NICE National Institute for Health and Care Excellence

Slides for public (redacted)

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

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Company: Janssen-Cilag

ACM1 5th May 2021

Key issues

Definition of minimal residual disease

- What is the appropriate definition of MRD negativity?
  - **IMWG definition:** requiring conventional complete response, or
  - **Company economic model:** regardless of conventional response

Landmark analysis 

- Is the company's censored landmark analysis, split by MRD status, acceptable for decision making?

Extrapolations 

- What is the most appropriate distribution?

Treatment effect 

- Would the daratumumab treatment effect be expected to wane over time? If so, how should this be modelled?

IMWG: International Myeloma Working Group; MRD: Minimal residual disease

Background

Disease background: multiple myeloma

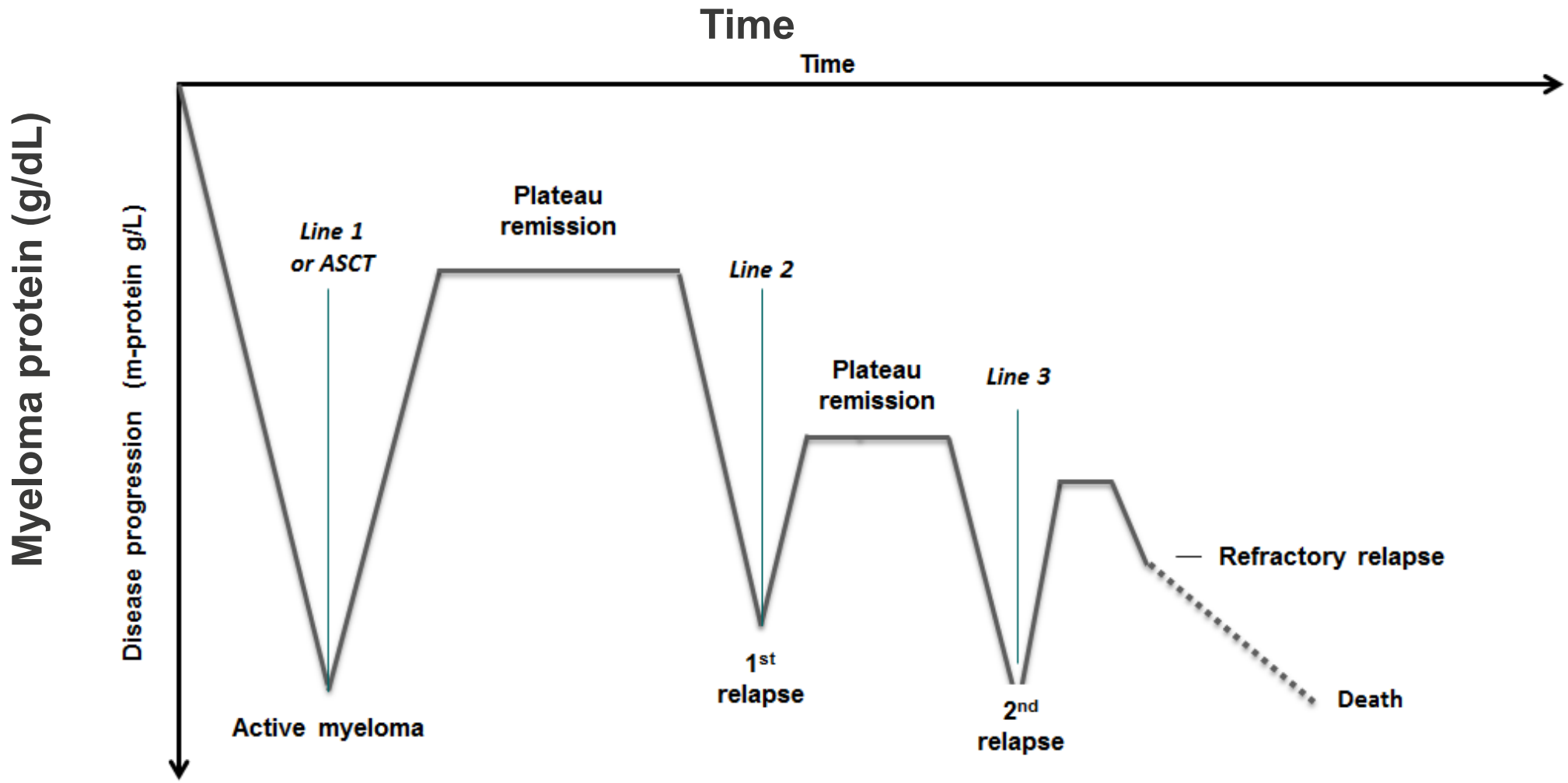
- Cancer from proliferating plasma cells (type of blood cell) in bone marrow
- Myeloma cells suppress development of normal blood cells responsible for:
  - fighting infection - white blood cells
  - carrying oxygen around the body - red blood cells
  - blood clotting - platelets
- Disease progression and response to therapy monitored by M-protein in plasma, and plasma cells/myeloma cells in bone marrow
- Symptoms and complications include bone pain, bone fractures, fatigue, anaemia, recurrent infections, renal failure, high calcium levels
- In 2017, around 5,000 people diagnosed with multiple myeloma in England
- More common in older people – 74% diagnosed aged ≥65
- More common in men than women
- More common in Afro-Caribbean than white people
- 5- and 10-year survival rates 52% and 29% respectively

