NICE National Institute for Health and Care Excellence

For public observers: confidential information redacted

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

2nd 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: Emily Leckenby, Ross Wilkinson, Charlie Hewitt, Nicole Elliott

Company: Janssen-Cilag

7th July 2021

Decision problem

Company excludes CYC+THAL+DEX as comparator

	Final scope	Company submission
Population	People with previously untreated multiple myeloma eligible for autologous stem cell transplantation (ASCT)	**Adult patients** with newly diagnosed multiple myeloma eligible for ASCT
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 (off-label)
Outcomes	Overall survival, progression-free survival, response rates, adverse effects of treatment, health-related quality of life (HRQoL)	

Daratumumab not recommended

Why the committee made these recommendations

- Long-term effects of treatment with daratumumab uncertain
- Unclear if company's survival modelling using a 'landmark analysis' split by minimal residual disease status more robust than fitting models directly to whole population data from trial
- Company's censored landmark analysis was likely biased, which made modelling for overall survival for BORT+THAL+DEX uncertain
- Economic model did not reflect NHS clinical practice because it did not include lenalidomide maintenance
- Cost effectiveness estimates were likely too high to be acceptable

BORT: Bortezomib; DEX: Dexamethasone; THAL: Thalidomide

Recap of clinical evidence and company's model

Managing newly diagnosed multiple myeloma

- ~ 1 in 3 newly diagnosed in UK eligible for autologous stem cell transplant (ASCT)
  - Eligibility based on age, performance status, comorbidities
- Treatment involves:

  1. 'Induction'
  - 3-drug regimen: bortezomib, thalidomide, dexamethasone (TA311) BORT+THAL+DEX. To reduce plasma cells in bone marrow

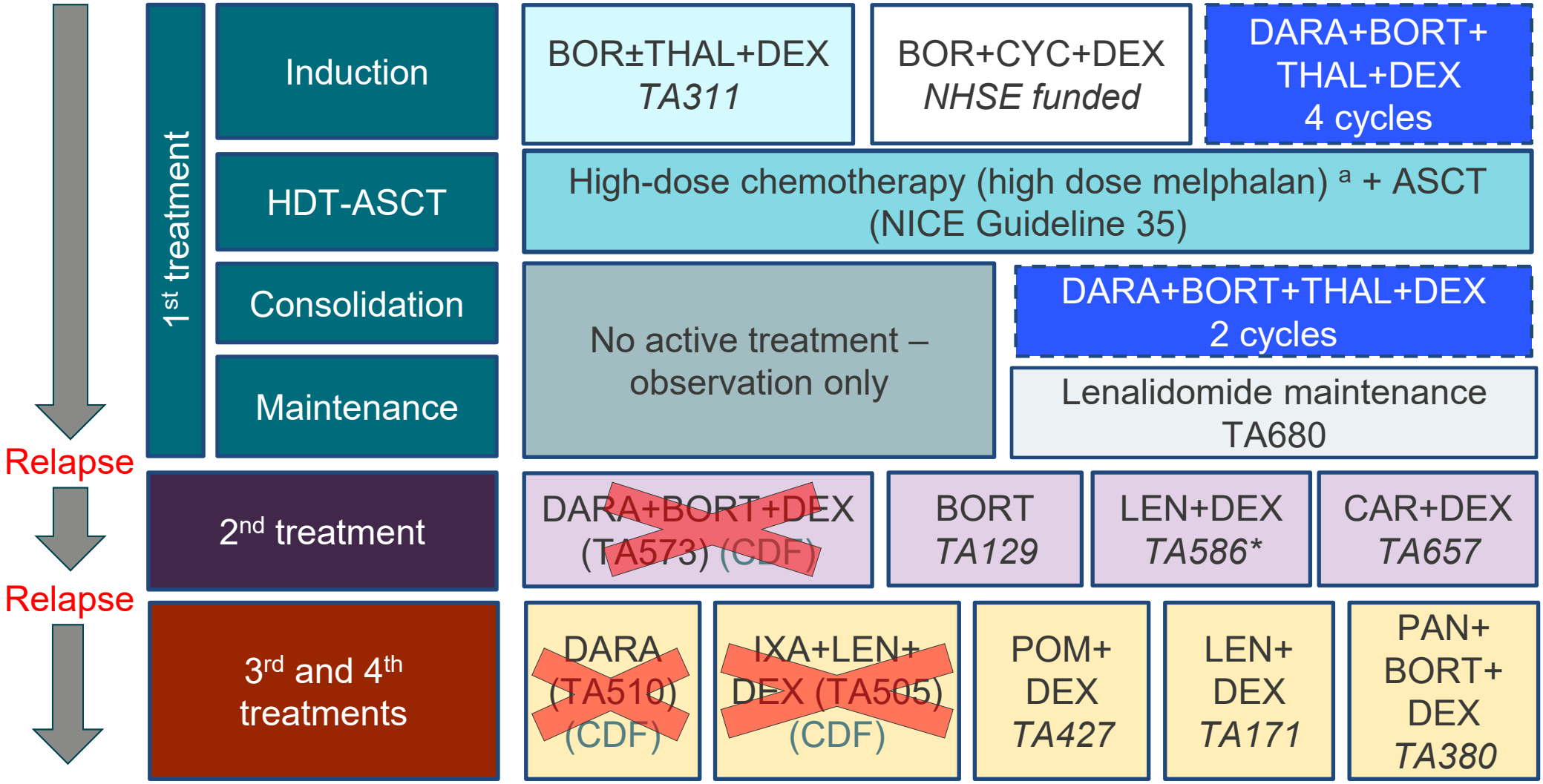
  2. 'High-dose therapy and then transplant'
  - High-dose therapy usually melphalan chemotherapy
    – to kill myeloma cells
  - Autologous stem cell transplant ASCT – infuse own healthy stem cells back

  3. 'Consolidation'
  - To 'deepen' response
  - Not standard care in UK
  - Part of licence and part of trial; so company includes in this appraisal despite not NHS care

Daratumumab (Darzalex, Janssen-Cilag)

Marketing authorisation (EMA Jan 2020)	*"in combination 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 and licensed dose	• Intravenous (IV) infusion, also • Subcutaneous (SC) injection • **Trial and licence**: 16 mg/kg IV once weekly for first 2 cycles (weeks 1-8), followed by every 2 weeks for cycles 3-4 and cycles 5-6 (consolidation) • Company expects patients prefer SC over IV
Mechanism of action	Human immunoglobulin G1 kappa monoclonal antibody that binds to CD38, overexpressed on surface of myeloma cells causes cell death
List price	1,800 mg (fixed-dose vial) for SC injection: £4,320 400 mg (IV): £1,440; 100 mg (IV): £360 Patient access scheme discount available

