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]

Lead team presentation

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Company: Celgene

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Definitions

Autologous stem cell transplant (ASCT): process of infusing a person's healthy stem cells back into their body
Decision problem cohort: the subgroup of people from the lenalidomide trial relevant to this appraisal
Kaplan–Meier graph: shows survival data from clinical trials
Maintenance: active treatment following ASCT, before first relapse
Observation: no current active treatment for myeloma, but may still have routine medical care (e.g. blood tests)
Overall survival (OS): how long somebody lives
Progression-free survival (PFS): how long somebody lives without experiencing a relapse
Relapse: return of signs, symptoms or laboratory indicators of disease after a period of improvement
Relative dose intensity (RDI): the percentage (or proportion) of the prescribed dose that a person actually received
Subsequent treatment: treatments received after the first relapse (i.e. at 2nd line and later lines)

Key issues

- Lenalidomide dosing regimen in company submission (10 mg every 21 days per 28-day cycle) not aligned with marketing authorisation (10 mg every 28 days per 28-day cycle)
- 4 potentially relevant clinical trials found in company literature review, but company's clinical effectiveness evidence only includes 1 of them (Myeloma XI)
- No adverse event data available for observation arm of target population from Myeloma XI
- Survival dependent on treatments at 2nd line and beyond used in Myeloma XI trial – these are no longer generalisable to UK practice, but company's partitioned survival model structure too simple to allow detailed exploration of issue
- Company and ERG disagree on the use of CALGB 100104 trial data in survival models, leading to different base case approaches
- Company and ERG use different cost assumptions for subsequent treatments in the model – which one best reflects clinical practice?
- Model is sensitive to dose adjustments and drug wastage assumptions but the ERG has concerns with the company's approach

