NICE National Institute for Health and Care Excellence

Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable [ID1510]

3rd committee meeting

Lead team: Mary Weatherstone, Mark Chapman, Tony Wootton

Chair: Amanda Adler

Evidence Review Group (ERG): Southampton Health Technology Assessments Centre (SHTAC)

Technical team: Ross Wilkinson, Lorna Dunning, Richard Diaz

Company: Janssen-Cilag

4th November 2021

Treatment not recommended

Why committee made recommendations

- Uncertain long-term effects of treatment with **daratumumab** in combination with bortezomib, thalidomide and dexamethasone (DARA+BORT+THAL+DEX)
- Economic model did not incorporate costs and benefits of maintenance with lenalidomide to represent current NHS practice after treatment with DARA+BORT+THAL+DEX
- Cost effectiveness estimates likely too high

Decision problem

Crossed out comparators reflect committee discussion

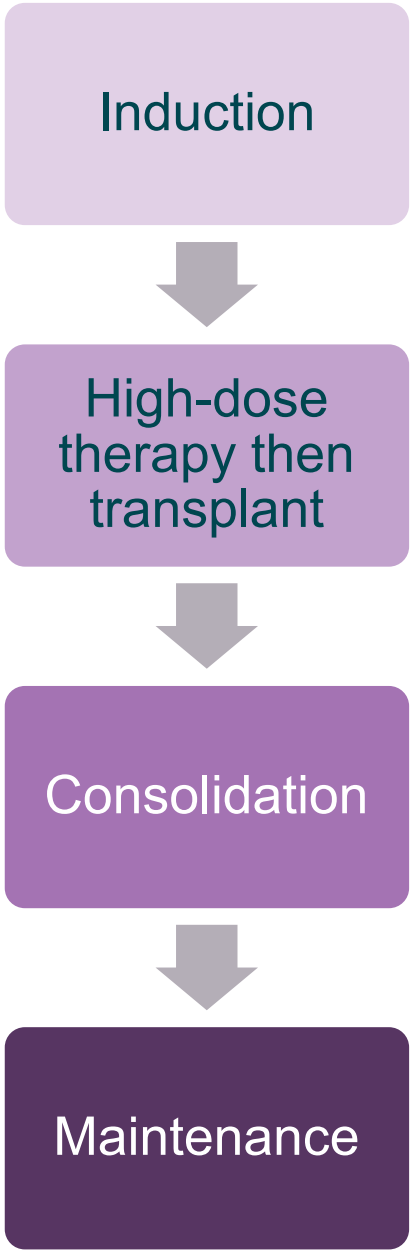
BORT+THAL+DEX relevant comparator for NHS

	Final scope	Company submission
Population	People with previously untreated multiple myeloma eligible for autologous stem cell transplantation	Adults with newly diagnosed multiple myeloma eligible for autologous stem cell transplantation
Intervention	DARA+BORT+THAL+DEX	
Comparators	• ~~BORT+DEX~~ • BORT+THAL+DEX • ~~BORT+CYC+DEX (off-label)~~ • ~~CYC+THAL+DEX (off-label)~~	• ~~BORT+DEX~~ • BORT+THAL+DEX • ~~BORT+CYC+DEX~~
Outcomes	Overall survival, progression-free survival, response rates, adverse effects of treatment, health-related quality of life	

BORT: Bortezomib; DEX: Dexamethasone; THAL: Thalidomide; CYC: Cyclophosphamide

Recap of treatment pathway

Managing newly diagnosed multiple myeloma eligible for autologous stem cell transplant



In NHS 3-drug regimen: BORT+THAL+DEX
bortezomib, thalidomide, dexamethasone (TA311)
Reduces plasma cells in bone marrow

DARA+BORT+THAL+DEX (new treatment) here

High-dose chemotherapy usually melphalan
Kills myeloma cells
Autologous stem cell transplant (ASCT)

Not standard care in NHS to 'deepen' response
But, part of licence and trial; so company includes