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



* 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. [a] NHS treatment algorithm recommends high-dose melphalan

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

Clinical effectiveness: overview

Comparing DARA+BORT+THAL+DEX with:

1. **BORT+THAL+DEX: used key trial CASSIOPEIA**
   - PFS adjusted for maintenance therapy with daratumumab in trial but not offered in NHS
   - Introduction to 2◦ endpoint on which company bases its model
2. **Other comparators:**
   - ‘Naïve’ comparison
   - Matching adjusted indirect comparison
   - Company excluded CYC+THAL+DEX

PFS: Progression-free survival

CASSIOPEIA: trial overview

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

Location of trial sites	France, Belgium and Netherlands. No UK sites
Study population	Adults to 65 years with untreated myeloma eligible for ASCT
Intervention	Daratumumab, bortezomib, thalidomide and dexamethasone DARA+BORT+THAL+DEX; N=543
Comparator	Bortezomib, thalidomide and dexamethasone BORT+THAL+DEX; N=542
1◦ outcome	% achieving stringent complete response (sCR) post-consolidation at or within 30 days of day 100 after transplant
Non-1◦ outcomes	Progression-free survival, overall survival, minimal residual disease (MRD), response rates, EQ-5D-5L
Latest available data	• 1◦ data cut June 2018 primary analysis for Part 1 of trial: *median follow-up 18.8 months* • Post-hoc data cut May 2019: *median follow-up 29.2 months* (unplanned EMA request) • Interim analysis Aug 2020: *median follow-up 44.5 months*

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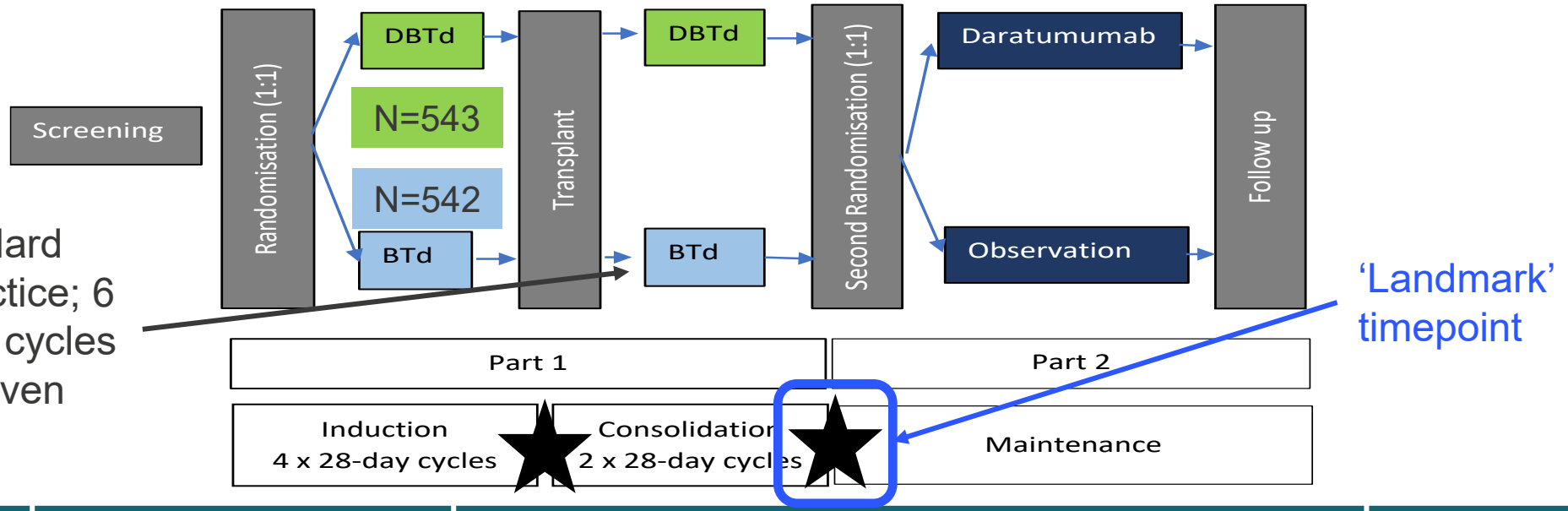
Sources: ERG report table 7 based on CS section B.2.3.1; CS Table 4; CS Figure 7; CS Appendix L.3
ASCT: Autologous stem cell transplant; EMA: European Medicines Agency

CASSIOPEIA: endpoints + when measured

- 'Response' variables include: stringent complete response (sCR), complete response (CR), very good partial response, objective response rate, best response over time, time to response



Not standard NHS practice; 6 induction cycles usually given

'Landmark' timepoint

Endpoint	Time assessment	Definition	Modelled?
sCR = 1◦ endpoint	Post-induction Post-transplant Post-consolidation (1◦ endpoint)	% who achieve CR + normal serum free light chain ratio + absent clonal cells in marrow by immunohistochemistry/ immuno-fluorescence/2- to 4-color flow cytometry	No
MRD	Post-induction	% who achieve MRD negative status	No
	Post-consolidation	% who achieve MRD negative status	Yes

DBTd: Daratumumab, bortezomib, thalidomide and dexamethasone;
BTd: Bortezomib, thalidomide and dexamethasone; MRD: Minimal residual disease

CASSIOPEIA: 1◦ and selected 2◦ results

Response outcomes favour DARA+BORT+THAL+DEX over BORT+THAL+DEX

Outcomes post-consolidation median follow-up=18.8 months	DARA (n=543)	Control (n=542)	Odds ratio (95% CI)	Used in model?
1◦ outcome				
Stringent Complete Response (CR)	157 (29%)	110 (20%)	1.60 (1.21, 2.12)	✗
2◦ outcomes				
Complete response or better (stringent CR+CR)	211 (39%)	141 (26%)	1.82 (1.40, 2.36)	✗
MRD negative (10^{-5}) [a]	346 (64%)	236 (44%)	2.27 (1.78, 2.90)	✓

[a] 10^{-5} threshold, standard Euroflow assay, MRD-negative regardless of response

