers further benefits to patients, families and to the NHS”
- **Frustration, upset and anger at lack of access**
  - “a real whammy for … patients who were diagnosed too late to be part of the UK Myeloma XI trial”
  - “I don't want to keep reading of, and meeting, patients who have short remission times because they are denied drugs that would be available to them in other first world countries”
  - “to know that I currently can't access this drug is devastating”

Summary of company ACD response

Issue	Committee preferences	Company response
Clinical effectiveness	• Present evidence from CALGB and GIMEMA trials	✔
Survival extrapolations	• Survival estimates based on Myeloma XI • CALGB data used to help longer-term extrapolation	?
Treatment switching	• Justification for using the rank-preserving structural-failure time method	✔
Waning of treatment effect	• Include waning of treatment effect in model	?
Subsequent treatment costs	• Should reflect world without CDF treatments • Include 2nd ASCT (5 to 10%) and 2nd line lenalidomide, & other scenarios explored	?
Relative dose intensity (RDI)	• Detailed methods for how RDI calculated (using Myeloma XI data)	?
1 to 28-day scenario	• Scenario reflecting a 1 to 28-day treatment regimen (i.e. marketing authorisation dosing)	?

Clinical effectiveness (1): *Clinical evidence from CALGB and GIMEMA trials*

Background:

- Company identified 4 studies: Myeloma XI, CALGB, GIMEMA and IFM 2005 02
- Applied further criteria – excluded CALGB, GIMEMA, and IFM 2005 02
- But used CALGB (and Myeloma XI) data for survival estimates in model
- ERG: company's approach inconsistent, CALGB and GIMEMA should have been included

Committee's conclusions:

- Myeloma XI (21-day dose) most generalisable, but company should present *all* trials meeting systematic literature review criteria
- And need to see evidence at licensed (28-day) dosage
- NB: top level clinical effectiveness results from CALGB and GIMEMA presented at 1st committee meeting

Company response to ACD:

- Presented clinical evidence from CALGB + GIMEMA

ERG satisfied with company's response

Clinical effectiveness (2): CALGB trial overview

Phase 3, randomised, double-blind, placebo-controlled trial based in US

Country	United States (47 centres)
N	460 (lenalidomide n=231; placebo n=229)
Dosing	10 mg daily, days **1 to 28** of 28-day cycle (as per license)
Comparator	Placebo
Selected eligibility criteria	• Active multiple myeloma • Received ≤2 induction therapies • Stable disease or marginal / partial / complete response after ASCT
Primary endpoint	Median time to progression
Key secondary endpoint	Overall survival
Other	• Dose increases to 15 mg per day permitted • **Treatment switching prior to disease progression permitted** • **Median follow-up = 91 months (vs 31 months in Myeloma XI)** • Note: company used both CALGB and Myeloma XI data to model survival in base cases (at both 1st and 2nd meetings)

NICE **GIMEMA trial also presented by company. Summary available as back-up slide.**

Sources: ERG report section 3.5.2, company submission document B, Tables 5 + 17.

Treatment switching

Company explored alternative methods, but kept RPSFTM as base case

Background:

- CALGB: placebo group could switch to lenalidomide at time of unblinding
- Company used RPSFTM to adjust for treatment switching
- Did not explore any alternative approaches

Committee's conclusions:

- Other methods available; no justification for RPSFTM provided

Company response to ACD:

- Retained RPSFTM in base case with added justification
- Explored alternatives including iterative parameter estimation, inverse probability of censoring weights, and 2-stage methods (next slide)

ERG:

- Noted some concerns but generally satisfied with RPFSTM rationale/results

RPSFTM, rank-preserving structural-failure time method.

Adjusting CALGB and survival extrapolations

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Company adjusted CALGB to reflect Myeloma XI + used in extrapolations

Background:

- Original model: company fitted survival curves to Myeloma XI data only. CALGB used for external validation of curve selection
- After technical engagement: company fitted survival curves to pooled Myeloma XI and CALGB data using fixed covariate effects for treatment and study

Committee's conclusions:

- Use Myeloma XI as main source of evidence where available
- Longer median follow up in CALGB (91 months) vs Myeloma XI (31 months)
- Could use CALGB for longer-term extrapolation when Myeloma XI data not available
- CALGB data should be adjusted to reflect Myeloma XI population and conditional on underlying survival in Myeloma XI

Company response to ACD:

1. Adjusted CALGB data to reflect Myeloma XI, using propensity score weighting (base case) and matching-adjusted indirect comparison (scenario analysis)
2. Fitted survival curves to adjusted CALGB data

Only OS presented – company + ERG agree that PFS not influential on results

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OS, overall survival; PFS, progression-free survival.