Sources: ID1510 final scope and CS document B
M-protein: Myeloma protein

Disease background: treated natural history

Characterised by cycles of remission and relapse

As number of lines of therapy increases, time in remission decreases



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Sources: ID1510 final scope and CS document B

Patient and carer perspectives

Myeloma UK

Unmet need

- People with myeloma value treatments that prolong life and remission and allow them to enjoy day-to-day life
- Newly diagnosed patients hope for as long a remission as possible post-transplant
- Unmet need for a range of treatment options with different mechanisms of action at each stage of treatment pathway

Quality of life impact

- Myeloma extremely challenging physically + emotionally for patients, carers and family members
- Complications significant, debilitating and painful;
  - include severe bone pain, bone destruction, kidney damage, fatigue, increased risk of infections
- People's lives impacted by adverse effects of treatment and hospital visits
- Lack of control due to increasing reliance on carers and reduced mobility
- Carers report significant emotional, social and practical impact

Professional organisation perspective

- **Myeloma** is incurable
- **Symptoms and signs of active disease include**: bone pain, fractures secondary to bone deposits, fatigue, anaemia, recurrent infections, renal failure
- **Aims of treatment:** prolong overall survival and progression-free survival, and maintain / improve quality of life
- **Response:** achieving minimal residual disease is associated with a longer duration of response and overall survival
- **Unmet need:** small group of patients do not respond to current treatments. Novel therapies can induce a longer and more durable period of remission and limit or prevent myeloma-associated complications
- **Well tolerated:** daratumumab has limited and manageable adverse effects
- **No increase in days visiting health facilities:** daratumumab administered at same time as combination (current) treatment. People will need to spend more time on day units to have daratumumab, but no increase in number of days

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
- ASCT involves:

  1. 'Induction'

  - 3-drug regimen: bortezomib, thalidomide, dexamethasone (TA311) to reduce plasma cells in bone marrow

  2. 'High-dose therapy and then transplant'

  - High-dose therapy usually melphalan chemotherapy
    – to kill the multiple myeloma cells
  - ASCT – infusion of own healthy stem cells back into body

  3. 'Consolidation'

  - To 'deepen' response
  - Not standard care in UK
  - Part of licence and part of trial; so company includes in this appraisal

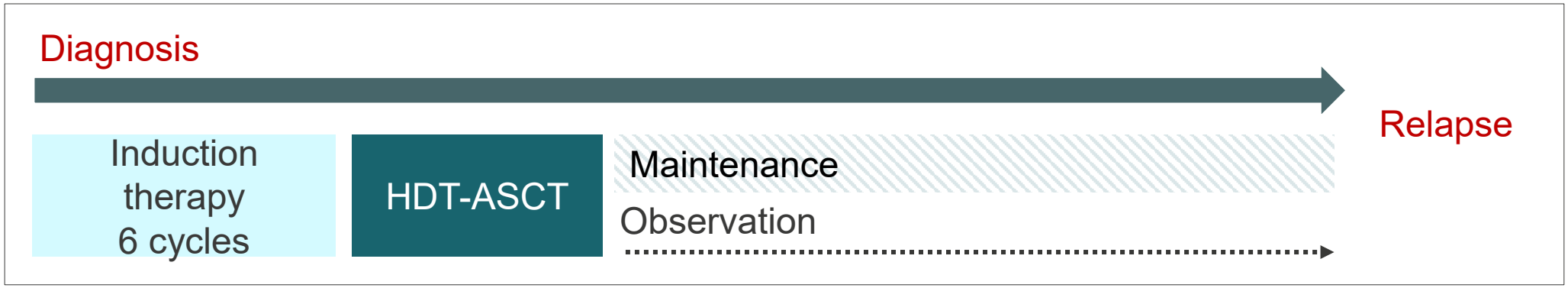
Daratumumab (Darzalex, Janssen-Cilag)