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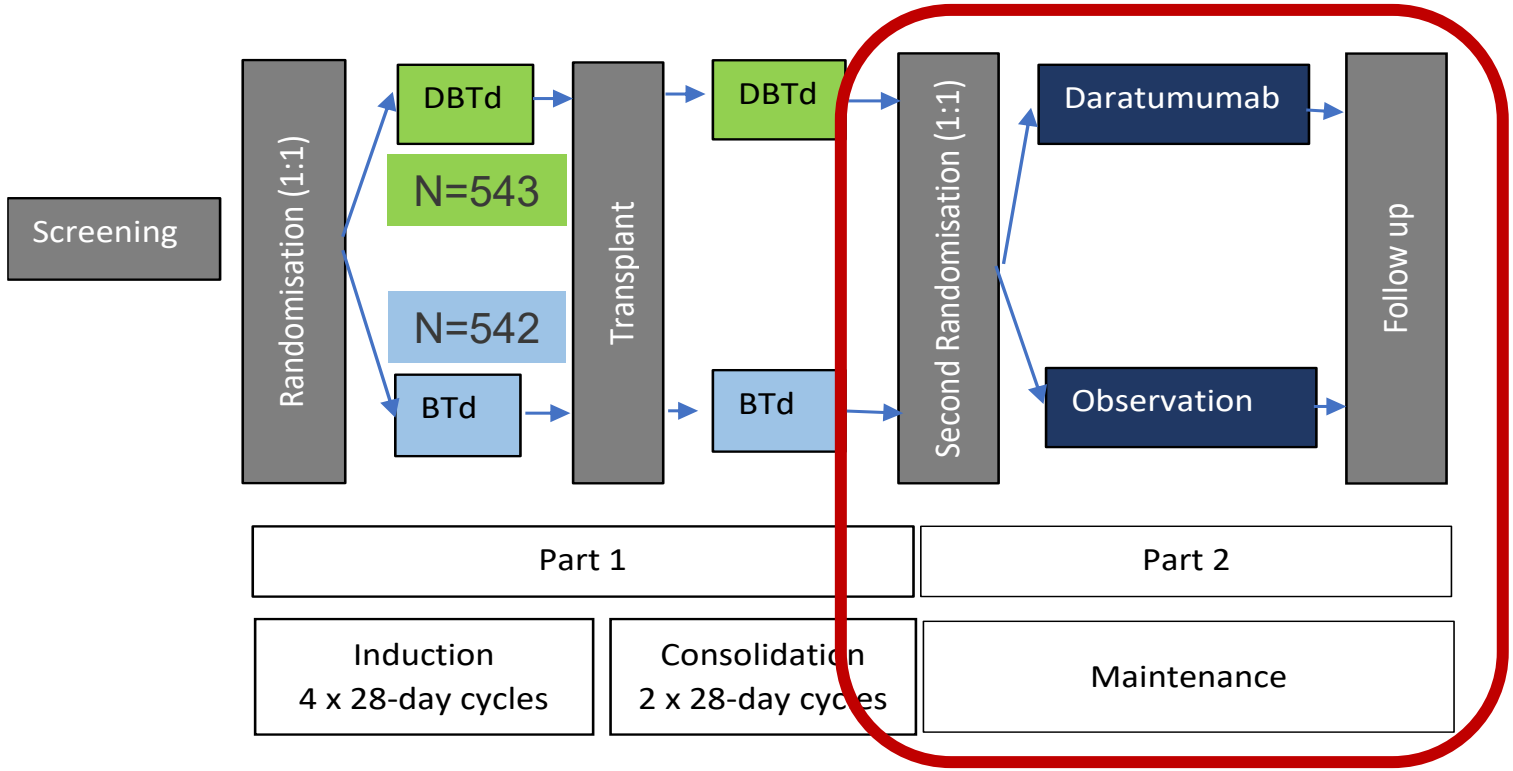
Sources: CS Tables 12-13; CS Figures 8-10; CS section B.2.6.1, EPAR
CI: Confidence interval; MRD: Minimal residual disease

CASSIOPEIA includes not licensed maintenance therapy

Company addresses 2nd randomisation after consolidation by adjusting or censoring



Company presents 2 different approaches to account for re-randomisation:

1. Adjust using inverse probability weighting – company didn't use at 1st committee meeting; used in ACD response in landmark analysis
2. Censor all who were re-randomised to daratumumab – company used in landmark analysis at 1st committee meeting; no longer uses in updated ACD response model

DBTd: Daratumumab, bortezomib, thalidomide and dexamethasone;
BTd: Bortezomib, thalidomide and dexamethasone

CASSIOPEIA: survival results adjusting for maintenance

DARA+BORT+THAL+DEX compared with BORT+THAL+DEX

Company adjusts for maintenance using inverse probability weighting (IPW)

Progression-free survival	1◦ analysis (med follow-up 18 mo)	1st post-hoc analysis (med follow-up 29 mo)	Interim analysis (med follow-up 44 mo)
Analysis no adjustment for maintenance			
HR (95% CI)	0.47 (0.33, 0.67)	0.50 (0.38, 0.65)	[redacted]
IPW analysis			
HR (95% CI)	0.47 (0.33, 0.67)	0.50 (0.34, 0.75)	[redacted]

Overall survival	1◦ analysis (med follow-up 18m)	1st post-hoc analysis (med follow-up 29m)	Interim analysis (med follow-up 44m)
Analysis no adjustment for maintenance			
HR (95% CI)	0.43 (0.23, 0.80)	0.52 (0.33, 0.85)	[redacted]
IPW analysis			
HR (95% CI)	n/a	n/a	[redacted]

ERG

- Uncertain if proportional hazards assumption has been met to use IPW
- For PFS, updated IPW analysis produces **counterintuitive** results based on MRD status
- Treatment effects obtained using censoring or IPW leads to inconsistent results, possibly because of bias from censoring

Sources: Company technical engagement response: Table 1 and 2

CI: Confidence interval; HR: Hazard ratio; MRD: Minimal residual disease

Comparators not in key trial: naive comparison and matching adjusted indirect comparison

- No studies comparing DARA+BORT+THA+DEX with BOR+CYC+DEX or BORT+DEX or CYC+THAL+DEX - rarely used according to clinicians

Company

- Did unanchored matching adjusted indirect comparisons (MAICs) for PFS and OS using data from GMMG-MM5 (BORT+CYC+DEX) and IFM 2005-01 (BORT+DEX)
- Reweighted CASSIOPEIA data to match mean baseline characteristics of target trials
- OS, PFS from CASSIOPEIA adjusted to be comparable to target trials
- Used to compare:
  - DARA+BORT+THAL+DEX with BORT+CYC+DEX and BORT+DEX
  - BORT+THAL+DEX with BORT+CYC+DEX and BORT+DEX
- Also did a naïve indirect treatment comparison unadjusted for prognostic factors
- Commissioned observational study using Public Health England dataset to support MAIC

ERG

- MAIC appropriate; would have preferred simulated treatment comparison as a scenario
- **MAIC for BORT+DEX:** effective sample size reduced by 24% for DARA, 27% for control
- **MAIC for BORT+CYC+DEX:** effective sample size reduced by 62% for DARA, 61% for control
- Satisfied that company included all **available** prognostic factors in the analysis
- Unable to verify that company correctly implemented MAIC

OS: Overall survival; PFS: Progression-free survival; PHE: Public Health England

Naive comparison and MAIC: results

Company assumes [redacted]; *both* [redacted]