Adjusting CALGB to reflect Myeloma XI (1)

Company explored 2 approaches: PSW and MAIC

Propensity score weighting (PSW)

- Uses patient-level data from both trials
- Estimates probability of each patient in CALGB being in Myeloma XI (i.e. the propensity score)
- Propensity scores used to reweight patients in CALGB to match Myeloma XI population
- Issue: reduces effective sample size

Company's base case

Matching-adjusted indirect comparison (MAIC)

- Adjusts for differences in effect modifiers between studies
- Uses individual patient data from CALGB and aggregate data from Myeloma XI
- More weight given to people in CALGB who are more similar to Myeloma XI
- Issue: reduces effective sample size

Company's scenario analysis

Company: MAIC assumptions violated – prognostic factors + treatment effect modifiers different between studies

Adjusting CALGB to reflect Myeloma XI (2)

ERG agrees with company that PSW most appropriate method

For both PSW (base case) and MAIC (scenario) company conduced 2 analyses, adjusting for the following covariates:

- Analysis 1 (base case): ISS scores, age, gender and prior use of lenalidomide
- Analysis 2: Same as 1, but also including a 'response to ASCT' term [a]
  - Company: analysis 2 not presented – results similar between analysis 1 and 2
  - ERG: confirms inclusion of 'response to ASCT' term has little influence on results

ERG critique of company's methods

- Broadly well conducted
- Agrees PSW more appropriate than MAIC

[a] Type of response after ASCT: complete response (CR) or very good partial response (VGPR), vs no CR/VGPR.

ASCT, autologous stem cell transplant; ISS, International Staging System.

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Survival extrapolations (1): company's methods

Fitted curves to PSW-adjusted CALGB data

Company fitted curves to PSW-adjusted CALGB data (without 'response to ASCT' term):

Step 1: assess proportional hazards → **Step 2:** statistical fit (AIC, BIC) → **Step 3:** visual fit and clinical assessment

Explored assumptions about treatment effect,[a] applied to observation arm to predict outcomes for lenalidomide:

Company's base case and ERG's preferred approach

1. Treatment effect from Myeloma XI until month 60, then adjusted CALGB
2. Treatment effect from Myeloma XI at all time points
3. Treatment effect from pooled analysis of CALGB and Myeloma XI at all time points [b]

[a]Company: using CALGB outcomes beyond month 60 would implicitly assume that the hazard ratio becomes that of CALGB at this point; [b]Incorporating covariates to control for study, treatment, and study-by-treatment interaction

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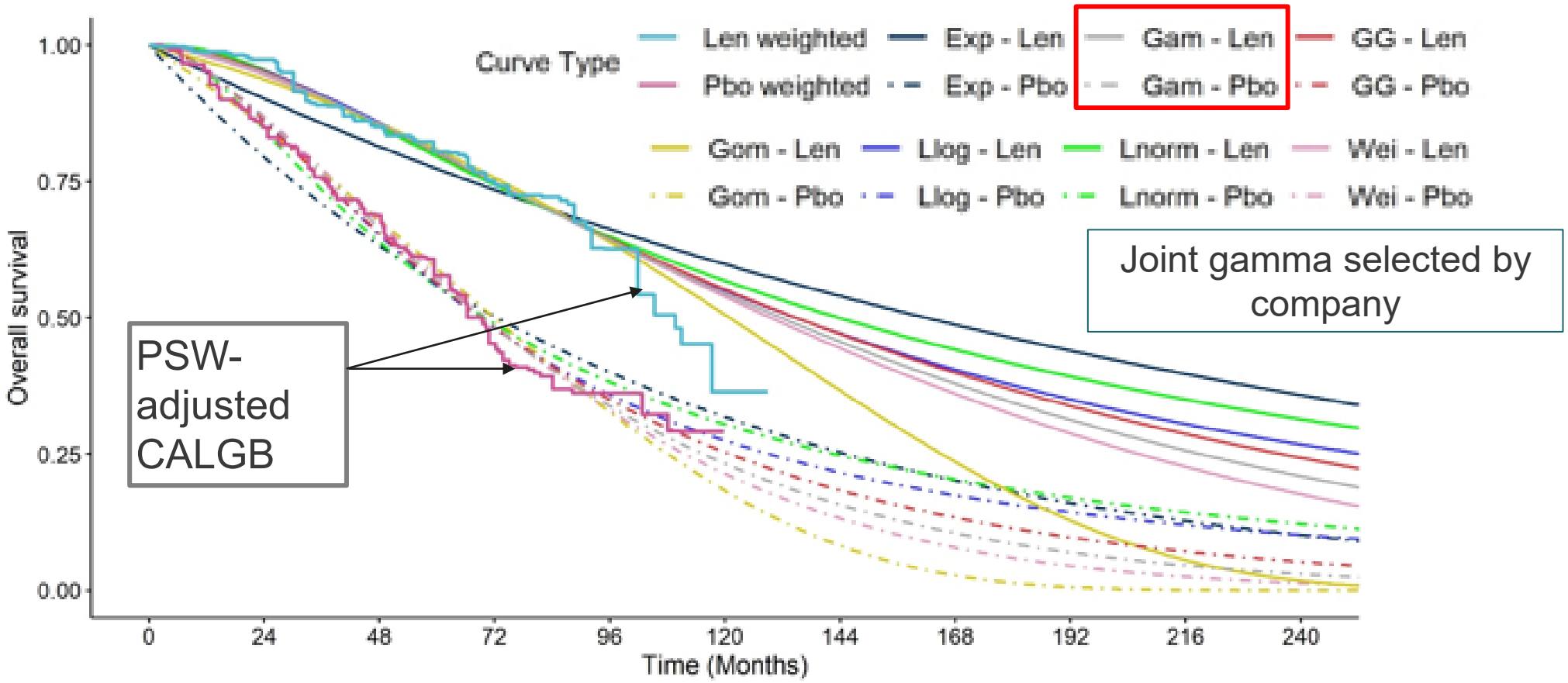
Survival extrapolations (2): Company approach