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 to prefer SC formulation over IV
Mechanism of action	Human immunoglobulin G1 kappa monoclonal antibody that binds to CD38, a glycoprotein overexpressed on surface of myeloma cells, inducing tumour 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

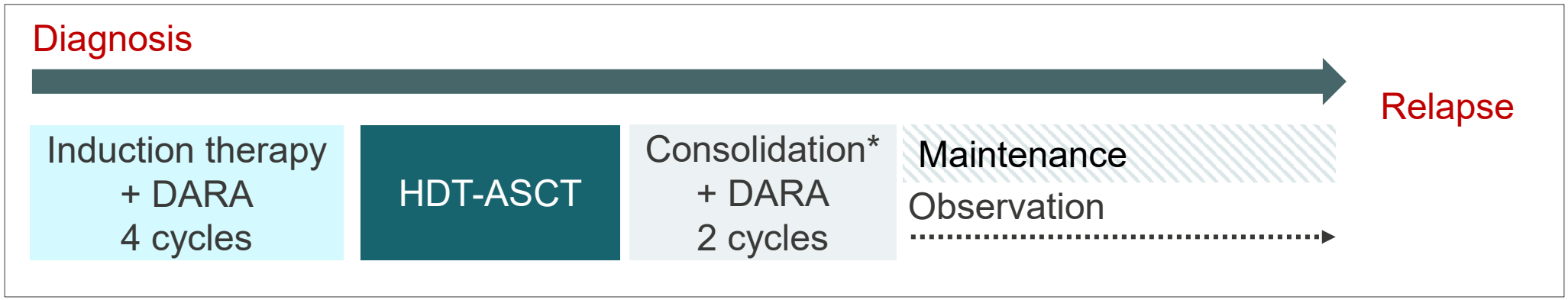
Daratumumab induction + consolidation if in NHS practice