	Naïve comparison		MAIC (Base case)	
	PFS	OS	PFS	OS
BORT+THAL+DEX vs BORT+CYC+DEX				
HR	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
BORT+THAL+DEX vs BORT+DEX				
HR	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
DARA+BORT+THAL+DEX vs BORT+CYC+DEX				
HR	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

ERG

- ERG's clinical experts agree that company's conclusion about relative treatment effectiveness is appropriate

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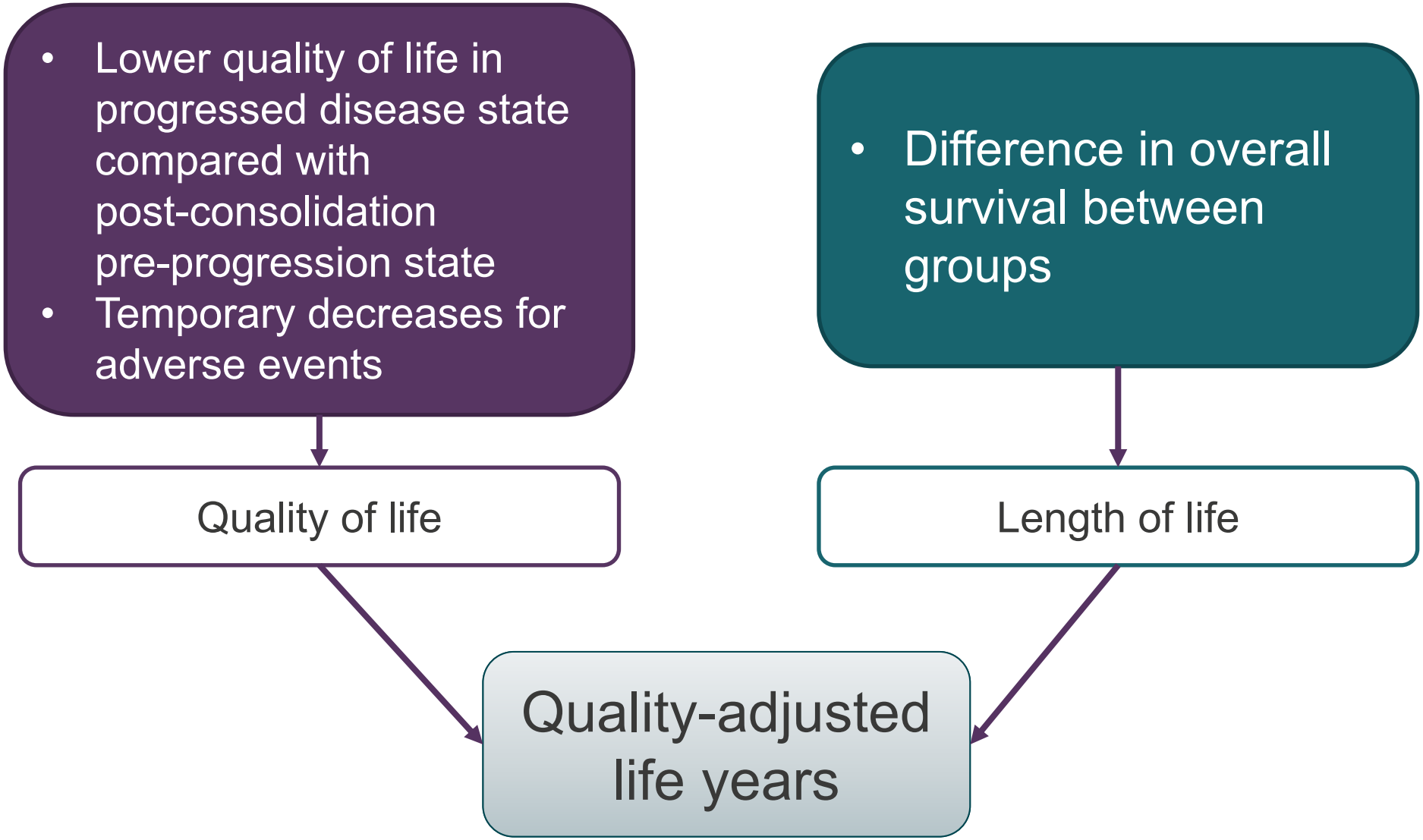
Sources: Reproduction of CS Tables 35 and 36
CI: Confidence interval; HR: Hazard ratio

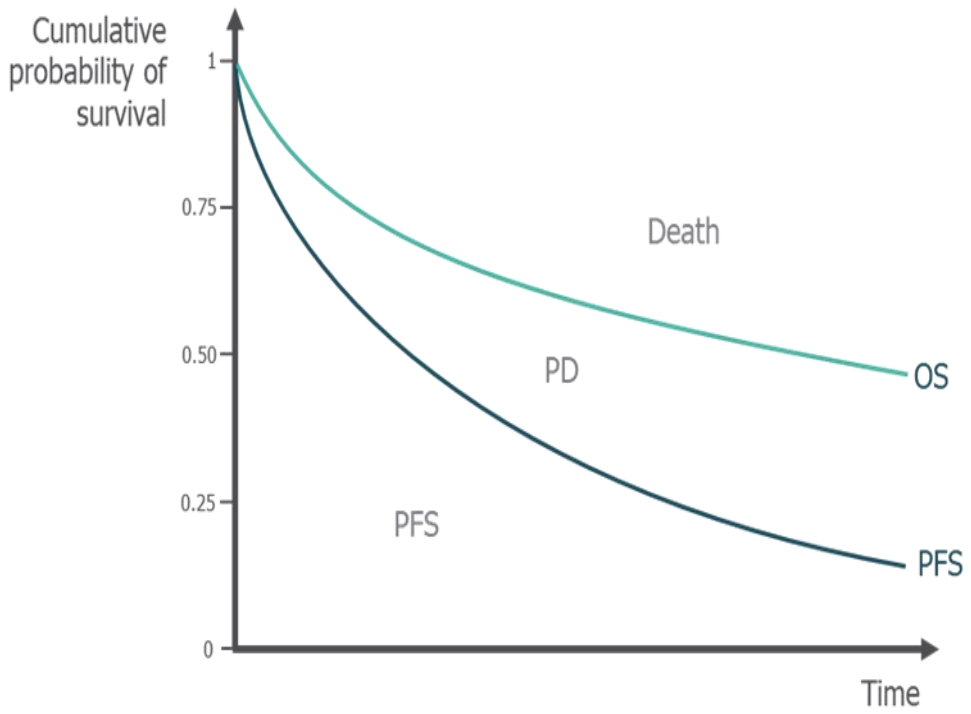
Cost effectiveness

How quality-adjusted life years accrue



Company's model summary

- Partitioned survival model
- 3 health states: pre-progression, progressed disease, death
- Cycle length: 4 weeks
- Time horizon: lifetime
- Extrapolating OS and PFS with 'MRD-based' modelling
  - Split by MRD positive/negative at post-consolidation assessment
  - MRD status determines PFS and OS extrapolations
  - Uses 'landmark' analysis
    - 'Landmark analysis' refers to designating a time point occurring during the follow-up period - landmark time - and analysing only those subjects who survive until the landmark time[1]
- Only comparator considered in model at 1st meeting was BORT+THAL+DEX
- Company has added a scenario with BORT+DEX as a comparator in response to ACD