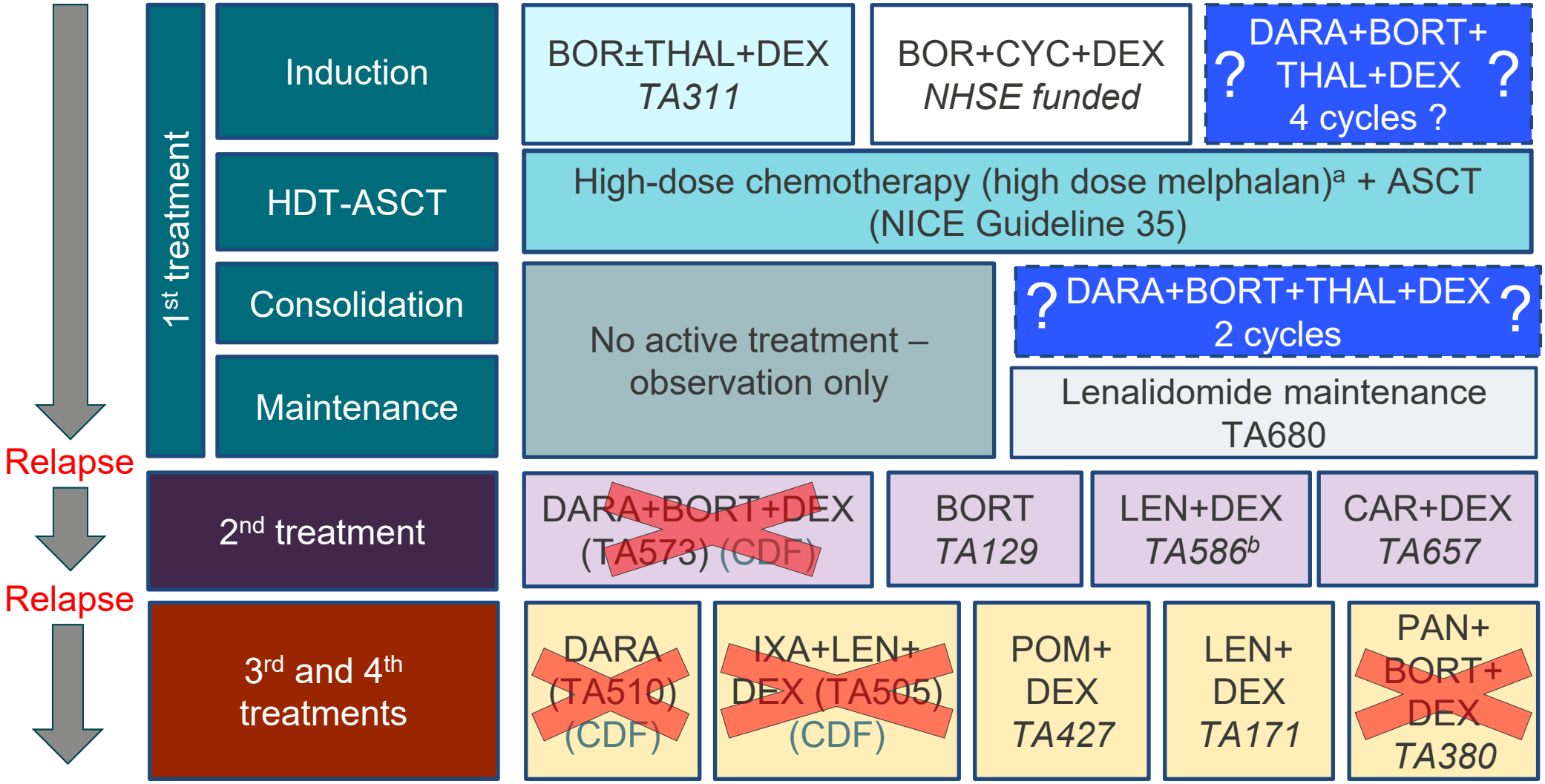
DARA+BORT+THAL+DEX (new treatment) here

Lenalidomide maintenance – (TA 680)
Lengthens time until 1st relapse

Daratumumab (*Darzalex, Janssen-Cilag*)

Marketing authorisation	*'...with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant'*
Administration + dose	• Intravenous (IV) infusion • Subcutaneous (SC) injection also • Trial + licence: 16 mg/kg IV once every week for cycles 1 + 2, followed by every 2 weeks cycles 3 + 4 and consolidation cycles 5 + 6 • Company expects patients prefer SC over IV
Mechanism of action	Human IgG1 kappa monoclonal antibody binds to CD38
List price	1,800 mg vial for SC: £4,320 400 mg IV: £1,440; 100 mg IV: £360 Simple patient access scheme discount available Increased for committee's 3rd meeting