Consolidation therapy can be integrated into existing NHS practice

Current clinical practice



Proposed use of daratumumab in clinical practice



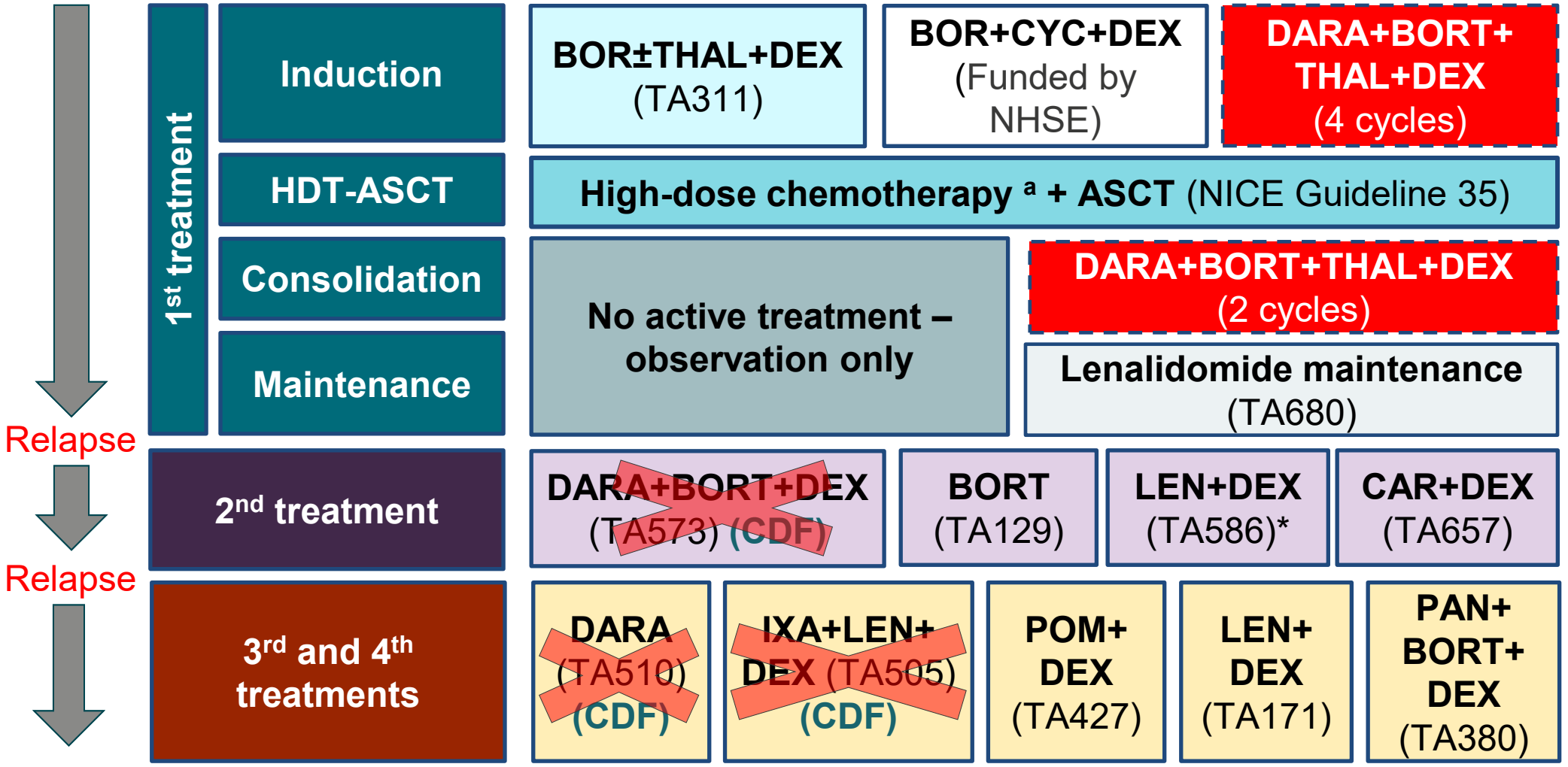
Clinical experts: Could integrate 4 induction and 2 consolidation cycles of DARA+BORT+THAL+DEX into existing practice but patients would stay longer on day-unit

⊙ *Reasonable to consider consolidation? What does maintenance comprise?*

NICE * BORT+THAL+DEX

HDT-ASCT: High-dose therapy followed by autologous stem cell transplant

ASCT-eligible NICE treatment pathway without Cancer Drug fund treatments



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

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)	

⊙ *What determines what treatment one receives?*

Pathway: comparators + follow-on treatments

Company considers BORT+THAL+DEX as main comparator

Company

- Excludes CYC+THAL+DEX (off-label) as a comparator
- BORT+THAL+DEX main comparator: Public Health England (PHE) dataset, [redacted] have BORT+THAL+DEX 1st line; [redacted] have BORT+CYC+DEX; [redacted] have BORT+DEX
- NICE recommended LEN maintenance only in March 2021 so not available at time of submission or technical engagement. Not included as subsequent treatment
  - **CDF team:** DARA would not increase number of people having LEN maintenance, but would increase duration of LEN maintenance
- CDF treatments also not included in modelling
- In model ~45% of people treated at 3rd line and none at 4th line have PAN+BORT+DEX

ERG

- Including LEN maintenance requires more work on model
- Reasonable to exclude CYC+THAL+DEX. Use in clinical practice estimated <5%
- PAN+BOR+DEX not currently used at 3rd/4th line in practice

- *What are the relevant comparators for induction? For consolidation?*
- *How should LEN maintenance be considered?*
- *What % of people who have 3rd/4th line treatment would have PAN+BORT+DEX?*