Company fitted curves to entire CALGB data rather than just post-60 months

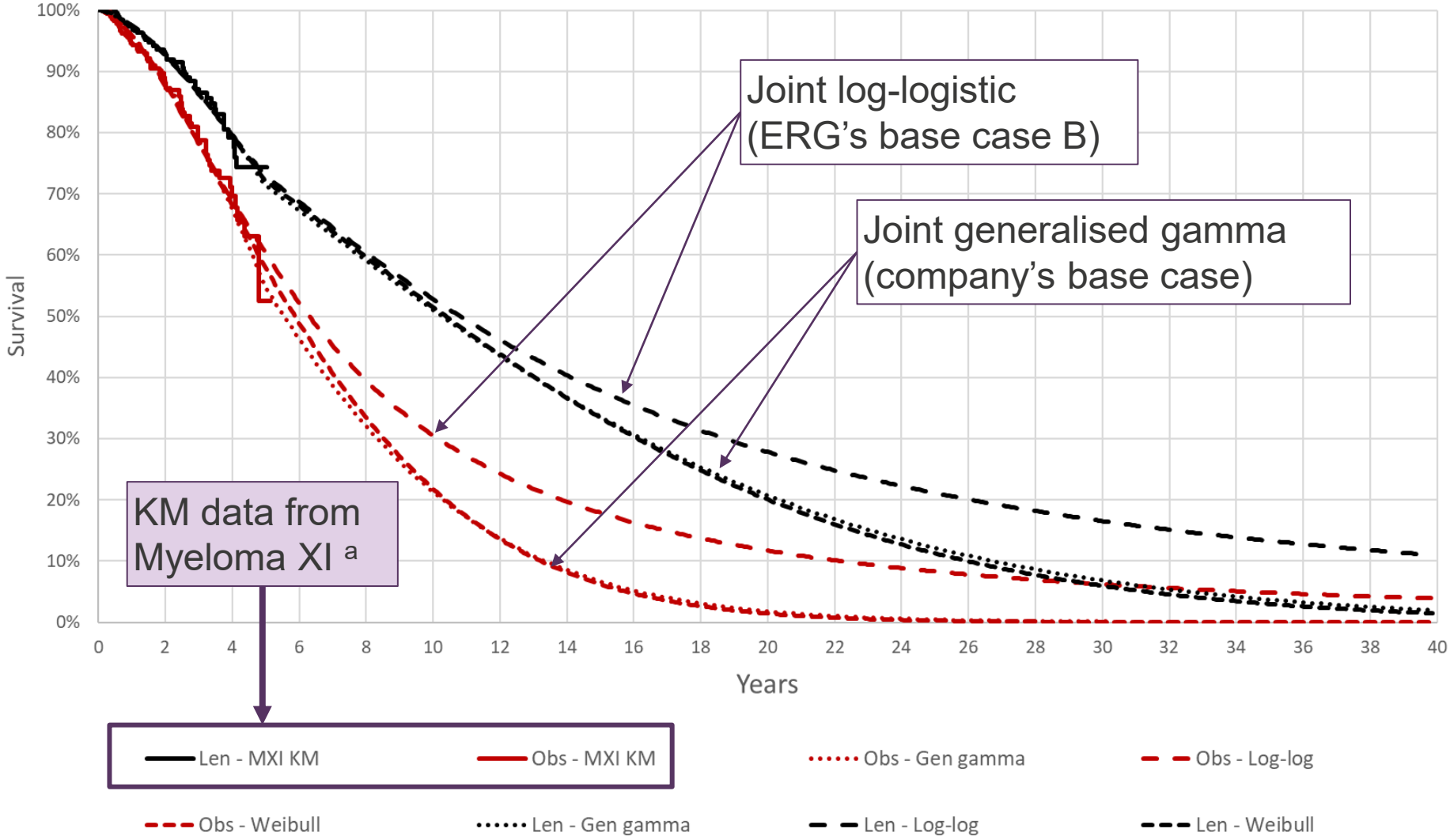


Model	AIC	AIC rank	BIC	BIC rank
Exponential	2003.2	7	2011.5	7
Gamma	1985.9	1	1998.3	1
Generalized Gamma	1987.5	4	2004.1	5
Gompertz	1992.2	6	2004.6	6
Log-logistic	1985.9	2	1998.3	2
Log-normal	1988.0	5	2000.4	4
Weibull	1986.9	3	1999.3	3

Source of figure: Company's addendum to ACD response, Figure 12.