NICE treatment pathway for people eligible for transplant without Cancer Drug Fund treatments



[a] NHS treatment algorithm recommends high-dose melphalan

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

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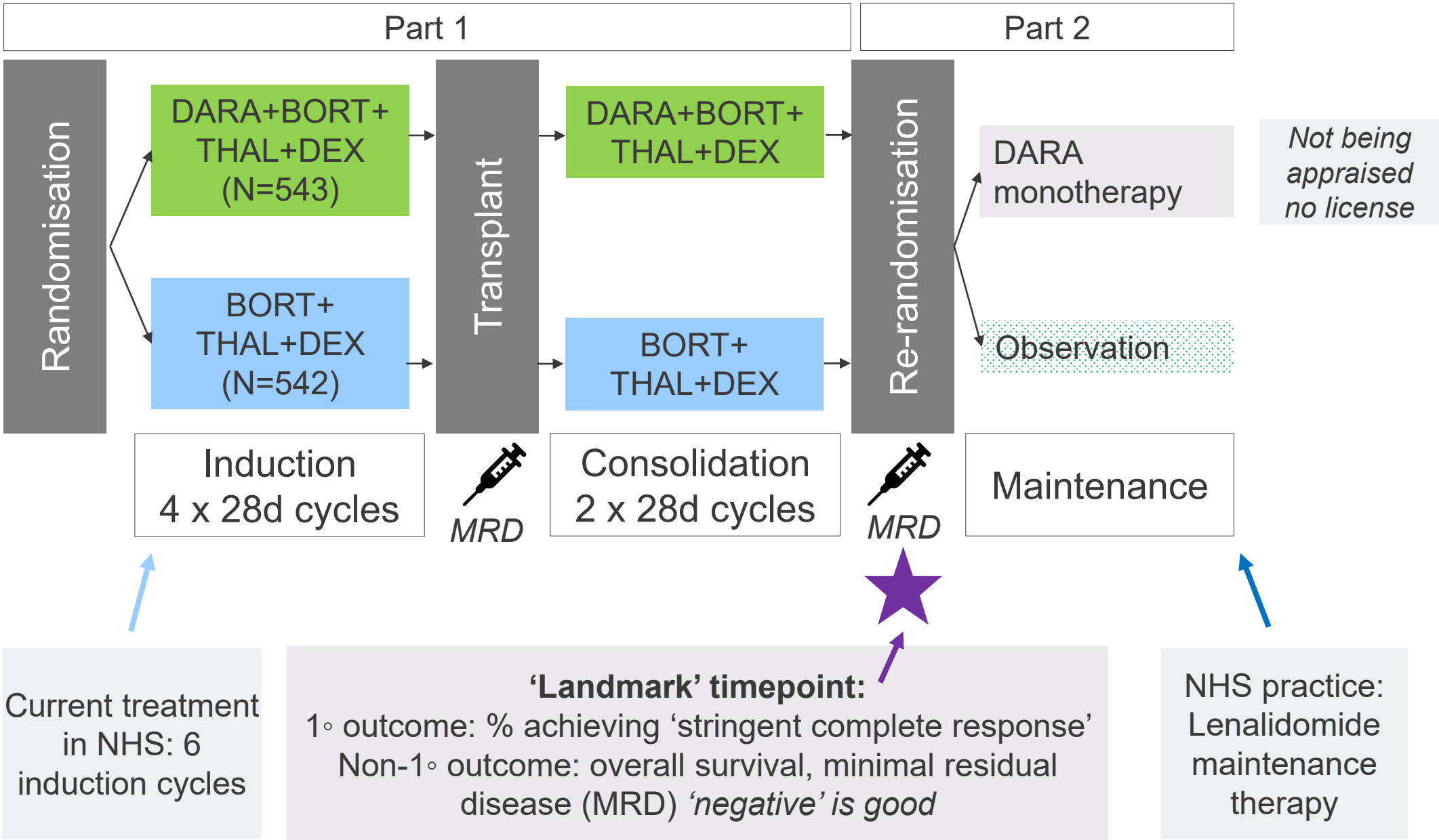
ASCT: Autologous stem cell transplant; CDF: Cancer Drugs Fund; HDT: High-dose therapy