CDF: Cancer Drugs Fund

Clinical effectiveness

Clinical effectiveness: overview

1. **Comparison with BORT+THAL+DEX: CASSIOPEIA trial**
   - PFS adjusted for maintenance therapy not offered in NHS
   - Introduction to 2◦ endpoint on which company bases its model
2. **Comparison of DARA+BORT+THAL+DEX with other comparators**
   - 'Naïve' comparison
   - Matching adjusted indirect comparison
3. **Health-related quality of life**
4. **Adverse effects**

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 post-ASCT
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): median follow-up 18.8 months (primary analysis for Part 1 of trial) • Post-hoc data cut 1 (May 2019): median follow-up 29.2 months (unplanned requested by EMA) • Interim analysis (Aug 2020): median follow-up 44.5 months

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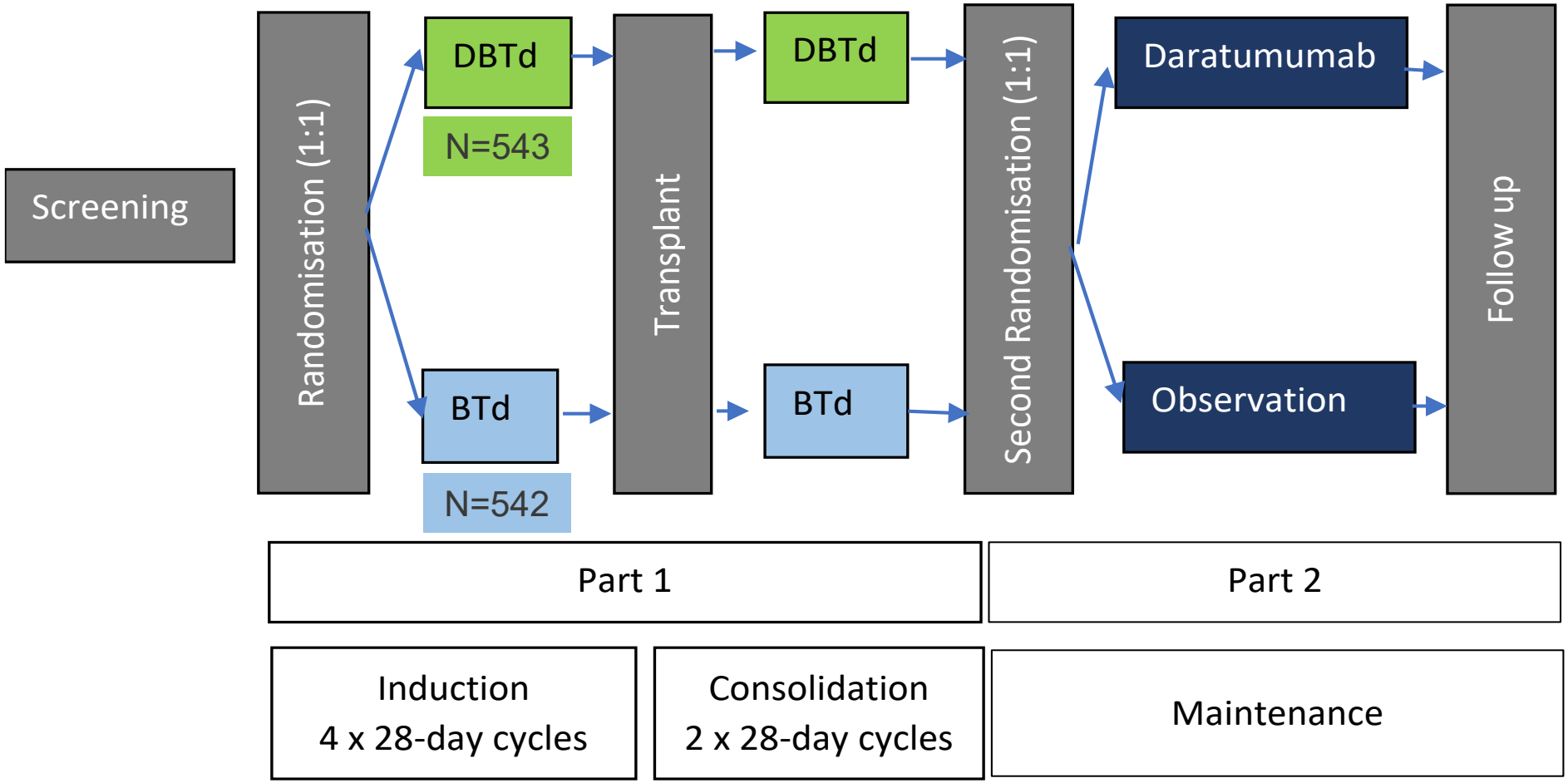
Sources: ERG report table 7 based on CS section B.2.3.1; CS Table 4; CS Figure 7; CS Appendix L.3