Survival extrapolations (3): ERG approach ?

ERG plotted curve fits for Myeloma XI data followed by PSW-adjusted CALGB – used in company's base case and ERG's base case B



N.B. Gamma not included because not available in company's model. Weibull included because had similar fit to log-logistic for adjusted CALGB data.

NICE [a]ERG would have preferred Myeloma XI for first 60 months then PSW-adjusted CALGB, but this was not available in company's model. Source of figure: ERG critique of company's ACD response, Figure 3.

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Survival extrapolations (4): ERG base cases

ERG presented 2 base case scenarios

- ERG concerned about comparability of Myeloma XI and CALGB trials – not fully addressed in company's analyses
- Also issues with treatment switching (discussed later in presentation)
- Presented 2 of own base case scenarios:

A. ERG's original preferred data source; Myeloma XI data only,

B. Myeloma XI data 60 months then PSW-adjusted CALGB (excluding 'response to ASCT' term[a])

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[a]Excluded to align with company's base (N.B. inclusion of term has little influence on the ICER).

Survival extrapolations (5): ERG critique

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	Company's approach	ERG's comment
Source of data	• Used Myeloma XI (to 60 months) then PSW-adjusted CALGB (post-60 months) as base case data source	• Prefer use of Myeloma XI alone (as per ERG base case in 1st meeting) • If pooled data is to be used, agree company's approach is most appropriate
Selection of curves	• In base case, selected joint generalised gamma to extrapolate OS for Myeloma XI + PSW-adjusted CALGB data [a]	• Company did not explore fitting curves to base case data source – instead selection based on PSW-adjusted CALGB data for the whole time period [a] • No supporting information or rationale provided for selection of generalised gamma
	• Selected curve must be same for initial Myeloma XI period (to 60 months) and adjusted CALGB period (post 60 months)	• Could have explored piecewise approach with 2 different distributions

[a] Company reported that it selected distribution based on fit to adjusted CALGB data alone and picked the gamma as the best fit. However, gamma distribution unavailable in company's model – generalised gamma implemented as base case instead.

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Waning of treatment effect

Company scenario includes treatment effect waning at 10 years

Background:

- Company did not include treatment waning in base case; implies lenalidomide more effective than monitoring for entire model time horizon, even if people stop taking it
- ERG scenario analysis shows cost-effectiveness estimate sensitive to waning
- Clinical experts: lenalidomide unlikely to have continued effect after people stop taking it

Committee's conclusions:

- Treatment effect of lenalidomide may wane over time, so model should reflect this

Company response to ACD:

- Treatment effect waning with lenalidomide unlikely and not verified
- Included treatment waning as scenario analysis, rather than base case:
  - Assumed to lose efficacy at 10 years (just after the end of follow-up in CALGB)

ERG critique:

- Agree there is evidence of constant treatment effect in observed period in CALGB
- But no evidence to support proportional hazards assumption holding indefinitely
- Could not replicate results in company's ACD response – presented own scenarios

Subsequent treatment (1) costs

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Updated scenarios based on Myeloma XI and CALGB

Background:

- Model includes costs of 2nd and 3rd line treatments after maintenance. But:
  - Subsequent therapies in Myeloma XI no longer generalisable
  - CDF treatments given in practice, but cannot be modelled (as per NICE position statement)
- Company and ERG developed subsequent therapy assumptions

Committee's conclusions:

- Assumptions should reflect treatments currently given in NHS, and what would be given in absence of CDF (i.e. approx. 50% lenalidomide 2nd line)
- Rates of 2nd ASCT would be 5% to 10%[a]
- Assumptions are hypothetical, uncertain, and not verified; explore further

Company response to ACD:

- Subsequent therapies given in Myeloma XI and CALGB comparable[b]
- Modelled scenarios that closely reflect these studies, validated by clinical opinion
- Scenarios aligned with efficacy data from studies and reflect real clinical choices before monoclonal antibodies had become available
- NICE team note: no scenarios reflect committee preferred assumptions

[a] In company's previous base case (post-technical engagement), rate of 2nd ACST was 2%;

[b] Subsequent treatments in Myeloma XI and CALGB presented as back-up slides.

Subsequent treatments (2) What does the *ASCT eligible* NICE treatment pathway look like without CDF treatments?