Recap of clinical evidence

Recap: CASSIOPEIA trial overview

Ongoing, phase 3, randomised, open-label, active-controlled trial

DARA + BORT + THAL + DEX given a 2 points



Recap: CASSIOPEIA results

Outcomes favour DARA+BORT+THAL+DEX over BORT+THAL+DEX
Company adjusts for re-randomisation to DARA monotherapy (not in license)
Data split by minimal residual disease status (negative or positive)
'Final' data cut then 2 more

Response outcomes – yes no		Odds ratio (95% CI)	
1◦ outcome Stringent Complete Response		1.60 (1.21 to 2.12)	Median 22.9 months follow up
Complete response or better		1.82 (1.40 to 2.36)	
MRD negative		2.27 (1.78 to 2.90)	
Survival outcomes – time to event		**Hazard Ratio (95% CI)**	
Progression free survival (IPCW adjusted)	MRD Positive	[redacted]	Median 44.5 months follow up
	MRD Negative	[redacted]	
Overall survival (IPCW adjusted)	MRD Positive	[redacted]	
	MRD Negative	[redacted]	

- Company presented 2 analyses to adjust for re-randomisation
  - IPCW
  - Censoring
- Results broadly comparable for PFS, slight differences for OS
- Uncertainty remained because not all relevant prognostic factors measured or included

IPCW: inverse probability censoring weights ; MRD: minimal residual disease

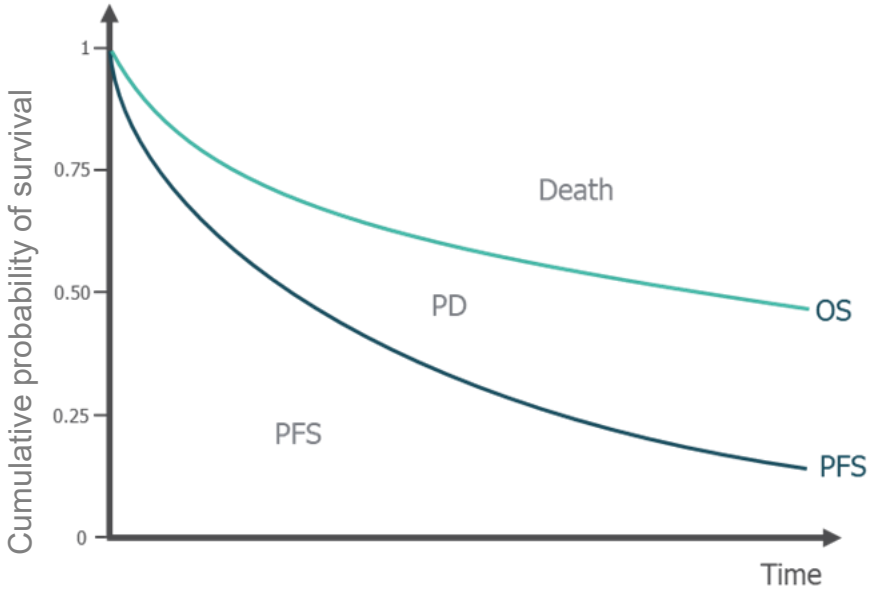
Recap of company's model and modelling approaches

Model summary

PFS, OS extrapolations determined by MRD status post-consolidation

Overview

- Partitioned survival model
- 3 health states: progression free (PFS), progressed disease (PD), death
- Cycle length: 4 weeks
- Time horizon: lifetime
- Comparator: BORT+THAL+DEX



MRD-based modelling

- Survival estimates follow PFS and OS Kaplan–Meier curve for DARA+BORT+THAL+DEX and BORT+THAL+DEX up to around month 9
- Model splits the cohort according to % of the CASSIOPEIA population achieving MRD negativity at the post-consolidation assessment
- PFS and OS extrapolations based on MRD status at the landmark timepoint

MRD status at 'landmark'	DARA+BORT+THAL+DEX	BORT+THAL+DEX
MRD-negative (better prognosis)	64% (95% CI: 60-68%)	44% (95% CI: 39-48%)