ASCT: Autologous stem cell transplant; EMA: European Medicines Agency

CASSIOPEIA: trial schema

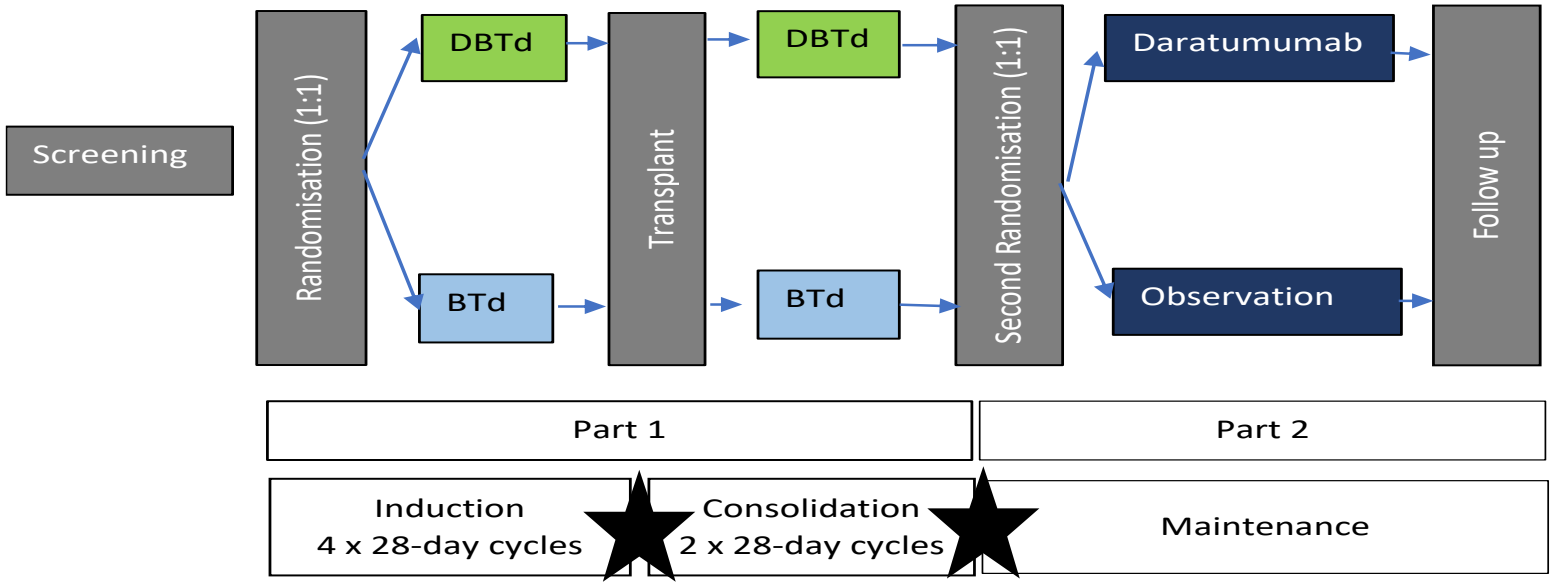
Trial compared DARA+BORT+THAL+DEX with BORT+THAL+DEX
Included part 2: re-randomisation to maintenance therapy (not included in licence)



Sources: Figure from ERG report page 38
DBTd: Daratumumab, bortezomib, thalidomide and dexamethasone;
BTd: Bortezomib, thalidomide and dexamethasone

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



Endpoint	Time assessment	Definition	Modelled?
sCR = 1◦ endpoint	Post-induction Post-transplant Post-consolidation (1◦ endpoint)	% who achieved 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 Post-consolidation	% who achieve MRD negative status	Yes

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⊙ *What is committee's view on using a secondary endpoint (MRD) as a surrogate for another secondary endpoint (PFS/OS)?*