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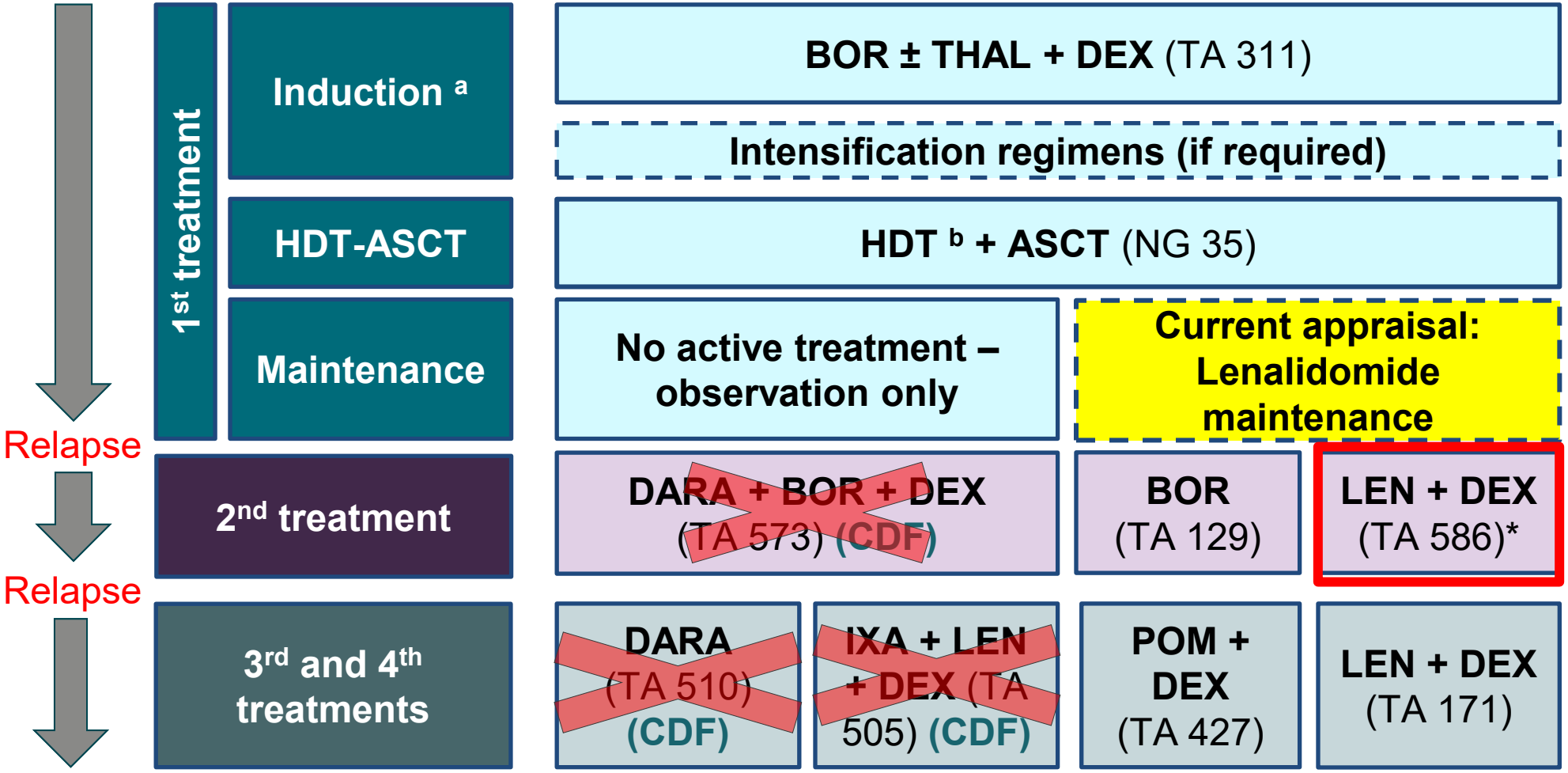

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Subsequent treatments (3): which set of assumptions are most appropriate?

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	Company's base-case at 1st meeting				Company's revised base-case for 2nd meeting				Subsequent treatment assumptions based on ACD [a]			
	2nd line		3rd line		2nd line		3rd line		2nd line		3rd line	
	Len	Obs	Len	Obs	Len	Obs	Len	Obs	Len	Obs	Len	Obs
Len + dex	–	15%	–	65%	–	**10%**	–	65%	–	**50%**	–	**30%**
Bor + dex	60%	60%	20%	10%	60%	60%	20%	10%	**65%**	**30%**	20%	**50%**
Car + dex	–	5%	–	–	–	5%	–	–	**2.5%**	**–**	–	–
Pan + bor + dex	–	–	20%	15%	–	–	20%	15%	–	–	**15%**	**–**
ASCT	2%	2%	–	–	**5%**	**5%**	–	–	**12.5%**	**7.5%**	–	–
Other [b]	33%	13%	50%	5%	**30%**	**15%**	50%	5%	**15.0%**	**7.5%**	**55%**	**12.5%**
No treatment	5%	5%	10%	5%	5%	5%	10%	5%	5%	5%	10%	**7.5%**

Figures that are different versus company's base case at 1st meeting are in red.

[a] Increases len + dex 2nd line in observation arm; [b] Company: assumes cost of chemotherapy.ASCT, autologous stem cell transplant; bor, bortezomib; car, carfilzomib; dex, dexamethasone; len, lenalidomide; obs, observation; pan, panobinistat; pom, pomalidomide. Note: For the purpose of informing the economic model, ASCT is considered in one line which may be under-costed when taking into account the costs of a reinduction regimen.