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2nd appraisal consultation document ACD Conclusions and uncertainties

2nd ACD conclusions and uncertainties – clinical effectiveness

Topic	Committee conclusion	To discuss?	ACD section
Relevant comparators	BORT+THAL+DEX	No	3.3
Consolidation	Consolidation treatment with DARA+BORT+THAL+DEX could be incorporated into NHS practice	No	3.4
Clinical effectiveness	Adding DARA to BORT+THAL+DEX improved progression free survival and overall survival	No	3.6
Landmark analysis	Company's IPCW-adjusted landmark analysis was likely less biased than naïve censoring approach. IPCW more appropriate for decision making	No	3.7
MRD status	Minimal residual disease negativity likely to predict survival outcomes better than conventional response	No	3.8
Adverse events	Adverse event profile DARA+BORT+THAL+DEX acceptable	No	3.9
Relationship between MRD and survival	Company's landmark analysis acceptable for making decision Meta-analysis on relationship between MRD +/- and survival uncertain, but minimally affects results	No	3.11 3.12

2nd ACD conclusions and uncertainties – modelling assumptions

Topic	Committee conclusion	To discuss	ACD Section
Defining MRD	Company's definition appropriate	No	3.13
Extrapolating survival	For people on BORT+THAL+DEX should use curves fitted to IPCW-adjusted data from landmark analysis	No	3.14
Mean age	Age at induction should be based on NHS	No	3.17
Treatments after 1st line	Model should not include PAN+BORT+DEX as 3rd or 4th-line treatment	No	3.18
Treatment effect waning	Model should include waning, but duration of daratumumab's treatment effect is highly uncertain	**Yes**	3.15
Lenalidomide maintenance	Model should include costs and benefits of lenalidomide maintenance	**Yes**	3.16
Cost-effectiveness	Incremental cost effectiveness ratios (ICERs) likely above range normally deemed cost-effective	**Yes**	3.19

Summary of appraisal consultation document 2 (ACD2) responses

Consultation responses

Responses received from:

- Company: Janssen-Cilag
- Stakeholders:
  Myeloma UK
  UK Myeloma Forum

Summary of company ACD2 response

Company increased discount

Topic ACD	Committee preferences	Addiitonal data provided?	In revised base case?
Lenalidomide maintenance *3.5, 3.16*	Include both costs and benefits of lenalidomide maintenance.	✓	✓
	Should include a longer duration of lenalidomide maintenance for people having DARA at first line compared with those who have not had it.	✓	✗
Duration of Treatment effect *3.15*	Scenario where treatment effect of DARA lasts 10 years or less after consolidation.	✓	✗
Survival outcomes for BORT+THAL+DEX *3.7, 3.14*	Should model survival for people having BORT+THAL+DEX using curves fitted to IPCW-adjusted data from landmark analysis	✓	✗

Lenalidomide maintenance

Lenalidomide maintenance - company

Revised base case includes costs & efficacy of lenalidomide maintenance

Background

Committee conclusion: Economic modelling should include both costs and benefits of lenalidomide maintenance + scenario of longer duration of LEN for people on DARA+THAL+BORT+DEX compared with those who do not

Company response

- Little efficacy data for DARA+THAL+BORT+DEX then LEN maintenance
- Data from Myeloma XI trial
  - *n.b. NHS multicentre, open-label, randomised LEN maintenance vs. observation in newly diagnosed multiple myeloma (main source of evidence, LEN maintenance appraisal TA680)*
- **Duration**
  - Base case: LEN maintenance same duration both treatments
- **Progression Free Survival (PFS)**
  - Additional treatment effect for both arms based on observed PFS HRs by MRD status in Myeloma XI
  - PFS HRs: MRD+ [redacted] MRD- [redacted]
- **Overall survival (OS) – no effect**
  - HRs for OS not significant and associated with wide confidence intervals in Myeloma XI
  - Current modelled OS for BORT+THAL+DEX in this appraisal greater than observed in lenalidomide maintenance arm in Myeloma XI
- **Costs**
  - Generic price for lenalidomide, relative dose intensity (89%), applied consistent with committee's conclusion in TA680.