Background

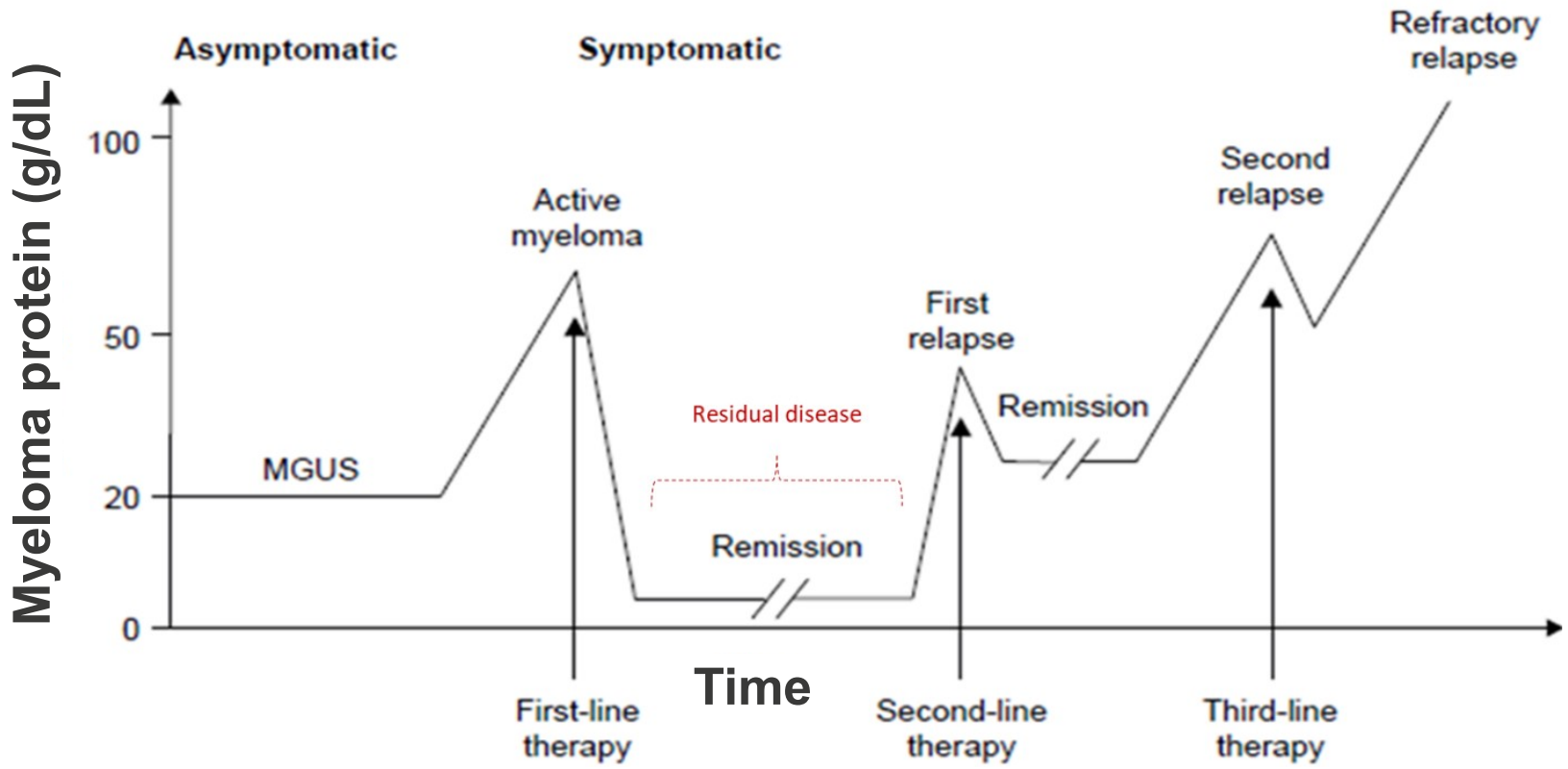
Disease background: multiple myeloma

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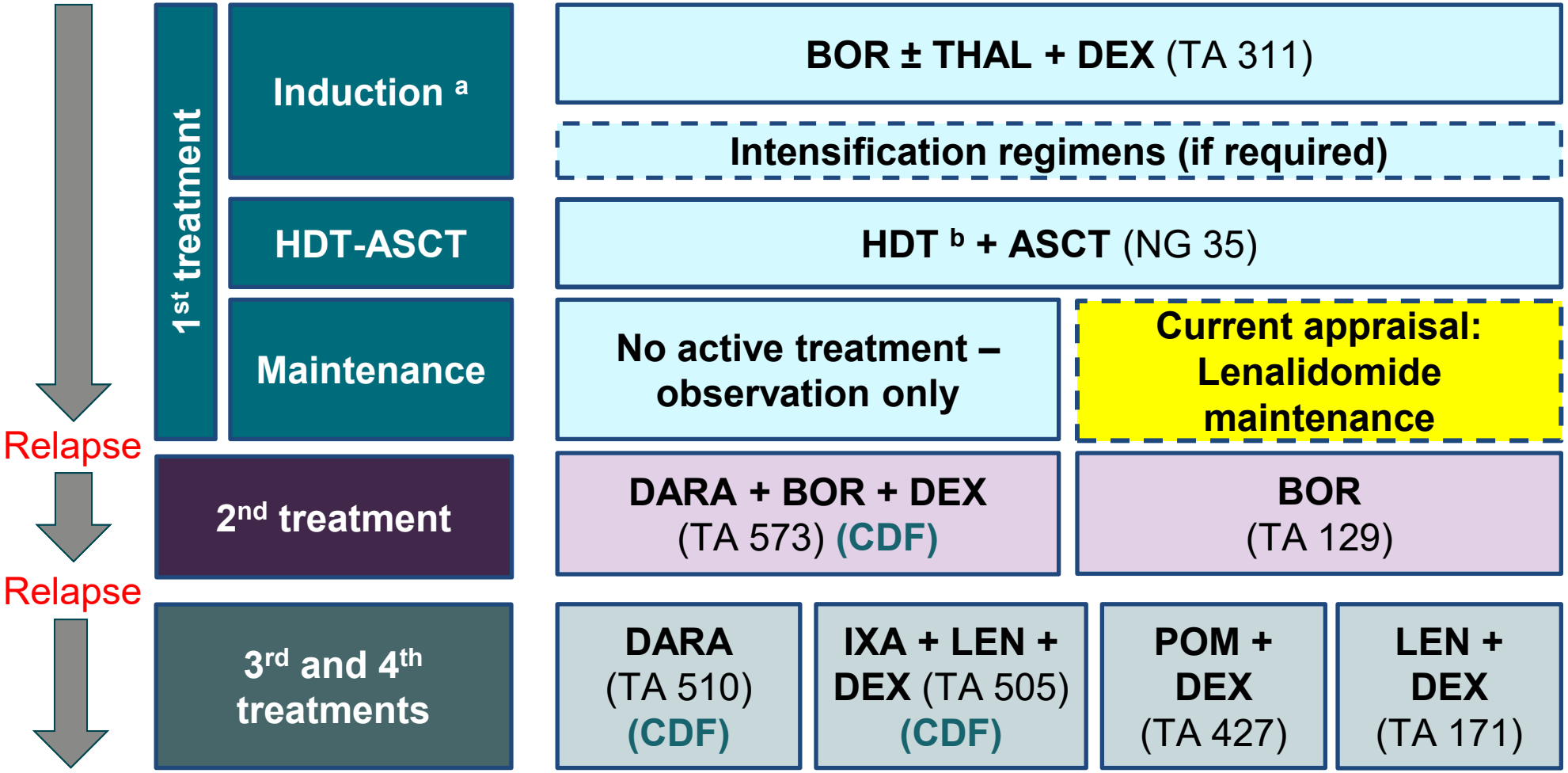
ASCT, autologous stem cell transplant
Post-ASCT consolidation therapy not currently recommended in UK, and was not used in Myeloma XI trial or company submission / model.

NICE recommended treatment pathway: *ASCT eligible (the population for this appraisal)*



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.

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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.

Patient and carer perspectives

Submission from **Myeloma UK**, based on survey of people with multiple myeloma conducted for this appraisal

- Extremely challenging physically and emotionally for patients, carers and family members
- Complications can be significant, debilitating and painful
  - Include: severe bone pain, bone destruction, kidney damage, fatigue, increased risk of increased infections
- People's lives impacted by side effects of treatment and hospital visits
- Lack of control due to increasing reliance on carers and reducing mobility
- Carers report significant emotional, social and practical impact
- People with myeloma value treatments that prolong their life, prolong remission and allow them to enjoy day-to-day life
- There is an unmet need for post-ASCT maintenance therapy
- People who received lenalidomide had a positive experience and would recommend it as a treatment

Professional perspective

- Aims of treatment: prolong overall survival and progression-free survival, and maintain / improve quality of life
- People do not currently receive any maintenance therapy following ASCT; current care is observation (usually 1 to 3 monthly clinic visits)
- Lenalidomide has clear benefits for patients and considered standard of care in Europe and USA – UK is "lagging behind"
  - Note: current appraisal was previously suspended (since 2016) because company did not have access to required data
- Lenalidomide would need more frequent monitoring than observation
  - But healthcare professionals would not need training / education because lenalidomide already established treatment
- People taking lenalidomide as maintenance would be excluded from having it at 2nd or 3rd line
- Some people may have side effects – in most cases manageable

Decision problem

	Final scope	Company submission	Differences from the final scope
Population	People with newly diagnosed multiple myeloma who have had ASCT		
Intervention	Lenalidomide		Dosing in lenalidomide trial and company's model different versus SmPC [a]
Comparator	Established clinical management without lenalidomide maintenance therapy, including monitoring and follow up		N/A
Outcomes	• Overall survival • Progression-free survival • Time to relapse or progression • Adverse effects of treatment • HRQoL		• Time to relapse or progression provided at clarification • N.B. HRQoL not collected in lenalidomide clinical trial

[a] SmPC = 10mg/day on days **1 to 28** of 28-day cycles, anticipated clinical practice and Myeloma X trial = 10mg/day on days **1 to 21** of 28-day cycles (discussed in later slides).

ASCT, autologous stem cell transplant; HRQoL, health-related quality of life; SmPC, summary of product characteristics. Sources: company document B, Table 10 and ERG report, Table 3.

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Clinical effectiveness

Summary of lenalidomide maintenance trials

	Myeloma XI	CALGB 100104	GIMEMA	IFM 2005-02 [a]
Countries	UK	USA	Italy, Israel	France, Belgium, Switzerland
N	[redacted]	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 100104 trial data used in company's base case but not ERG's base case – to be discussed as an issue. EMA, European Medicines Agency.