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Relative dose intensity (RDI) (1)

Company provided more detailed methods for RDI calculation

Background:

- RDI = percentage of prescribed dose that people take
- **Assumptions about RDI can affect cost-effectiveness estimate**
- Company used individual patient data from Myeloma XI to estimate RDI as XXX
- ERG
  - company's RDI estimate too low, so cost-effectiveness estimate optimistic
  - company's methods not clear so RDI calculation could not be validated
  - ERG base case uses alternative estimate from TMM1 trial (94.9%)[a]

Committee's conclusions:

- Myeloma XI data should be used for RDI – directly relevant to the decision problem and was based in the UK
- Company should have provided full methods so ERG could validate approach

Company response to ACD:

- Methods for RDI calculation provided (next slides)

[a] Patients in TMM1 trial received 25 mg lenalidomide (in combo with dexamethasone) on Days 1–21 of 28-day cycles. Trial in relapsed and/or refractory multiple myeloma, people had 1 to 3 prior therapies.

?

RDI (2): Summary of company's RDI calculation

Myeloma XI – dosing adjustments were allowed in trial:

1. Dose reduction: from 10 mg to 5 mg
2. Dose frequency reduction: e.g. dosing on alternate days
3. Intervals: prolong breaks (to >7 days) or shorten treatment periods (to <21 days)

Company used Myeloma XI prescription data to calculate the RDI:

- Analysed number of packs over the duration of therapy for a participant, and number of packs that would be required to cover 100% compliance
  - per protocol treatment for the same patient for the same duration of treatment
- Calculated RDI per treatment cycle (28 days), separately for cycles of 10 mg/day and 5 mg/day
- Incorporated RDI into the model, weighted by the proportion of cycles that were of 10 mg and those that were 5 mg over the total number of treatment cycles

	10 mg dose	5 mg dose
RDI (SD)	XXXXXXXXX	XXXXXXXXX

?

RDI (3): ERG: company's approach remains unclear

Proposes own simplified calculation

ERG critique of company's ACD response:

- Company's approach may be conservative in some areas
- Some inconsistencies in calculations – numbers do not total
- Unable to interpret or re-calculate company's RDI estimates
- Unclear why RDI was separated out by dosing regimens of 5 mg and 10 mg – any reduction of 10 mg dose means reduction in RDI
- Reduced dose of 5 mg being treated separately means true assumed RDI in company's model is lower (XXX)

ERG's proposed new, simplified approach:

- Based on prescribing of packs as opposed to doses received
- XXXXX cycles were 10 mg doses and XXXXX cycles were 5 mg
- Average dose assuming all patients received 21 days at 10 or 5 mg is XXXXX mg (XXX of 10 mg):

$$\frac{(\text{XXXXX} \times 10\text{ mg}) + (\text{XXXXX} \times 5\text{ mg})}{\text{XXXXXX} \times 10\text{ mg (i.e. 100\% compliance)}} = \text{XXX}$$

- Accounts for reduced dose of lenalidomide and non-linear pricing
- Explored effect in ICER in a range of scenarios (presented in Part 2)

NICE

ICER, incremental cost-effectiveness ratio.

?

RDI (4): Overview of RDI assumptions

	Source of data	5 mg	10 mg
Company's base case[a]	Myeloma XI	XXX	XXX
ERG: true assumed RDI in company's base case[b]	Myeloma XI	XXX	
ERG's new simplified approach [c]	Myeloma XI	XXX	

[a] In model, RDI weighted by proportion of cycles that were 10 mg and 5 mg over total number of treatment cycles.
[b] ERG: reduced dose of 5 mg being treated separately means true assumed RDI in company's model is lower.
[c] Not technically a RDI calculation – focuses on what was prescribed rather than what was directly received.

?

Dosing (1) 1 to 28-day treatment regimen

1 to 28-day scenario reflects marketing authorisation

Background:

- Marketing authorisation: 10 mg daily on days **1 to 28** of 28 day cycles
- Company submission + Myeloma XI: 10 mg daily on days **1 to 21** of 28 day cycles
- Company:
  - healthcare professionals familiar with 21 days of dosing
  - safety and tolerability benefits of treatment-free week
  - licence specifies 28 day schedule because based on the CALGB and IFM 2005 02 trials (which used 28 day dosing schedule)
- ERG, patient + clinical experts, stakeholders all agree with company

Committee's conclusions:

- 21 day dosing schedule likely in clinical practice (N.B. this is off label)
- Need to consider 28-day schedule because reflects the marketing authorisation

Company response to ACD:

- Presented results for a 28-day scenario
- Only change versus 21-day base case is costs scaled up to reflect 28-day dosing
- Efficacy curves, time-on-treatment curves, adverse events, resource use, RDI all same as 21-day base case

?