Lenalidomide maintenance – company cont

Scenario – ↓ effectiveness by 20% DARA+BORT+THAL+DEX

Company response

- **Scenario:** longer treatment duration on LEN maintenance for DARA+BORT+THAL+DEX than comparator to reflect committee's preference
- **Duration:** DARA+BORT+THAL+DEX, MRD-negative receive 18 **additional** cycles
- ~20% increase in drug acquisition costs for lenalidomide
- **Efficacy:** Improved HRs for PFS and OS by 20% for DARA+BORT+THAL+DEX MRD-negative versus BORT+THAL+DEX MRD-negative
- Adjusting HRs equivalent to 0.24 (2.63%) QALY gain
- **Justification:** People who receive additional cycles of LEN maintenance live longer, base case assumes no OS benefit associated with LEN maintenance
- Treatment waning for LEN maintenance applied at between 10 and 25 years in line with TA680, 'Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma'

Lenalidomide maintenance – stakeholders, ERG

ERG 20% improvement arbitrary,

Did sensitivity analysis and scenario analyses restricting lenalidomide to MRD negative

Myeloma UK and UK Myeloma Forum:

- Modelling effects of lenalidomide maintenance on cost effectiveness is challenging
- Encourage committee to take a 'pragmatic and proportionate' approach to uncertainty
- No data evaluating lenalidomide maintenance after induction with DARA+BORT+THAL+DEX
- Welcome to use data from Myeloma XI trial, but acknowledges uncertainty combining data

ERG response:

Base case:

- Company's base case appropriately based on Myeloma XI results
- Not modelling a change to OS in base case is reasonable to reflect survival in standard care

Scenario 1:

- Assume that extended lenalidomide maintenance is restricted to patients with MRD-negative response and accompanied with survival benefits
- Magnitude of changes highly uncertain
- 20% change for both lenalidomide costs + effectiveness is arbitrary
- Sensitivity analysis:
  - Duration of lenalidomide maintenance - additional 12 / 24 months
  - Effect of lenalidomide maintenance 20% reduction PFS only / 10% reduction PFS + OS / 30% reduction PFS + OS

Lenalidomide maintenance – new analyses

Scenarios presented by the company and sensitivity analysis performed by the ERG

Company	**Revised base case**	**Median time to stopping treatment with LEN maintenance (costs):** Myeloma XI, [redacted] months ([redacted] model cycles) **Efficacy**: LEN treatment effect applied to PFS based on hazard ratio by MRD status. Equal for DARA+BORT+THAL+DEX and BORT+THAL+DEX
	Scenario	**Additional duration of LEN maintenance:** DARA+BORT+THAL+DEX: = base case + 18 additional = ~20% ↑ drug costs & efficacy • Applied only to DARA+BORT+THAL+DEX MRD-negative patients most likely to have prolonged time before recurrence • PFS and OS benefit assumed by adjusting PFS and OS hazard ratios downwards by 20%

ERG	**Additional duration of LEN maintenance**	12 additional cycles
		24 additional cycles
	Effect of LEN maintenance	20% reduction PFS only
		10% reduction PFS & OS
		30% reduction PFS & OS

◉ *What is the committee's view on preferred way to model lenalidomide maintenance?*

Duration of treatment effect

Duration of treatment effect

Uncertainty in long term treatment effect DARA+BORT+THAL+DEX

Background:

- **Company:** lifetime treatment effect
- **ERG:** long-term survival benefit uncertain
- **CDF lead:** CASSIOPEIA part 2 suggest that effect has not waned
- **Committee:** Effect after consolidation would likely last 10 years or less

Company response:

- 10-year effect for *DARA+BORT+THAL+DEX* not evidence-based or clinically plausible
- After median follow up 3.7 years - DARA associated with [redacted] reduction in progression or death on 2nd line therapy ('PFS2'), demonstrating lasting benefit
- Revised base case now includes LEN maintenance so lasting *DARA+BORT+THAL+DEX* treatment effect not relevant
- GIMEMA-MMY-3006 study: 10 year median follow up (*BORT+THAL+DEX vs THAL+DEX)*, provides supportive evidence of maintenance of a treatment effect driven by deeper responses.
  - DARA+*BORT+THAL+DEX* proven to have deeper responses than *BORT+THAL+DEX*
- IPCW-adjusted landmark analyses demonstrate depth of response