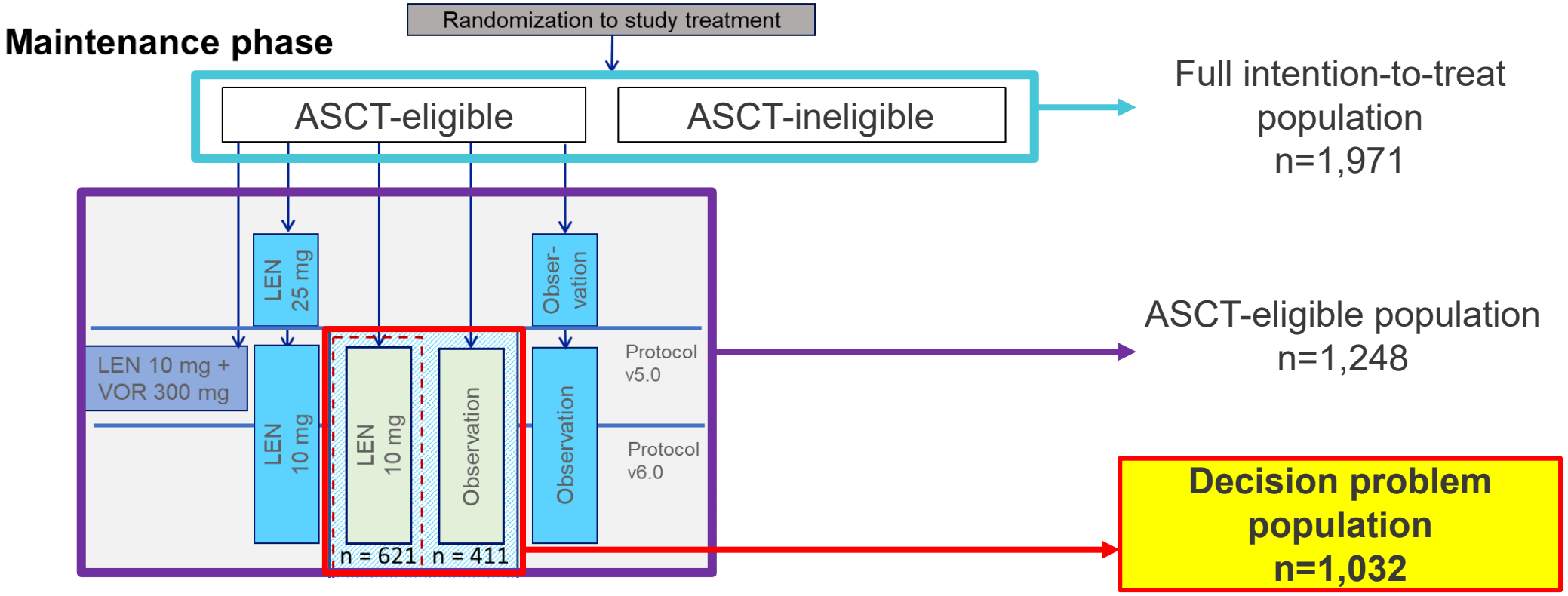
Myeloma XI: trial overview

Phase 3, UK, multicentre, open-label, adaptive-design, randomised trial

- UK study (110 NHS centres)
- Population: newly diagnosed patients stratified by eligibility for ASCT
- Trial design incorporates complex treatment pathway: multiple levels of randomisation and planned comparisons, numerous protocol amendments
- Adaptive design: ongoing trial results used to inform changes in protocol
- Key primary endpoints: progression-free survival[a], overall survival
- Key secondary endpoints: progression-free survival 2[b], response rates
- **Company submission focused on cohort relevant to the decision problem:**
  - **received induction therapy**
  - **then high-dose therapy with melphalan and ASCT**
  - **then randomised to maintenance with lenalidomide 10 mg or observation**
- Trial used to support application for marketing authorisation? **NO**
- Trial used in economic model? **YES**

[a] Time from maintenance randomisation to progressive disease or death from any cause; [b] Time from maintenance randomisation to the date of second progression, start of third antimyeloma treatment or death from any cause (whichever was first). ASCT, autologous stem cell transplant.

Myeloma XI: trial design for cohort relevant to decision problem



- Myeloma XI trial had multiple rounds of protocol amendments
- Only v5.0 and v6.0 are relevant to this appraisal
- Data obtained from October 2017 data cut

ASCT, autologous stem cell transplant; ITT, intension-to-treat; LEN, lenalidomide; VOR, vorinostat.
Figure adapted from company submission document B, Figure 5.

Myeloma XI: design, decision problem cohort

Phase 3, UK, multicentre, open-label, adaptive-design, randomised trial

Selected eligibility criteria for maintenance therapy:

- Aged ≥ 18 years
- Newly diagnosed symptomatic MM or non-secretory MM
- Maximum response ≥4 cycles of randomized induction therapy with CTD, RCD or KCRD with or without up to 8 cycles of VCD

R 2:1

Lenalidomide
10 mg daily on days 1 to 21 of 28-day cycle
([redacted])

Observation
([redacted])

Duration of follow-up = 2 years from recruitment of last participant (median planned follow-up reached [31 months])

Primary endpoints

- **PFS** [a]
- **OS**

Secondary endpoints

- PFS2 [b]
- Response rates

Safety endpoints

- **Adverse events**

Endpoints in bold used in company's model

- Lenalidomide continued until disease progression or unacceptable toxicity (presence of Grade 3 or 4 neutropenia or platelet count <30 x 10^9/L)
- Dose reductions allowed in the case of adverse reactions

[a] Time from maintenance randomisation to progressive disease or death from any cause; [b] Time from maintenance randomisation to the date of second progression, start of third antimyeloma treatment or death from any cause (whichever was first). CTD, cyclophosphamide, thalidomide and dexamethasone; KCRD, carfilzomib, lenalidomide, cyclophosphamide and dexamethasone; RCD, lenalidomide, cyclophosphamide and dexamethasone; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; VCD, bortezomib, cyclophosphamide and dexamethasone. Source: company document B, pages 31 to 41.

Lenalidomide regimen in company submission not aligned with marketing authorisation (1)

Background

- Lenalidomide SmPC: 10 mg once daily on days **1 to 28** of repeated 28-day cycles
- Myeloma XI trial: 10 mg once daily on days **1 to 21** of repeated 28-day cycles
- Company model mostly relies on Myeloma XI data and assumes 1 to 21-day dosing

Company

- 21 days used in Myeloma XI because lenalidomide not licensed for maintenance therapy following ASCT at time of trial – so trial used same dosing schedule as population not eligible for ASCT
- Clinicians are used to 21-day schedule with 7-day break
- Duration of treatment more important than dose – potential safety and tolerability benefits associated with treatment-free week

Lenalidomide regimen in company submission not aligned with marketing authorisation (2)

ERG clinical advisers

- 21 days of treatment per 28-day cycle appropriate and aligned with future NHS clinical practice
- 7-day break in treatment likely to prolong treatment duration
- Both dosing schedules likely have similar efficacy

Stakeholder responses to technical engagement

- 1 to 21 days of a 28-day cycle would be standard in the UK
- Haematologists have experience with this schedule
- 10 mg would be the recommended dose
- Uncertain if 21-day dose same effectiveness as 28-day dose

⊙ *Is lenalidomide 10 mg per day for 21 days of each 28 day cycle an acceptable assumption in the company submission?*

Myeloma XI: clinical effectiveness, decision problem cohort

Trial did not reach median overall survival for lenalidomide arm

	Lenalidomide [redacted]	Observation [redacted]	HR (95% CI)
Selected baseline characteristics			
Median age (IQR)	[redacted]	[redacted]	–
Female, n (%)	[redacted]	[redacted]	–
ISS stage, n (%)			
I / II	[redacted]	[redacted]	–
II	[redacted]	[redacted]	–
III	[redacted]	[redacted]	–
Primary outcome: progression-free survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
Events	[redacted]	[redacted]	–
Censored [a]	[redacted]	[redacted]	–
Primary outcome: overall survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
Events	[redacted]	[redacted]	–
Censored	[redacted]	[redacted]	–