Dosing (2): ERG critique of company's 28-day scenario

Highlighted several concerns

Dosing changed, but effectiveness, time-on-treatment, RDI, MRU and AEs same as 21-day regimen

- MRU likely similar in 21-day and 28-day regimens
- RDI and AEs may differ between the regimens – RDI highly influential on results

Could not replicate company's ICERs

- Due to lack of scenario description and provision of time on treatment curves

NICE

AE, adverse events; MRU, medical resource use; RDI, relative dose intensity.

Innovation and equality: recap

Company considers maintenance therapy with lenalidomide to be innovative:

- It prolongs remission after autologous stem cell transplant
- It is taken orally – this route of administration is generally preferred by patients

Committee's conclusions:

- No evidence to suggest additional benefits not adequately captured by the quality-adjusted life years
- No equality or social value judgement issues identified

Key issues

- Company conducted new analyses to adjust CALGB (longer term supportive trial) to match Myeloma XI (MXI, main trial) – are methods appropriate?
- For survival extrapolations in the model, what is the most appropriate:
  - source of data? i.e. MXI, CALGB, or MXI followed by CALGB?
  - distribution? i.e. generalised gamma etc
- Is the treatment effect of lenalidomide likely to wane over time? If so, at what timepoint should the treatment effect wane in the model?
- What are the most realistic model assumptions about treatments given after lenalidomide maintenance?
  - N.B. Cancer Drugs Fund treatments are given in practice, but cannot be included in model (as per NICE position statement)
- Should the company's or the ERG's estimate of relative dose intensity be used in the model?
- Is the company's representation of a 28-day dosing regimen appropriate?

Back-up slides

GIMEMA trial: overview

Phase 3, 2x2 factorial, randomised, open label trial based in Italy + Israel

Country	Italy and Israel (62 centres)
Design	2x2 factorial design • 1st randomisation: MPR or high-dose melphalan + ASCT • 2nd randomisation: lenalidomide maintenance or no maintenance
N	402 enrolled (1st randomisation n=273; 2nd randomisation n=251)
Dosing	10 mg daily, days **1 to 21** of 28-day cycle
Comparator	No maintenance
Selected eligibility criteria	• Symptomatic, measurable, newly diagnosed multiple myeloma • Aged ≤65 years
Primary endpoint	Progression-free survival
Key secondary endpoint	Overall survival
Other	• Not powered to investigate treatment differences in decision problem cohort • Lack of clear reporting – patient characteristics not provided separately for the ASCT-eligible cohort

ASCT, autologous stem cell therapy; MPR, melphalan–prednisone–lenalidomide.

Treatment switching methods explored by company

Method and how it works	Notes
Simple method: Exclude or censor switchers	• Switching often associated with prognosis (company: not the case in CALGB, so might be suitable)
Rank preserving structural failure time models (RPSFTM): Estimates survival if switching had not occurred	• Relies on 'common treatment effect' assumption [a] • **Company preferred method.** No evidence common treatment effect assumption violated (ERG agree)
Iterative parameter estimation (IPE): Iterative extension of RPSFTM	• Relies on 'common treatment effect' assumption [a] • Assumes survival follows parametric distribution
Inverse probability of censoring weights (IPCW): Switchers censored, non-switchers re-weighted to represent selves + switchers	• Relies on 'no unmeasured confounders' assumption [b] • Prone to error if >90% control switch to experimental • Company: not recommended because n=34
2-stage method: Consider trial randomised until disease progression, then consider observational. Estimate switcher treatment effect, & survival times adjusted. Then estimate experimental treatment effect	• Company: not recommended because only applicable when switching occurs only after disease-related time-point (e.g. disease progression) whereas CALGB switching prognosis driven

[a] Treatment effect received by switchers must be same (relative to time treatment taken for) as the treatment effect received by patients initially randomised to the experimental group.
[b] Data must be available on baseline and time-dependent variables that predict both treatment switching and prognosis.

Subsequent therapy costs: assumptions from 1st committee meeting

	Company's base-case at 1st meeting				ERG's base-case at 1st meeting [a]				Company's scenario at 1st meeting [a]			
	2nd line		3rd line		2nd line		3rd line		2nd line		3rd line	
	Len	Obs	Len	Obs	Len	Obs	Len	Obs	Len	Obs	Len	Obs
Len + dex	–	15%	–	65%	–	–	–	70%	–	–	–	65%
Bor + dex	60%	60%	20%	10%	60%	70%	20%	10%	60%	60%	20%	10%
Car + dex	–	5%	–	–	–	–	–	–	–	5%	–	–
Pan + bor + dex	–	–	20%	15%	–	–	20%	5%	–	–	20%	15%
ASCT	2%	2%	–	–	15%	5%	–	–	5%	5%	–	–
Other [b]	33%	13%	50%	5%	20%	20%	50%	5%	30%	25%	50%	5%
No treatment	5%	5%	10%	5%	5%	5%	10%	10%	5%	5%	10%	5%

[a] Len + dex removed from 2nd line as not part of NICE algorithm; [b] Company: assumes cost of chemotherapy. ERG: assumes cost of cyclophosphamide, thalidomide, and dexamethasone (CTD). ASCT, autologous stem cell transplant; bor, bortezomib; car, carfilzomib; dex, dexamethasone; len, lenalidomide; obs, observation; pan, panobinistat; pom, pomalidomide. Note: For the purpose of informing the economic model, ASCT is considered in one line which may be under-costed when taking into account the costs of a reinduction regimen.