CASSIOPEIA: selected baseline characteristics

Balanced between arms and generally representative of UK patients

Characteristic	DARA (n=543)	Control (n=542)
Sex (female), n (%)	227 (42%)	223 (41%)
Age, years, n (%)		
Mean (SD)	57 (6.9)	57 (7.0)
Baseline ECOG score, n (%)		
0	265 (49%)	257 (47%)
1	225 (41%)	230 (42%)
2	53 (10%)	55 (10%)
Revised International Staging System (ISS) staging, n (%)		
N	535	540
I	103 (20%)	146 (27%)
II	383 (72%)	344 (64%)
III	49 (9%)	50 (9%)

ERG: Patients over 65 excluded; age not prognostically important

ERG: Patients had good functional status (90% ECOG score 0 or 1)

ERG: % with revised ISS stage III low (~20-25% in practice). Potentially better prognosis in control arm

⊙ *Would patients over 65 years/ISS stage III be offered daratumumab therapy in NHS? Is age likely to modify treatment effect?*

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Sources: Excerpts from CS Tables 6, 7, 33 and 34
ECOG: Eastern Cooperative Oncology Group; SD: Standard deviation

Minimal residual disease (MRD)-positive or -negative

MRD 2◦ endpoint % who achieve 'negative status by end of consolidation'.
Not used in clinical practice – company bases economic model on it

- MRD status – residual tumour in bone marrow
- MRD-negative defined as undetectable clonal or sub-clonal cancerous cells
- Not used in practice; recommended for clinical trials

Published meta-analysis[1]:

- 6 RCTs newly-diagnosed MM patients
- Odds ratio for MRD-negative vs MRD-positive response correlated with the hazard ratio for PFS
- Suggests MRD status can be a surrogate for PFS
- Myeloma IX and Myeloma XI show a correlation between MRD status and OS

Clinical experts

- Sustained MRD-negative patients post-transplant live longer
- 5-10% survival improvement would probably be seen amongst patients with sustained MRD negativity

ERG

- Satisfied that MRD status is appropriate for informing the economic analysis
- Clinical experts: MRD negativity likely better predictor of survival than sCR

TA573 FAD (DARA+BORT+DEX for previously treated MM): The committee concluded that relationship between MRD and OS in the long-term in people with relapsed disease had not been established and could not inform the economic model

1. Avet-Loiseau et al. Clinical Lymphoma Myeloma & Leukemia 2020

MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival; RCT: Randomised controlled trial

Inconsistency in defining and using MRD negativity

Company

- Clinical trials - International Myeloma Working Group (IMWG) definition of MRD negativity requires a conventional complete response
- CASSIOPEIA: MRD-negativity regardless of response
- Meta-analysis: Inconsistent definitions of MRD across studies
- Base-case updated at technical engagement to use a consistent definition of MRD (regardless of conventional response). Little impact on ICER
- Scenario analysis applying IMWG definition for MRD negativity not possible because no studies report OS based on the IMWG definition

ERG

- No consensus on which of the MRD definitions (per IMWG criteria or regardless of response) is the most clinically appropriate
- MRD regardless of response consistently defined in all three data sources (MRD meta-analysis, rates of MRD negativity at post-consolidation, landmark analysis)

⊙ *What is committee's view on the appropriate definition of MRD negativity?*

ICER: Incremental cost-effectiveness ratio; MRD: Minimal residual disease; OS: Overall survival