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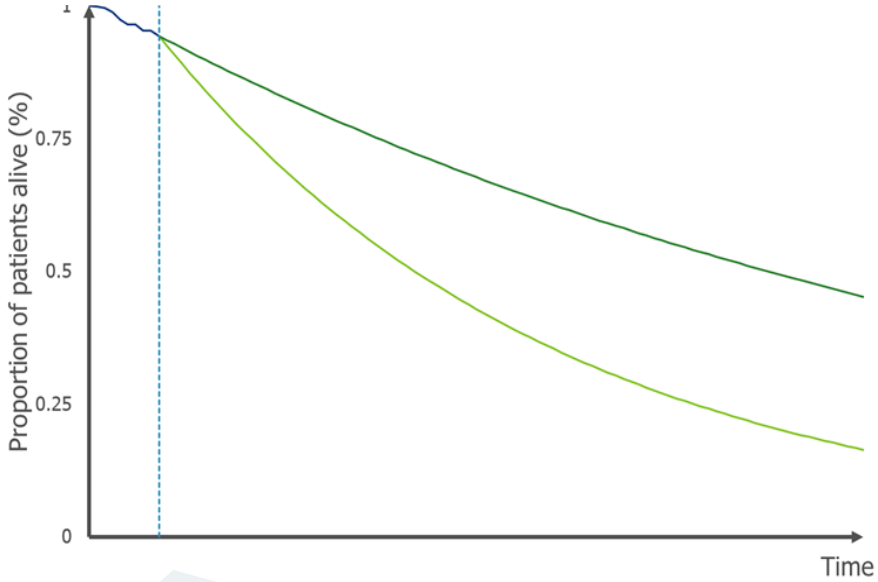
HR: Hazard ratio; MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival. [1] Landmark analysis: A primer Morgan 2019

Company's MRD-based modelling

MRD status post-consolidation determines PFS, OS extrapolations

- 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 ITT population achieving MRD negativity at the post-consolidation assessment



'Landmark' timepoint: 100 days post-ASCT

MRD status	DARA+BORT+THAL+DEX	BORT+THAL+DEX
MRD-negative (good)	64% (95% CI: 60%, 68%)	44% (95% CI: 39%, 48%)
MRD-positive (bad)	36%	56%

Sources: CS Table 48

ASCT: Autologous stem-cell transplant; CI: Confidence interval; ITT: Intention-to-treat; MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival

Appraisal consultation document
Conclusions and uncertainties

ACD conclusions and uncertainties (1)

To discuss: BORT+DEX as a comparator and including NHS lenalidomide maintenance

Topic	Committee conclusion	Area of uncertainty?	ACD section
New treatment option	People with untreated multiple myeloma would welcome new treatment options with longer remission/improved survival	No	3.1
Treatment pathway	• BORT+THAL+DEX a relevant comparator – • Should include BORT+DEX	Yes	3.2
Consolidation	Could incorporate consolidation treatment with daratumumab into NHS practice	No	3.3
Lenalidomide maintenance	Scenario analysis incorporating lenalidomide maintenance as a subsequent treatment should be provided to reflect clinical practice	Yes	3.4
Clinical effectiveness	Adding daratumumab to BORT+THAL+DEX improved progression-free and overall survival	No	3.5
Indirect Treatment comparisons	Results of the company's matching adjusted indirect comparisons are uncertain	No	3.9
Adverse events	Adverse event profile of DARA+BORT+THAL+DEX acceptable	No	3.8

ACD conclusions and uncertainties (2)

To discuss: MRD-based vs. 'standard' survival modelling, bias with landmark analysis

Topic	Committee conclusion	Area of uncertainty?	ACD section
MRD status	Minimal residual disease negativity likely to predict survival outcomes better than conventional response	No	3.7
Defining MRD	Company's definition is appropriate	No	3.12
Relationship between MRD and survival	Meta-analysis on the relationship between MRD status and survival is uncertain, but has minimal effect on results	No	3.11
'Standard' vs MRD-based survival modelling	Unclear if company's MRD-based approach to long-term survival modelling reduces uncertainty	Yes	3.10
Landmark analysis	Company's landmark analysis based on MRD using censoring to adjust for unlicensed use of daratumumab maintenance is likely biased, though direction of bias is unclear	Yes	3.6

ITC: indirect treatment comparison; MRD: minimal residual disease

ACD conclusions and uncertainties (3)

To discuss: Long-term survival modelling including extrapolations, effect waning

Topic	Committee conclusion	Area of uncertainty?	ACD section
Survival extrapolation	Company's extrapolation likely **underestimates** survival for patients having BORT+THAL+DEX	Yes	3.13
Treatment effect waning	Should model, but duration of daratumumab's treatment effect is highly uncertain	Yes	3.14
Mean age	Age at induction should be based on NHS	*Included in updated company base case*	3.15
Cost of subsequent treatments	Should not include PAN+BORT+DEX as 3rd or 4th-line treatment in the model		3.16
Cost-effectiveness	ICER likely to be closer to ERG estimate and not a cost-effective use of NHS resources	Yes	3.17
Equalities issues	Would not restrict guidance to trial's age inclusion	No	3.18
Innovation	No additional gains in health-related quality of life over those already included	No	3.19

MRD: minimal residual disease; PSM: partitioned survival model

Summary of appraisal consultation document (ACD) responses

Consultation responses

Responses received from:

- Company: Janssen-Cilag
- Stakeholders: Myeloma UK
- Experts: 2 clinical experts

Summary of company ACD response

Issue ACD section	Committee preferences	Provided?	In revised base case?
Treatment pathway *3.2*	Include BORT+DEX as comparator	✓	✗
Lenalidomide maintenance *3.4*	Scenario with lenalidomide maintenance to reflect current NHS clinical practice	✓	✗
Landmark analysis *3.6*	• Using less biased approach than censoring to adjust landmark analysis for re-randomisation to daratumumab maintenance • A more optimistic OS extrapolation for BORT+THAL+DEX, not based on censored landmark analysis which was likely biased	✓	✓
BORT+THAL+DEX survival *3.13*		✓	✓
Conventional modelling *3.10*	Scenario using a conventional approach of fitting PFS and OS models directly to whole trial population	✓	✗
Effect waning *3.14*	Scenarios for DARA treatment effect lasting 5 to 10 years after consolidation therapy	✓	✗
Mean age *3.15*	Mean age at start of induction based on NHS from Public Health England	✓	✓
Later treatments *3.16*	Omit PAN+BORT+DEX as 3rd or 4th line treatment	✓	✓