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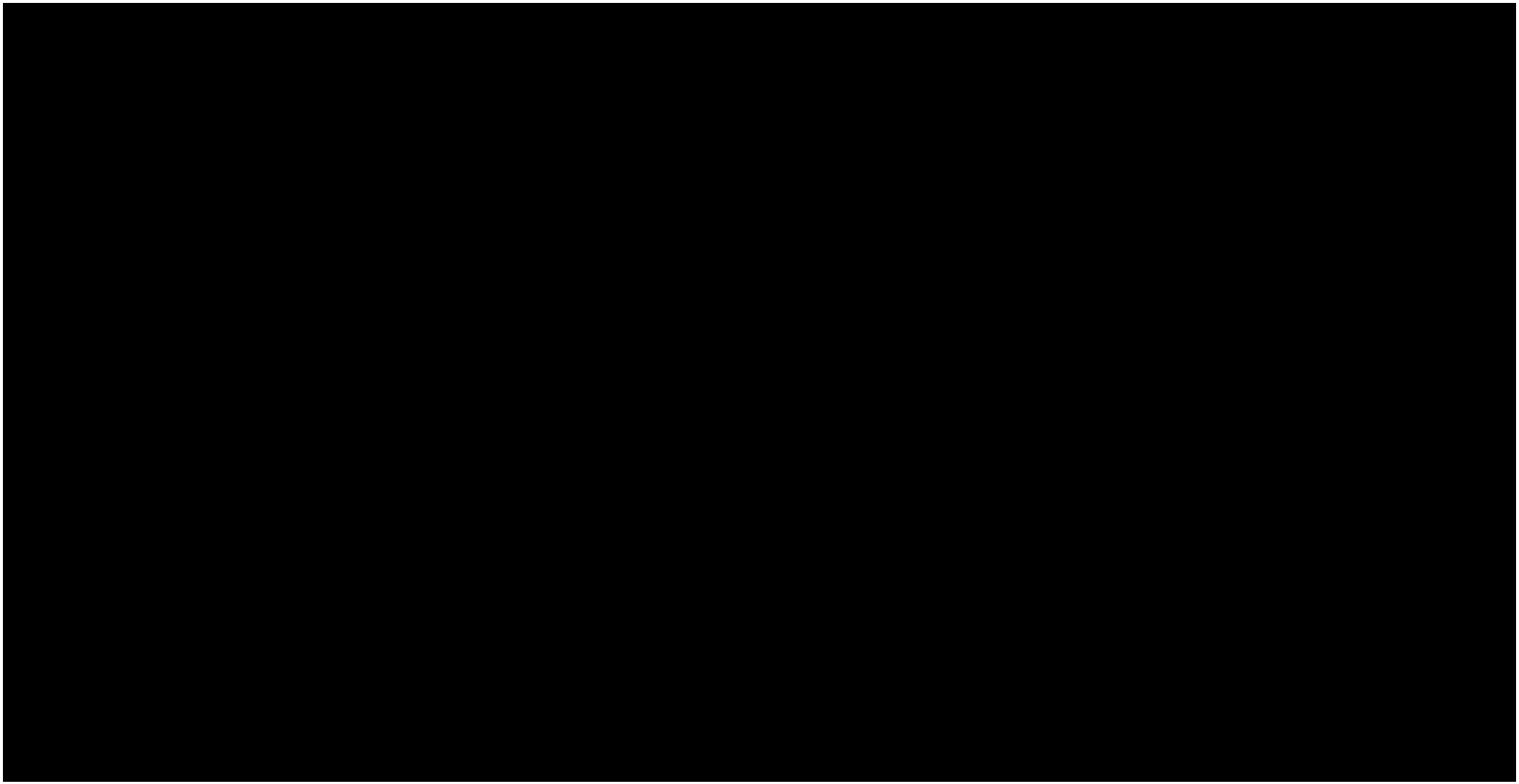
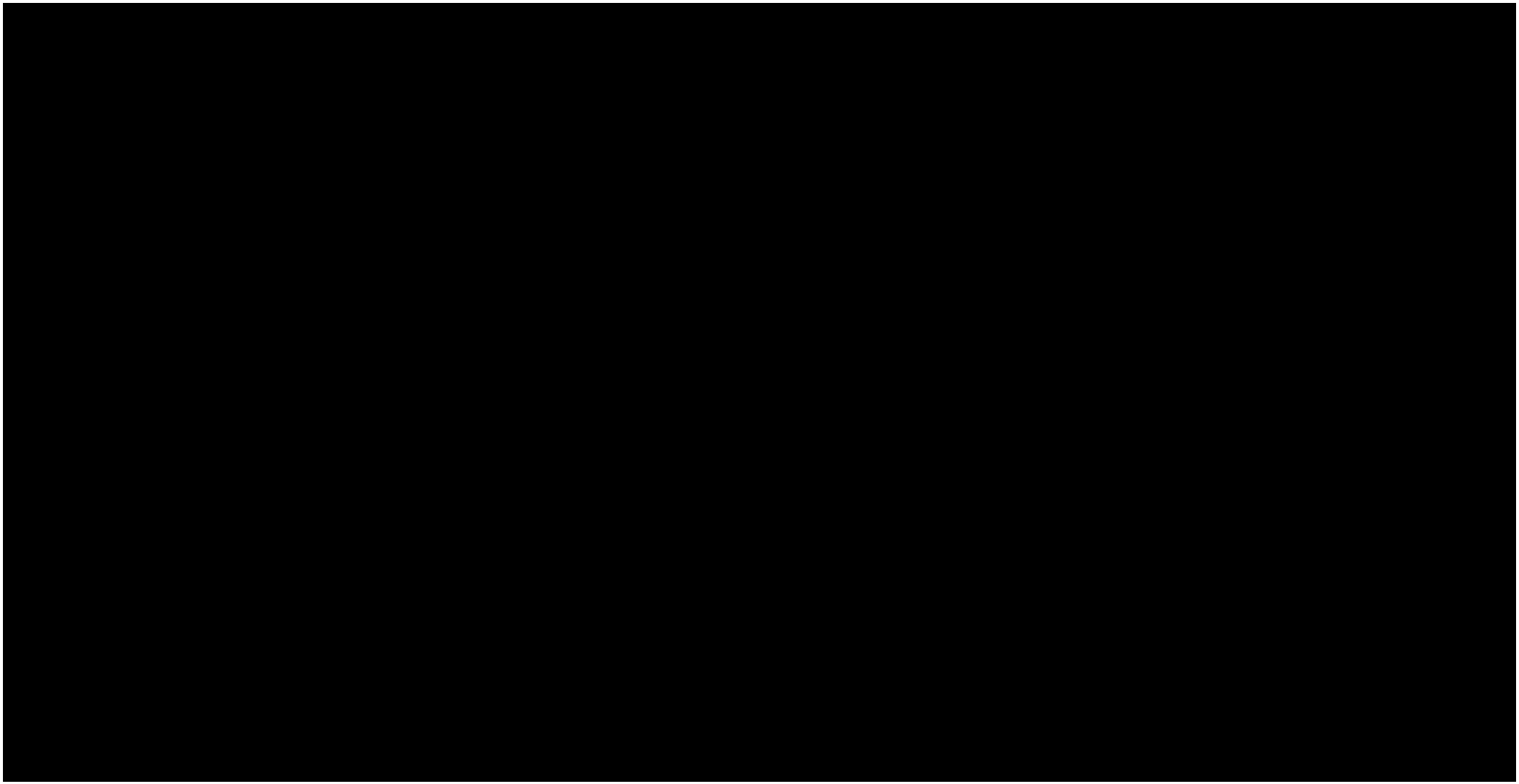
[a] Censored = did not exhibit the outcome during follow-up (i.e. did not relapse or die, discontinued treatment, or died before relapse). CI, confidence interval; HR, hazard ratio; ISS, international staging system; NE, not estimable; NR, not reached. Source: company document B, pages 47 and 48.