Base case: Company models lifetime treatment effect but includes LEN maintenance treatment waning

Scenario 2: waning between 10–25 years

Scenario 3: treatment effect ends at 10 years

Duration of treatment effect – stakeholders + ERG

Myeloma UK and UK Myeloma Forum:

- Clinical opinion and evidence does not support treatment effect lasting < 10 years
- No treatment waning for *DARA+BORT+THAL+DEX* in CASSIOPEIA trial after 4 years
- If treatment waning applied in this appraisal, should be consistent across appraisals
  TA for lenalidomide maintenance - waning applied between 10 and 25 years
- *DARA+BORT+THAL+DEX* given for short duration so less chance of developing resistant disease that alters long term outcomes
- GIMEMA comparing BORT+THAL+DEX vs THAL+DEX 10 year median follow up no waning

ERG response:

- Do not agree with company's base case which has a lifetime treatment effect

Reiterated:

- Company's model structure already 'hard wires' treatment effect from inducing and consolidating MRD negative response
- Evidence from CASSIOPEIA for additional survival benefits within MRD groups uncertain, with wide confidence intervals: HRs for DARA+BORT+THAL+DEX vs. BORT+THAL+DEX
  - [redacted] for MRD-positive
  - [redacted] for MRD-negative

Scenarios:

- Gradual loss of DARA's effect starting at year 5 and ending at year 10
- Sudden loss of DARA's effect at year 5

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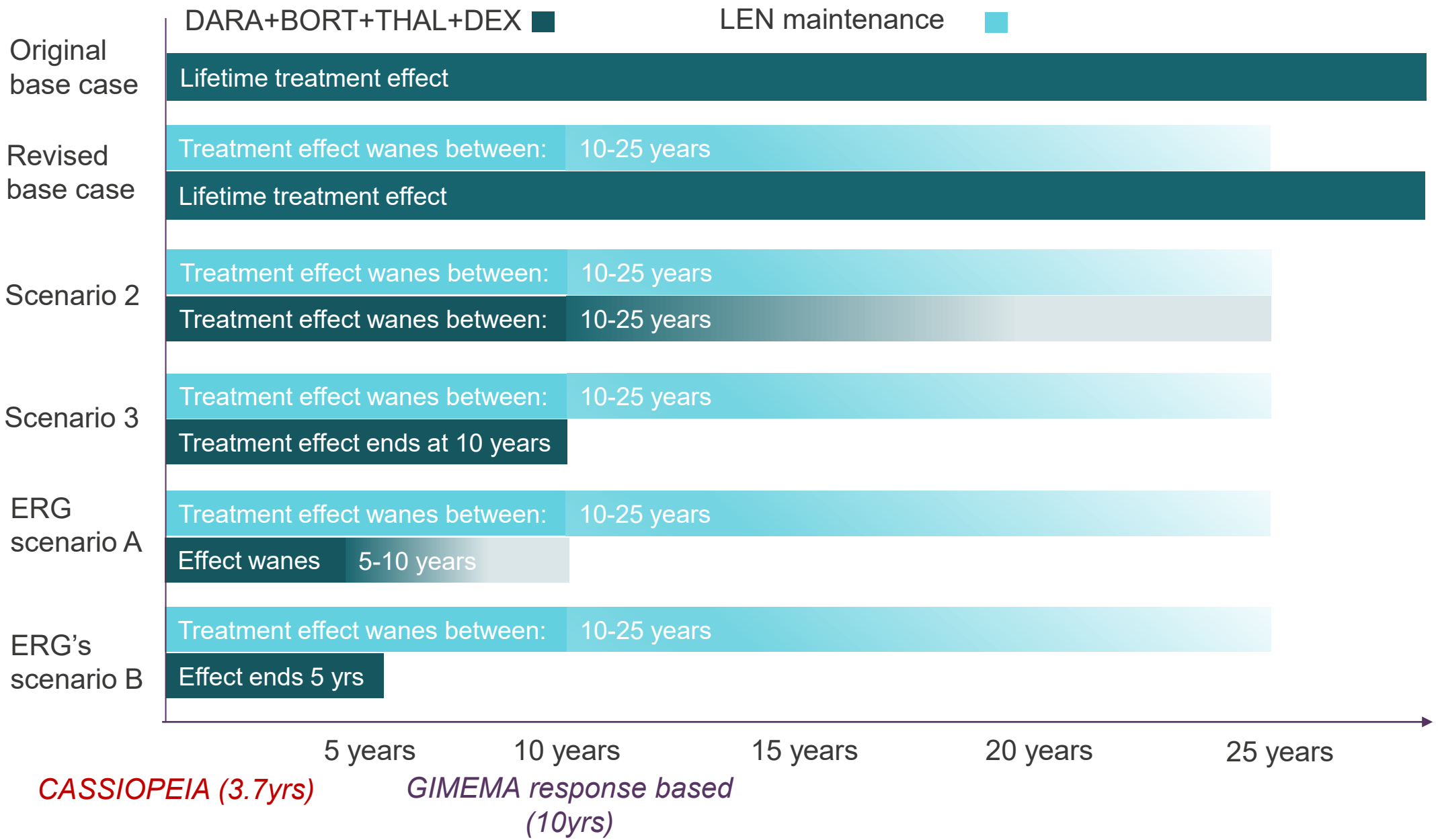
Duration of treatment effect - scenarios