IPCW: inverse probability censoring weights; ITT: intention to treat; PFS: Progression-free survival; OS: Overall survival

Treatment pathway – omitted comparators

Cost-effectiveness results are similar vs. BORT+DEX as vs. BORT+THAL+DEX

Background (ACD 3.2):

- BORT+DEX included as comparator in NICE scope but company excluded
- **Company:** considered BORT+DEX had similar cost but lower efficacy than BORT+THAL+DEX, which it included as comparator in model
- **Committee:** BORT+DEX is cheaper than BORT+THAL+DEX.
  So, DARA+BORT+THAL+DEX is not necessarily cost-effective vs BORT+DEX
  - *Conclusion: Would have preferred to include BORT+DEX in model*

Company response:

- Did not have data for BORT+DEX i.e. MRD negativity rates 100 days post-ASCT
- Did exploratory analysis assuming BORT+DEX has equivalent efficacy to BORT+THAL+DEX, but lower costs
  - Incorporated IPCW-adjusted landmark analysis and revised survival models for MRD+ having BORT+THAL+DEX, but not other changes following consultation
- Results suggest DARA+BORT+THAL+DEX is cost-effective versus BORT+DEX

Clinical experts:

- Few patients have BORT+DEX. Clinicians always prefer to give 3 drugs rather than 2
- Datasets should be available from NHS England to validate this

ERG response:

- BORT+DEX is less costly than the other comparators (BORT+THAL/CYC+DEX)
- Unlikely to be equally effective

ASCT: autologous stem cell transplant; IPCW: inverse probability of censoring weighting; MRD: Minimal residual disease

Lenalidomide maintenance

Company provided conservative scenario analyses incorporating costs of lenalidomide maintenance, with no consideration of improved clinical outcomes

Background ACD 3.4:

- At time of company submission, NICE was appraising lenalidomide
- March 2021: Lenalidomide approved as a maintenance treatment (TA680)
- **CDF lead:** Adding daratumumab to induction and consolidation would likely increase the duration and costs of lenalidomide maintenance
- **Committee:** impact on cost effectiveness of including lenalidomide maintenance unclear
  - *Conclusion: Scenario incorporating lenalidomide maintenance as subsequent treatment*

Company response:

- Final scope provides a relevant point of reference throughout appraisal; request off process
- Provides 2 scenarios, including costs of lenalidomide maintenance but no efficacy impact:
  - **Scenario 1:** Median time to stopping treatment with lenalidomide from Myeloma XI in transplant eligible subgroup for both arms ([redacted] mos = [redacted] model cycles);
  - **Scenario 2:** treatment duration of lenalidomide following BORT+THAL+DEX and DARA+BORT+THAL+DEX in line with observed ratio between median time to stopping treatment and PFS for transplant-eligible subgroup from Myeloma XI (DARA+BORT+THAL+DEX: [redacted] cycles; BORT+THAL+DEX: [redacted] cycles)
  - DARA+BORT+THAL+DEX cost effective if committee considers anticipated lenalidomide price discounts after patent expiry in January 2022

CDF: Cancer Drugs Fund; CS: company submission; mos: months; PFS: Progression-free survival; TE: technical engagement; TTD: Time to discontinuation

Lenalidomide maintenance – cont.

Stakeholders cautious about incorporating lenalidomide maintenance

Myeloma UK:

- Lenalidomide maintenance not mentioned in final scope; therefore company and other consultees not asked to submit evidence on this as part of decision problem
- Recognise committee's desire to reflect NHS practice in its deliberations; balance to be struck between this and preserving integrity of appraisal process

Clinical experts:

- Subsequent therapy changes impact on new induction regimens; unintentionally favours maintenance therapies as induction and maintenance therapies are tested separately in trials

ERG response:

- Scenarios with costs, but no effects of lenalidomide maintenance are subject to uncertainty
- May expect these scenarios to be biased against daratumumab, as they assume equal or longer lenalidomide maintenance after daratumumab induction and consolidation

◉ How should the company's possibly conservative scenario analysis with lenalidomide maintenance be considered?

Landmark analysis

Company has provided IPCW-adjusted landmark analysis

Background ACD 3.6:

- Landmark analysis provided at technical engagement censored people from both arms who were re-randomised to daratumumab maintenance
  - Daratumumab maintenance is not in EMA license, does not reflect UK practice
- **Committee**: results of landmark analysis likely biased because of informative censoring; direction of bias unclear because it effects both treatment arms
  - *Conclusion: use an approach less subject to bias to adjust landmark analysis*

Company response to ACD:

- Technical engagement: applied censoring approach as company says it had no access to patient level data for those re-randomised to daratumumab maintenance. Not possible to provide adjusted landmark analysis similar to inverse probability weights (IPW) PFS/OS analysis from ITT population
- Has now provided an inverse probability censoring weights (IPCW) adjusted landmark analysis following recent publication of CASSIOPEIA Part 2 results
- [redacted]

EMA: European Medicines Agency; ITT: Intention to treat; PFS: Progression-free survival, MHRA: Medicines and Healthcare products Regulatory Agency; OS: Overall survival; SmPC: Summary of Product Characteristics

Landmark analysis new company results

Compared to censoring approach, IPCW-adjusted landmark analysis broadly comparable effect of daratumumab on PFS, but different for overall survival

Cox proportional hazard model results (median follow up = 44.5 months)

DARA+BORT+THAL+DEX vs BORT+THAL+DEX	Landmark analysis censoring for maintenance	Landmark analysis revised IPCW-adjusted
Progression-free survival *(broadly comparable results between approaches)*		
MRD+ HR (95% CI)	[redacted]	[redacted]
MRD- HR (95% CI)	[redacted]	[redacted]
Overall survival *(MRD+ stronger depth of response using IPCW, weaker effect for MRD-)*		
MRD+ HR (95% CI)	[redacted]	[redacted]
MRD- HR (95% CI)	[redacted]	[redacted]

ERG response:

- IPCW-adjusted landmark analysis is appropriate; but ERG could not fully validate
- Uncertainties remain:
  - Company excludes potential prognostic factors: renal function, comorbidities, extent of extramedullary disease, high-risk FISH abnormalities
  - 'High uncertainty' over effect on overall survival
  - Proportional hazards potentially violated; adds uncertainty to cost-effectiveness results since model uses fixed HRs from landmark analysis to adjust PFS/OS extrapolations