Myeloma XI: Kaplan–Meier plot for PFS



PFS, progression-free survival.
Source: company document B, page 49.

Myeloma XI: Kaplan–Meier plot for OS



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OS, overall survival.
Source: company document B, page 50.

Company excluded some potentially relevant trials

Company

- Identified 4 studies in systematic literature review:
  - Myeloma XI, CALGB 100104, GIMEMA, and IFM 2005-02
- Applied subsequent set of criteria to studies after initial systematic review
- Used Myeloma XI for clinical effectiveness (arguing that only trial that reflects decision problem and UK clinical practice) but pooled CALGB 100104 with Myeloma XI for survival estimates in model

ERG

- Company did not pre-specify subsequent criteria to exclude trials (arbitrary rationale)
- CALGB 100104 and GIMEMA trials met inclusion criteria – should have been included in company submission for scrutiny by ERG and committee
- Company should NOT have pooled Myeloma XI and CALGB data for survival estimates in its model as Myeloma XI data are appropriate
- (IFM 2005-02 should be excluded because not applicable to UK practice)

CALGB 100104 trial: overview

Phase III, 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 pooled CALGB and Myeloma XI data to model survival in revised base case (following technical engagement)

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

Meta-analysis, indirect and mixed treatment comparison

- Company did not perform meta-analysis, indirect or mixed treatment comparison of lenalidomide trials (CALGB 100104, IFM 2005-02, GIMEMA and Myeloma XI, all versus placebo) because of a high degree of heterogeneity between the trials
  - ERG agree that evidence synthesis inappropriate due to differences in trials

Source: company document B, pages 50 and 60.

Comparison of clinical effectiveness results between lenalidomide maintenance studies

	Myeloma XI (decision problem cohort) [a]	CALGB 100104 [b]	GIMEMA [c,d]
Country	UK	USA	Italy, Israel
N	[redacted]	460	273
Median follow-up	31 months	91 months	38 months
Primary outcome: progression-free survival			
Hazard ratio (95% CI)	[redacted]	0.53 (0.42 to 0.72)	0.50 (0.31 to 0.80)
Primary outcome: overall survival			
Hazard ratio (95% CI)	[redacted]	0.47 (0.35 to 0.62)	0.72 (0.37 to 1.38)

Comparison between results limited due to differences in trials, e.g. different doses and treatment durations

[a] From company submission document B, Table 15; [b] From Table 9 of ERG report (adjusted values); [c] From ERG's critique of technical engagement response, cited as being reported in McCarthy et al. (2017); [d] Trial was underpowered. CI, confidence interval; HR, hazard ratio.

Comparative safety profile of lenalidomide unclear

No adverse event data available for Myeloma XI observation arm

Company

- In Myeloma XI trial
  - only **serious** adverse events safety data available and only for the full Myeloma XI population
  - does not expect large differences between full Myeloma XI population and decision problem cohort
- Safety profile of lenalidomide is well characterised – used in myeloma for ~15 years
- Provided adverse event data from lenalidomide and observation arms of CALGB 100104 trial at technical engagement – allows between-arm comparison

ERG

- Unclear whether observation arm data for serious adverse events in the full population generalisable to decision problem cohort
- CALGB 100104 data useful to compare between arms but not directly relevant to decision problem cohort – uncertainty remains
- Unlikely lenalidomide would have unacceptable rate of serious adverse events but risks remain unclear

Stakeholder responses to technical engagement

- Lenalidomide likely to have acceptable safety profile

Myeloma XI: adverse events in decision problem cohort

- Analyses based on safety population: [redacted] (People who received at least one dose of 10 mg lenalidomide maintenance). No safety data for the observation arm

Most frequently reported adverse events in lenalidomide group, decision problem cohort

	Grade 1 / 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

⊙ *Are the lack of safety data for the observational arm of the decision problem cohort of significance to this appraisal?*

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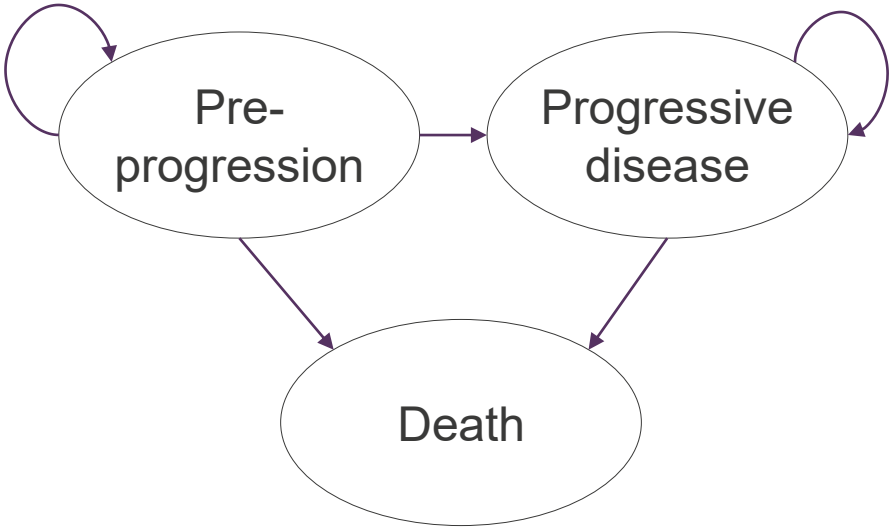
Grade 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = death.
Source: company document B, Table 16.