◉ *Has the committee seen new evidence that changes its decision?*

Extrapolating overall survival

Landmark analysis + extrapolating survival

Company states no residual confounding and model overestimates OS for BORT+THAL+DEX, so cost-effectiveness results 'conservative'

Committee conclusion :

- IPCW-adjusted landmark analysis less biased than censoring
- But, residual confounding remains
- Should model survival for BORT+THAL+DEX using curves fitted to IPCW-adjusted data from landmark analysis

Company Response

- No residual confounding as all patients followed-up in part 2 were re-randomised
- Model overestimates OS for BORT+THAL+DEX; estimates based on post-consolidation response rates; exceeded company clinical expert opinion and Myeloma XI trial

ERG Response:

- Confounding remains - informative censoring and missing prognostic factors
- Comparing modelled extrapolations with clinical opinion and data from external sources is uncertain
- Difference between model estimates and Myeloma XI survival outcomes quite small
- Survival rates observed in BORT+THAL+DEX arm of GIMEMA study remarkably similar to extrapolations from the company's revised base case

Landmark analysis + extrapolating survival

Company's predicted survival rates from revised base case compared to other sources

Data Source	% alive at time (months)						
	12	18	24	36	48	60	120
BORT+THAL+DEX							
Company revised base case[a]	97%	95%	92%	88%	83%	79%	62%
CASSIOPEIA	98%	95%	93%	-	-	-	-
GIMEMA study	-	-	-	86%	-	79%[b]	60%
Clinical opinion[c]						≈70%	50–60%
Standard of care[d] + lenalidomide maintenance							
MYELOMA XI[e]	96%	94%	92%	88%	79%	73%	-

◉ *What is the committee's view on the modelled survival estimates for BORT+THAL+DEX?*

a: Excl. efficacy uplift for lenalidomide maintenance, b: Janssen estimate based on visual inspection of the published Kaplan-Meier curves from Tacchetti et al. 2020, c: Clinical opinion from ACM1, d: CTD: cyclophosphamide, thalidomide, and dexamethasone, RCD: lenalidomide, cyclophosphamide and dexamethasone, KCRD: carfilzomib, cyclophosphamide, lenalidomide and dexamethasone, e: Estimated from Kaplan-Meier, transplant-eligible

Innovation

Stakeholders and clinical experts believe DARA+BORT+THAL+DEX is innovative

Company: Innovative - different mechanism of action from other treatments

Committee: DARA+BORT+THAL+DEX may improve survival, but no additional gains in health-related quality of life over those included in QALY calculations

Myeloma UK:

- Innovative
- Psychological benefits – people receive a treatment with improved chances of achieving MRD-negative status
- May mean a treatment free period and opportunity to receive lenalidomide later

Clinical experts:

- DARA's innovative mechanism extending treatment-free period will positively impact quality of life for people receiving treatment and care givers

No new equalities issues identified

◉ Has the committee heard evidence to change its view that there are QALY benefits not accounted for in model?

Cost-effectiveness results

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