◉ *How to adjust for non-licensed daratumumab maintenance incorporated in trial results? How to deal with uncertainties?*

CI: confidence interval; FISH: Fluorescence in situ hybridization; HR: hazard ratio; IPCW: inverse probability censoring weights; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival

BORT+THAL+DEX survival extrapolation

Company now uses updated landmark analysis which improves comparator survival

Background ACD 3.13:

- **Company**: OS for MRD+ BORT+THAL+DEX: parametric distributions fit to post-landmark data
- **ERG**: exponential distribution to model BORT+THAL+DEX MRD+ OS "reasonable", but Weibull and Gompertz better. Concerned that censoring of landmark analysis biases results
- **Committee** conclusion: company's extrapolations likely underestimated overall survival

Company response:

- Survival analysis updated based on results from IPCW landmark analysis
- PFS: Gompertz; Overall survival: Exponential
- Revised IPCW-adjusted landmark analysis: upward shift in OS for BORT+THAL+DEX (both MRD+ and MRD-): 5/10yr OS: 79% vs 76%; 62% vs 57%

BORT+THAL+DEX survival predictions (all patients*): comparison of models

Model version	PFS (months)		OS (months)	
	Median	Mean	Median	Mean
Technical engagement model	37	59	146	185
Updated model at ACD	38	44	172	205

- Survival outcomes modelled based on post-consolidation response. BORT+THAL+DEX survival likely overestimated, as consolidation therapy not currently clinical practice

* MRD- and MRD+ at landmark timepoint

ASCT: autologous stem cell transpant; BTd: BORT+THAL+DEX; IPCW: inverse probability censoring weights; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival

BORT+THAL+DEX survival extrapolation

Improved comparator OS when IPCW adjusted landmark analysis used – ERG agrees

Comparing model overall survival predictions for MRD+ patients having BORT+THAL+DEX

ERG response:

- Reasonable
- Resulting survival extrapolations for the comparator exceed clinical expectations:
  - Alternative baseline OS survival models (e.g. Weibull) would be more optimistic
  - May relate to nature of population and interventions in trial, or way model estimates survival for MRD- group (with a constant hazard ratio applied to MRD+ curve)

◉ *Which model?*

IPCW: inverse probability censoring weights; KM: Kaplan-Meier; MRD: minimal residual disease; OS: overall survival; TE: technical engagement

Standard vs MRD-based partition model

Model updated to include parametric models fitted to IPCW-adjusted whole trial data

Background ACD 3.10:

- **Company:** presented a conventional partitioned survival model comprising 3 health states yet noted that conventional approach of fitting parametric models to ITT data from CASSIOPEIA led to 'wide variation' in OS predictions
- Used KM curves from CASSIOPEIA up to landmark timepoint, split by MRD+/-; followed by 5-step approach to modelling long-term survival
- **ERG:** OS data too immature for parametric distributions
- **Committee**: uncertainties with choices of survival extrapolation for BORT+THAL+DEX and MRD+; results of meta-analysis; censored landmark analysis
  - *Conclusion: scenario using a conventional approach of fitting models*

Company response:

- Continues to prefer modelling approach using post-consolidation MRD status
- Updated economic model includes functionality to compare outcomes from fitting standard parametric models directly to IPCW-adjusted whole trial data
- Scenario using Weibull for both BORT+THAL+DEX and DARA+BORT+THAL+DEX progression-free and overall survival (company response, table 5)

IPCW: inverse probability censoring weights; ITT: intention to treat; KM: Kaplan-Meier; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival; PSM: partitioned survival model

Standard vs MRD-based partition model

Residual uncertainty remains; explored in sensitivity and scenario analysis

Median OS predictions (yrs)	DARA+BORT+THAL+DEX		BORT+THAL+DEX	
	MRD-based PSM	Standard PSM	MRD-based PSM	Standard PSM
Exponential	**22.5** ↓	25.9	**14.3** ↓	19.0
Weibull	24.8	17.6	17.1	13.8
Log normal	**26.8** ↑	25.7	24.1	**22.7** ↑
Log logistic	26.0	21.4	21.5	16.5
Gompertz	26.8	**11.3** ↓	**24.4** ↑	**11.4** ↓
Gen gamma	26.5	**27.0** ↑	23.3	22.0
Diff. highest vs lowest	4.3	15.7	10.1	11.3

Company response (continued):

- Demonstrates significant variability in predicted survival outcomes by distribution
- Uncertainties reduced for DARA when adopting MRD-based PSM (smaller range)
- Residual uncertainty remains with HRs incorporated from MRD meta-analysis (ACD 3.11) and landmark analysis (ACD 3.6); explored in sensitivity and scenario analysis

ERG response:

- Further information would have been beneficial to support choice of Weibull distribution
- ERG provides IPCW-adjusted PFS and OS extrapolations for 2 scenarios:
  - Weibull for PFS and OS as in company's non-MRD-based scenario
  - Gompertz PFS and exponential OS as in company's MRD-based revised base case

◉ *Does the company's scenario with survival models fitted directly to the whole trial data reduce the uncertainty around the company's MRD-based survival modelling approach?*

↓ Lowest value ↑ Highest value

HR: hazard ratios; MRD: minimal residual disease; OS: overall survival; PSM: partitioned survival model

Duration of treatment effect/waning

Company provides additional scenarios for duration of daratumumab treatment effect

Background ACD 3.14:

- **Company:** Base case included a lifetime treatment effect for daratumumab
- **ERG:** not enough evidence to support a lifetime treatment effect; preferred scenario with effect lasting 5 years after consolidation therapy
- **CDF lead:** likely treatment effect would wane
- **Clinical expert**: based on GIMEMA, DARA treatment effect would last more than 5 years
- **Committee conclusion:** *include treatment waning in model; scenarios with treatment effect lasting 5 to 10 years were reasonable*

Company response:

- Results from IPCW-adjusted landmark analyses demonstrate no evidence of waning
- GIMEMA: 10 year median follow up for BORT+THAL+DEX; supports no waning
- Scenario with waning of effect at a constant rate between 5- and 10- years, and a scenario with treatment effect lasting 7.5 years

Myeloma UK:

- Increasingly challenging to deliver overall survival results within timelines of a clinical trial; must not prevent patients from accessing the most promising new treatments

CDF: Cancer Drugs Fund; CE: cost-effectiveness

Duration of treatment effect/waning – cont.