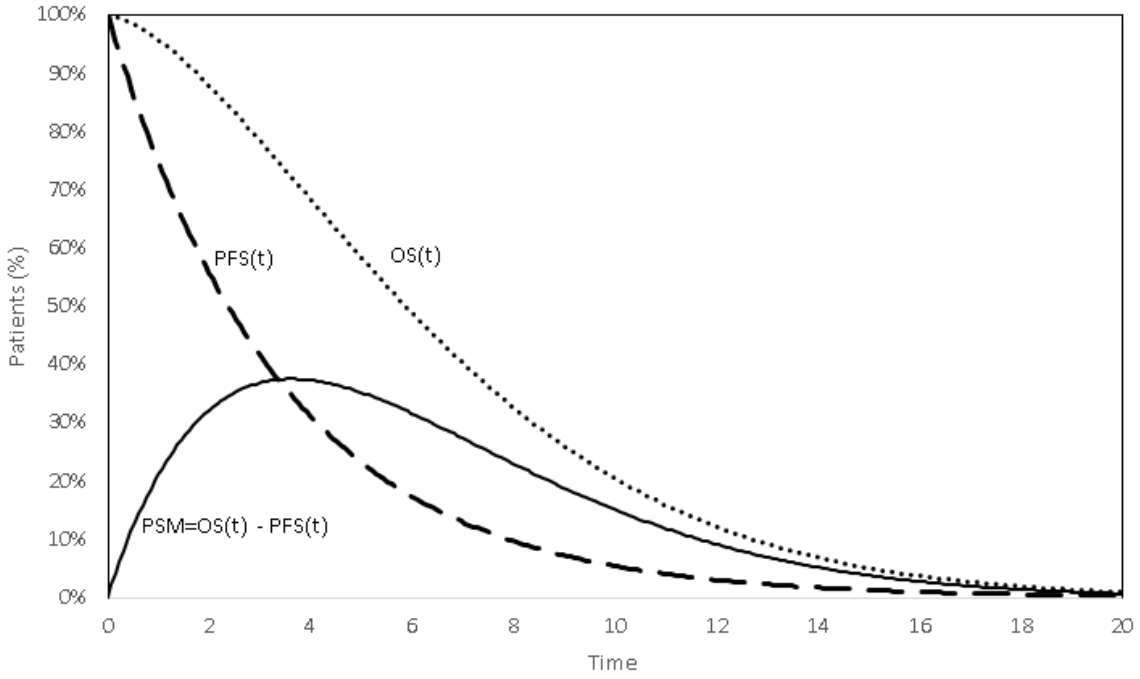
Cost effectiveness

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



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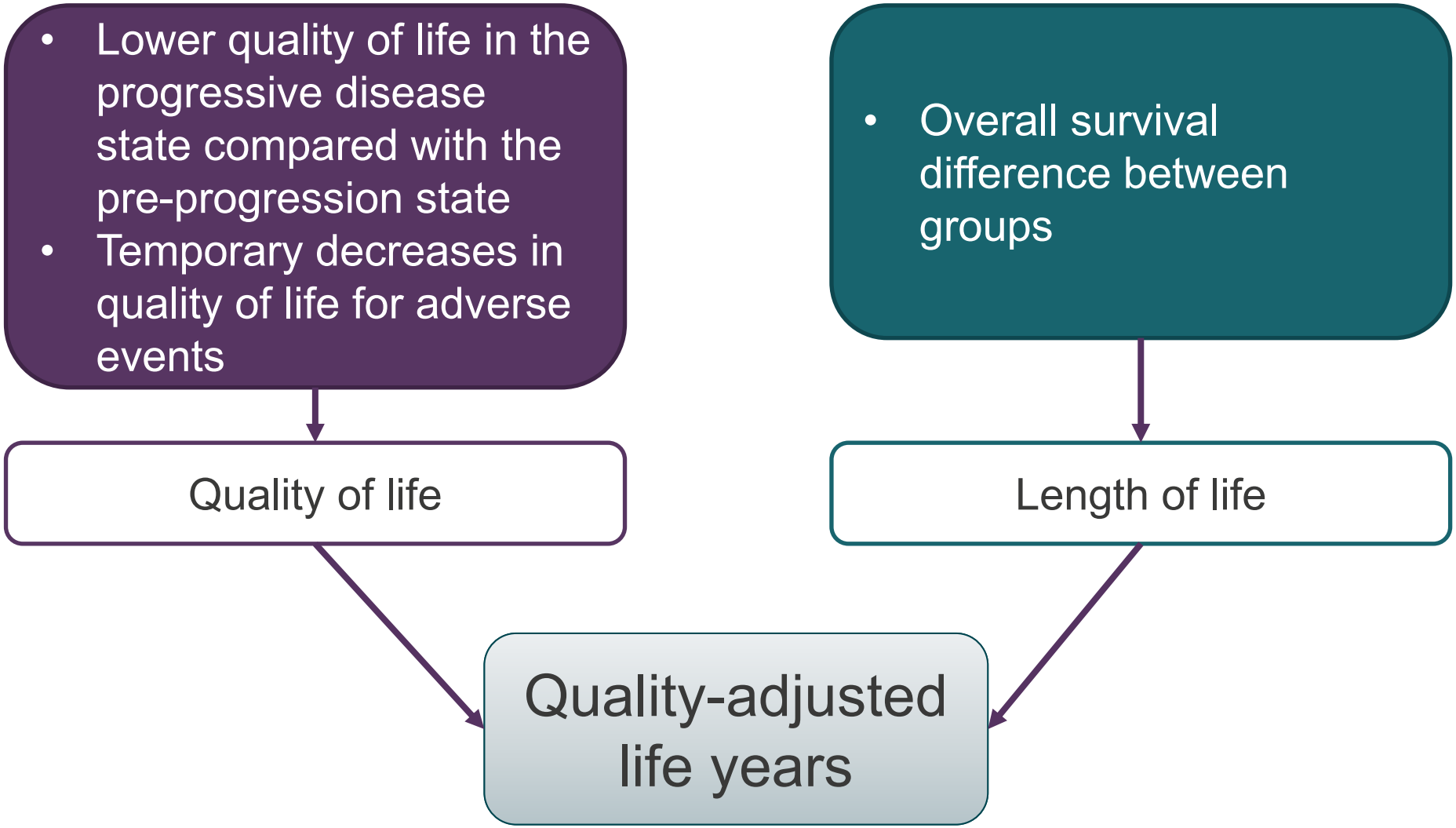
OS, overall survival; PFS, progression-free survival; PSM, progressive state membership; t, time. Source: company document B, pages 64 and 65.

Overview: how quality-adjusted life years accrue



Company's revised base case: key model assumptions

Assumption	Company's justification	Source
Survival extrapolations		
Overall survival: joint model, Weibull	Updated at technical engagement Proportional hazards assumption could not be rejected Curve selection based on model fit statistics and visual inspection	Pooled Myeloma XI and CALGB 100104 trial data
Progression-free survival: joint model, generalised gamma		
Subsequent treatments		
No adjustment was made for effects of subsequent treatments	Limitations of model structure	N/A
Costs adjusted for subsequent treatments	Subsequent therapies in Myeloma XI do not reflect current UK clinical practice	Re-weighted survey from clinical experts

Company's revised base case: key model assumptions

Assumption	Company's justification	Source
Medical resource use and costs		
Lenalidomide costs estimated using TTD: joint model, exponential	Curve selection based on model fit statistics and visual inspection	Myeloma XI
Resource use higher for lenalidomide vs observation	Updated at technical engagement	Clinical advice
AE costs were not included for subsequent therapies	Simplifying assumption, lack of data	N/A
Utility values		
Utilities depend on health state, equal for both arms	No data that show evidence for a lenalidomide-specific utility benefit	Literature (no HRQoL from trials)
Adverse events		
Included Grade 3 or greater occurring in ≥2% of patients	Included AEs expected to affect cost. Utility decrements for these AEs also applied	Myeloma XI
AEs only applied in treatment arm	No active treatment is used in the observation arm	N/A

AEs, adverse events; TTD, time to discontinuation.