Subsequent therapy costs: comparison of company and ERG base cases at 2nd meeting

	Company's base-case at 2nd meeting (ACD response)				ERG revised base case at 2nd meeting			
	2nd line		3rd line		2nd line		3rd line	
	Len	Obs	Len	Obs	Len	Obs	Len	Obs
Len + dex	–	**10%**	–	**65%**	–	**–**	–	**70%**
Bor + dex	60%	60%	20%	10%	60%	60%	20%	10%
Car + dex	–	**5%**	–	–	–	**–**	–	–
Pan + bor + dex	–	–	20%	**15%**	–	–	20%	**5%**
ASCT	5%	5%	–	–	5%	5%	–	–
Other [a]	30%	**15%**	50%	5%	30%	**30%**	50%	5%
No treatment	5%	5%	10%	**5%**	**5%**	5%	10%	**10%**

Figures that are different between base cases are in red. [a] Company: assumes cost of chemotherapy. ASCT, autologous stem cell transplant; bor, bortezomib; car, carfilzomib; dex, dexamethasone; len, lenalidomide; obs, observation; pan, panobinistat; pom, pomalidomide. Note: For the purpose of informing the economic model, ASCT is considered in one line which may be under-costed when taking into account the costs of a reinduction regimen.

Subsequent treatments received in Myeloma XI

	After 1st relapse		After 2nd relapse	
	Len	Obs	Len	Obs
Lenalidomide + dexamethasone	9%	10%	9%	20%
Daratumumab	0%	0%	1%	2%
Bortezomib + dexamethasone	48%	46%	6%	10%
Carfilzomib + dexamethasone	1%	8%	1%	1%
Thalidomide + melphalan + prednisolone	6%	5%	9%	4%
Ixazomib + lenalidomide + dexamethasone	0%	2%	1%	1%
Panobinostat + bortezomib + dexamethasone	2%	1%	1%	2%
Autologous transplant	3%	1%	0%	1%
Allograft	0%	1%	1%	0%
Bendamustine (alone or combination)	1%	1%	2%	2%
Conventional chemo (e.g. C-weekly, MP, ABCM, CVAD, Z-Dex)	9%	8%	4%	3%
DTPACE or similar	3%	2%	2%	1%
Steroid only	4%	4%	1%	1%
Pomalidomide	1%	2%	11%	11%
Other	0%	0%	0%	0%
No treatment	0%	0%	0%	0%
Daratumumab + bortezomib + dexamethasone	0%	0%	0%	0%

Company: proportions are for the decision problem cohort only

ABCM, Adriamycin, BCNU, cyclophosphamide + melphalan; CVAD, cyclophosphamide, vincristine, doxorubicin + dexamethasone; C-weekly, cyclophosphamide; DTPACE, dexamethasone, thalidomide, cisplatin, Adriamycin, cyclophosphamide, etoposide; MP, melphalan + prednisone; Z-Dex, idarubicine + dexamethasone. Source: company submission appendix, Table 65.

Second line treatments received in CALGB

	Lenalidomide maintenance (n=233)	Placebo (n=229)	Placebo Switchers[a] (n=76)
Any 2nd line myeloma treatment	45.9%	62.9%	48.7%
Bortezomib +/- dexamethasone	16.5% (36%)	12.7% (20%)	15.8% (33%)
Lenalidomide +/- dexamethasone	12.6% (27%) [c]	26.6% (42%)	15.8% (33%)[c]
Other novel drugs / combinations[b]	11.7% (25%)	18.8% (30%)	9.2% (19%)
Thalidomide	6.9%	8.7%	3.9%
Pomalidomide	5.2%	9.2%	7.9%
Carfilzomib	9.5%	10.9%	10.5%
No novel drug	3.5% (8%)	2.6% (4%)	3.9% (8%)
Transplantation	1.7% (4%)	2.2% (3%)	3.9% (8%)
No second-line myeloma treatment	54.1%	37.1%	51.3%
Not progressed	38.1%	21.8%	40.8%
Died before 2nd line	7.4%	1.7%	0.0%
Other	8.7%	13.5%	10.5%

Percentages in brackets are as a proportion of total number of patients treated with 2nd line therapies. [a] Participants switched to len maintenance before progression, as part of study unblinding procedures; [b] Including thalidomide, carfilzomib, pomalidomide; [c] Excluding lenalidomide received by people who had not progressed and were switched to maintenance after study unblinding. Source: Company ACD response addendum (Table 28), referenced to CALGB: clinical study report, 2015 cut-off.