ERG provides scenario with loss of DARA OS effect at 5 years in MRD-, and gradual waning for remaining patients

Clinical experts:

- Difficult to determine because no long-term data
- Improved MRD rate seen with DARA+BORT+THAL+DEX may show similar (if not better) improvements at 10 years than BORT+THAL+DEX

ERG response:

- Scenario with gradual waning between 5 and 10 years reflects committee's preferred assumptions
- Company should include in revised base case; not currently included
- Acknowledge company's comments that 5-year treatment effect is not plausible
- However highlight high uncertainty over direct evidence of a daratumumab survival benefit, **particularly in patients with MRD- at the landmark timepoint**
- Provides a scenario with DARA losing effect on OS at 5 years in MRD- patients, and a gradual waning of treatment effect from 5 to 10 years after consolidation for PFS MRD+ and MRD- and OS (MRD+)

◉ Has committee seen new evidence for it to change its conclusion that it would like to consider scenarios with waning?

MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival

Cost-effectiveness results

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

Back-up slides

MRD- at landmark assessment
MRD+ at landmark assessment

Landmark analysis (ACD 3.6)

IPCW adjustment has minimal difference compared with censoring

Landmark analysis BTd PFS: Censoring-adjusted

Landmark analysis BTd PFS: IPCW-adjusted

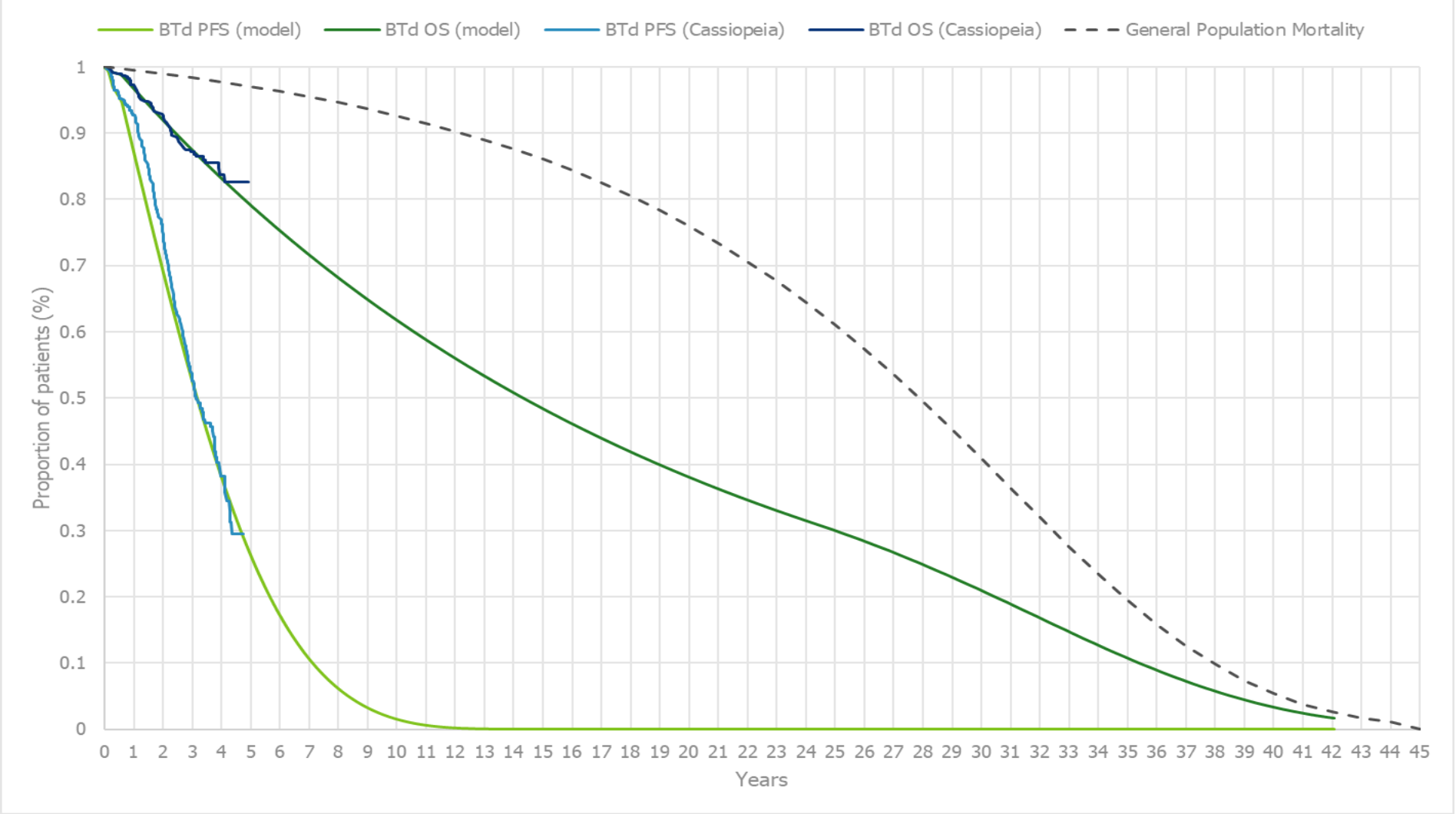
Landmark analysis BTd OS: Censoring-adjusted

Landmark analysis BTd OS: IPCW-adjusted

BTd: bortezomib, thalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; IPCW: inverse probability censoring weights; OS: overall survival; PFS: progression-free survival

Survival extrapolation (ACD 3.13)

Comparison of modelled survival predictions for BTd and the data from CASSIOPEIA



NICE

Survival extrapolation (ACD 3.13)

Upward shift in OS rate when IPCW adjusted landmark analysis used in analysis

Extrapolation of OS for BTd MRD+
(revised IPCW adjusted landmark analysis)

Survival model	OS survival rates			
	5 years	10 years	20 years	30 years
Clinician estimate	≤70%[a]	44%[b]	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Extrapolation of OS for BTd MRD+
(from TE stage)

Survival model	OS survival rates			
	5 years	10 years	20 years	30 years
Clinician estimate	≤70%[a]	44%[b]	-	-
Exponential	[redacted]	[redacted]	[redacted]	
Weibull	[redacted]	[redacted]	[redacted]	
Lognormal	[redacted]	[redacted]	[redacted]	
Loglogistic	[redacted]	[redacted]	[redacted]	
Gompertz	[redacted]	[redacted]	[redacted]	
Generalised Gamma	[redacted]	[redacted]	[redacted]	

NICE

BTd: bortezomib, thalidomide and dexamethasone; IPCW: inverse probability censoring weights; MRD: minimal residual disease; OS: overall survival; TE: technical engagement

ERG response to ACD 3.10: Standard vs response-based PSM

Conventional PFS extrapolations:

IPCW adjusted data cut August 2020

ERG response to ACD 3.10: Standard vs response-based PSM

Conventional OS extrapolations:

IPCW adjusted data cut August 2020

ERG response to ACD 3.10: Standard vs response-based PSM

Non response based extrapolations: Weibull for PFS and OS

Non response based extrapolations: Gompertz for PFS, exponential for OS