ERG generally agrees with company's approach to health state and adverse event utilities

Health state utility values

	Utility value	95% CI	Reference
Pre-progression	0.72	0.69, 0.75	Acaster et al. 2013
Progressive disease	0.67	0.64, 0.70	

Adverse event utility decrements

	Utility decrement	95% CI	Reference
[redacted]	[redacted]	[redacted]	TA510

Two key issues with survival data used in the company's model

1

Survival dependent on subsequent treatments at 2nd line and beyond in Myeloma XI trial – these are no longer generalisable to UK practice, but company's partitioned survival model structure too simplistic to allow detailed exploration of this issue

- (Note this also affects costs – see later issue)

2

Company and ERG disagree on the use of CALGB 100104 trial data in survival models, leading to different base case approaches

- Company pools Myeloma XI and CALGB 100104 data
- ERG uses Myeloma XI data only

1 Subsequent treatments in Myeloma XI are no longer generalisable to UK practice

Subsequent treatments	
Company	• Acknowledges model structure has limitations • Considered multi-state model but limited data to estimate state transitions
ERG	• Survival estimates based on relatively immature Myeloma XI trial data • Subsequent treatments in Myeloma XI no longer generalisable to UK practice (treatment landscape changed during course of the trial) • Structure of company's partitioned survival model does not allow alternative assumptions about subsequent treatments to be explored • N.B. **Modelled survival is based on the effects of subsequent treatments that are not generalisable to NHS practice** • Company's model does not capture uncertainty in cost-effectiveness estimates • **Model limitations mean there is likely to be uncertainty in the ICER**

2 Extrapolating overall and progression-free survival

ERG does not agree with company's use of CALGB 100104 data

Extrapolating OS & PFS: Company's original approach	
Company	• Fitted parametric survival curves to Myeloma XI data and used CALGB 100104 for external validation of curve selection
ERG	• Did not think CALGB 100104 should be used for validation

Extrapolating OS & PFS: Company's revised approach following technical engagement	
Company	• Fitted parametric survival curves to pooled Myeloma XI and CALGB 100104 data using fixed covariate effects for treatment and study. • Selected model based on model statistics and visual fit.
ERG	• Did not request pooling of data and are unclear why the company took this approach. Pooling data is not suitable because: • 1) Differences in trial populations, dosing regimens, need for statistical methodology to account for treatment switching in CALGB 100104 – introduces further uncertainty • 2) Company has not provided sufficient justification for pooling data • Preferred approach: use Myeloma XI data only

Technical team notes company did not provide in-depth methods used for pooling of Myeloma XI data or adjusting for treatment switching in CALGB 100104

⊙ *Was it appropriate for the company to pool data from Myeloma XI and CALGB 100104 trials? Should survival be based on Myeloma XI only?*

Summary of company and ERG base case assumptions: extrapolating progression-free survival

Component	Company original base case	ERG preferred base case	Company revised base case
Trial data	Myeloma XI	Myeloma XI	Myeloma XI + CALGB pooled
Independent/Jointly-fitted	Jointly-fitted	Jointly-fitted	Jointly-fitted
Curve fit lenalidomide	Exponential	Weibull	Generalised gamma
Curve fit observation			

NICE Table adapted from ERG response to technical engagement, Table 1.

Which progression-free survival estimates are more appropriate?

[redacted]

Proportion estimated to be progression-free at 10 years	Company original base case	ERG preferred base case	Company revised base case
Lenalidomide	[redacted]	[redacted]	[redacted]
Observation	[redacted]	[redacted]	[redacted]

Figure source: ERG response to technical engagement, Figure 2

Summary of company and ERG base case assumptions: extrapolating overall survival

Relatively immature data from Myeloma XI – increases uncertainty in survival extrapolations
Important driver of cost effectiveness

Component	Company original base case	ERG preferred base case	Company revised base case
Trial data	Myeloma XI	Myeloma XI	Myeloma XI + CALGB pooled
Independent/Jointly-fitted	Independent	Jointly-fitted	Jointly-fitted
Curve fit lenalidomide	Log-logistic	Log-logistic	Weibull
Curve fit observation	Weibull		
Treatment effect assumption	Consistently improving	Constant	Constant

NICE Table adapted from ERG response to technical engagement, Table 1.

Which overall survival estimates are more appropriate?

Comparison of OS estimates: company original base case, ERG base case and company revised base case

[redacted]

Proportion estimated alive at 10 years	Company original base case	ERG preferred base case	Company revised base case
Lenalidomide	[redacted]	[redacted]	[redacted]
Observation	[redacted]	[redacted]	[redacted]

Figure source: ERG response to technical engagement, Figure 1

Treatment effect of lenalidomide maintenance therapy over time

Company revised base case assumes relative treatment effect remains constant over entire time horizon (40 years)

Treatment waning	
Company	• Assessment of log hazard plot shows hazard likely to remain proportional in long term from Myeloma XI and CALGB 100104 data • Potential waning of treatment effect not supported by the data from Myeloma XI and CALGB 100104
ERG	• Does not include treatment waning effect in base case analysis • In the absence of long-term data (after 5 years), scenario could be plausible • Effect on ICER explored in Part 2

⊙ *Would the efficacy of lenalidomide maintenance therapy be expected to diminish over time?*

Subsequent therapy costs

Company and ERG agree that subsequent therapies in Myeloma XI do not reflect current UK clinical practice.
Assumptions are required about proportions of people receiving different therapies at 2nd line and beyond so costs can be estimated in the model

Subsequent therapy assumptions	
Company	• Conducted survey to elicit types of treatments that would be used after 1st and 2nd relapse from a sample of 8 UK multiple myeloma specialists[1] • Clinical advice – second ASCT highly unlikely in NHS practice • ERG's assumption that 15% of people have second ASCT unrealistic

[1] CDF treatments were removed following clarification and remaining treatments were reweighted. Company revised assumptions following technical engagement.

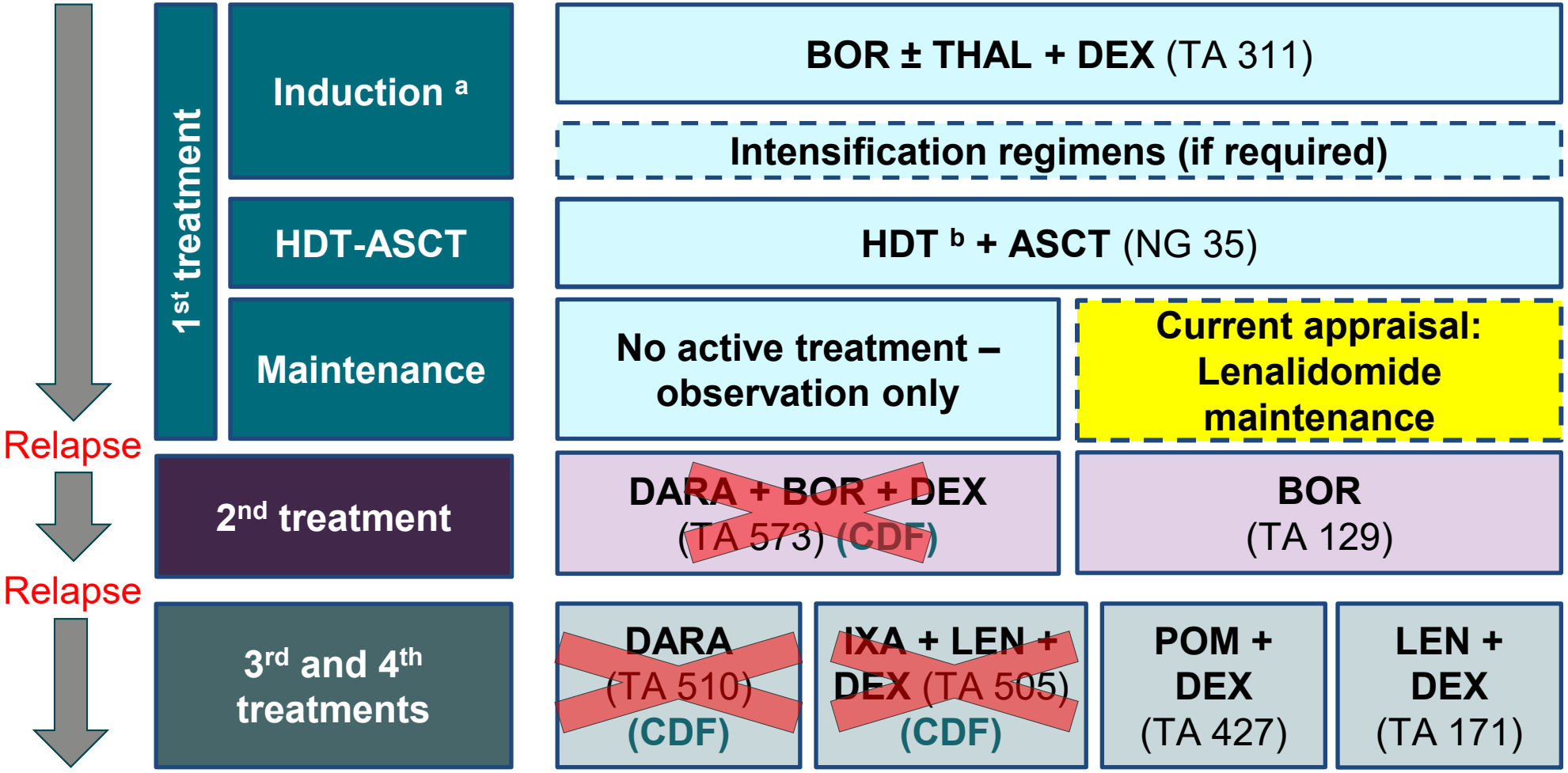
⊙ *Are people likely to receive a second ASCT?*

Subsequent therapy costs

ERG identified issues with company's assumptions

Subsequent therapy assumptions	
ERG	• Disagree with the following company assumptions: 1) Use of lenalidomide 2nd line – not currently reimbursed by NICE 2) Use of carfilzomib at 2nd line – highly unlikely as it is not reimbursed by NICE following treatment with bortezomib (which in current practice would be administered as induction for ASCT) 3) Differences in proportion of patients set to receive 'no treatment' at 3rd line between arms ([redacted] for lenalidomide maintenance versus [redacted] for observation) • NICE policy to omit CDF therapies from analysis - distribution of subsequent treatments used at the 2nd and 3rd line may not reflect NHS practice, creating uncertainty in the pathway following relapse • Developed own set of assumptions based on clinical advice • **ICER is sensitive to assumptions about subsequent therapies**
Stakeholder response	Options outside of CDF extremely limited. Non-CDF options include: • carfilzomib and dexamethasone (for bortezomib naïve patients) • panobinostat with velcade (3rd line) • pomalidomide and dexamethasone (4th line)

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



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.

Subsequent therapy costs: which set of assumptions are most appropriate?

	Company's base-case				ERG's base-case [a]				Company's scenario [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%

⊙ *Which subsequent therapies are people likely to receive?*

[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.

Model is sensitive to dose adjustments and drug wastage assumptions

Lenalidomide dose in Myeloma XI trial: 10 mg on days 1 to 21 of 28-day cycle

Some people deviated from this dosing schedule in the trial and people may miss doses or have dose adjustments in NHS practice

This has implications for cost-effectiveness so important to capture in the model

Relative dose intensity: Company original approach	
Company	• Originally estimated relative dose intensity (RDI) as [redacted]– proportion of average dose / recommended dose of lenalidomide

ERG	• Highlighted concerns with original approach at technical engagement:
	  • numbers of missed or delayed doses unclear
	  • unclear how company's use of RDI accounts for wastage
	  • RDI estimate from Myeloma XI lower than another trial (TMM1[a]) in which dose was higher – counterintuitive
	  • non-linear pricing structure not accounted for
	• So company re-estimated

[a] Patients in TMM1 trial received 25 mg lenalidomide on Days 1–21 of a 28-day cycle. Trial is in relapsed and/or refractory multiple myeloma

Model sensitive to dose adjustments and drug wastage assumptions

Relative dose intensity: Company revised approach	
Company	• Reanalysed lenalidomide consumption data using individual patient data from Myeloma XI • Consider new estimate addresses ERG's concerns – accounts for non-linear price of 10 mg and 5 mg packs, treatment-free intervals, wastage • Updated RDI estimate: [redacted] for both lenalidomide 10mg and 5mg

ERG	• Acknowledge company had to make assumptions to address concerns about dose adjustments and wastage raised in ERG report
	• Some of company's assumptions clear and reasonable
	• Not all assumptions transparent or reported, some difficult to follow – not transparent enough to be validated
	  • ERG did not change own base case
	• Model results sensitive to dose adjustment and wastage assumptions
	• Company's RDI estimate highly uncertain
	• ERG base case uses estimate from TMM1 trial (94.9%)[a]
	  • Also explored scenario with RDI set to 100%

⊙ *Which estimate of the lenalidomide relative dose intensity is most appropriate?*

[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.

Innovation

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

Equalities

No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts

Note: Company did not consider lenalidomide maintenance to be a candidate for 'End-of-life' criteria or Cancer Drugs Fund

Company's model following technical engagement

In response to technical engagement, company made numerous changes to model and base case

ERG

- Identified errors in company's revised model, including incorrect application of some ERG preferred assumptions
  - Corrected errors and presented revised company base case
  - But could not perform full review of the company's revised model – cannot guarantee all errors were identified and corrected
- Validity of the new analysis is questionable
- Note: company incorporated these amends in its revised base case

Issues resolved following technical engagement

- Concerns with the company's systematic review of economic evidence
- Whether medical resource use should differ between treatments and between relapse status

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts

Key issues

- Lenalidomide dosing regimen in company submission (10 mg every 21 days per 28-day cycle) not aligned with marketing authorisation (10 mg every 28 days per 28-day cycle)
- 4 potentially relevant clinical trials found in company literature review, but company's clinical effectiveness evidence only includes 1 of them (Myeloma XI)
- No adverse event data available for observation arm of target population from Myeloma XI
- Survival dependent on treatments at 2nd line and beyond used in Myeloma XI trial – these are no longer generalisable to UK practice, but company's partitioned survival model structure too simple to allow detailed exploration of issue
- Company and ERG disagree on the use of CALGB 100104 trial data in survival models, leading to different base case approaches
- Company and ERG use different cost assumptions for subsequent treatments in the model – which one best reflects clinical practice?
- Model is sensitive to dose adjustments and drug wastage assumptions but the ERG has concerns with the company's approach