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 (sCR)	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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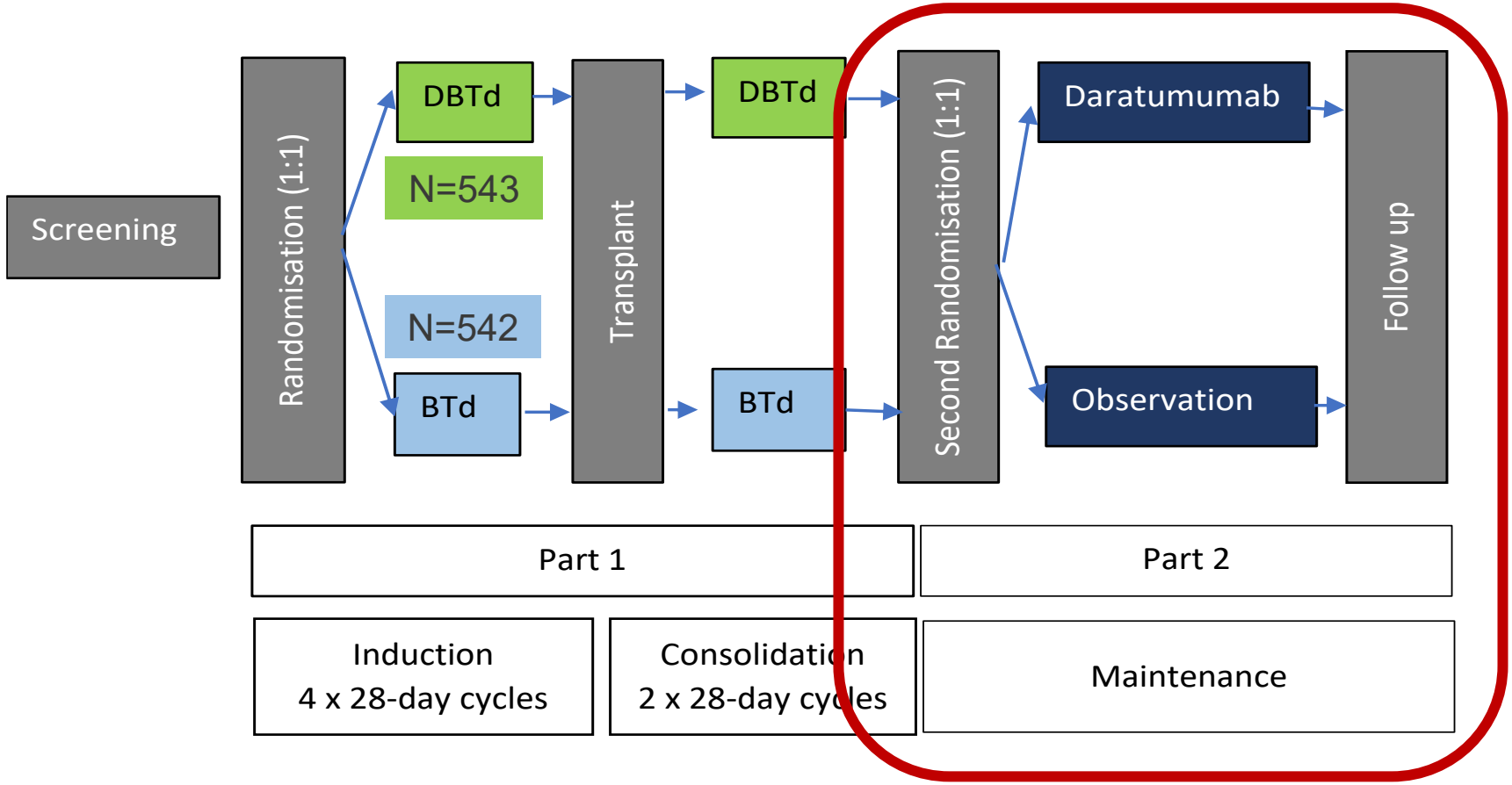
Sources: CS Tables 12-13; CS Figures 8-10; CS section B.2.6.1, EPAR

CI: Confidence interval; MRD: Minimal residual disease

CASSIOPEIA included maintenance therapy

And randomisation to maintenance therapy (which is not included in the EMA license for Part 1)



Trial re-randomised after consolidation treatment. Company presented 2 different approaches to account for re-randomisation:

1. Adjustment using inverse probability weighting (not used in modelling)
2. Censored all who were re-randomised to daratumumab (used in landmark analysis)

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 18m)	1st post-hoc analysis (med follow-up 29m)	Interim analysis (med follow-up 44m)
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]

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- Uncertain if proportional hazards assumption has been met for application of IPW
- For PFS, updated IPW analysis produces counterintuitive results based on MRD status
- Inconsistency in estimated treatment effects obtained using censoring and IPW adjustment approaches, possibly due to bias from censoring

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Sources: Company technical engagement response: Table 1 and 2

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

Comparators not in key trial BORT±CYC+DEX: naive comparison and matching adjusted indirect comparison

- No studies comparing DARA+BORT+THAL+DEX with BORT+CYC+DEX or BORT+DEX

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)
- CASSIOPEIA data reweighted so that mean baseline characteristics match 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 real-world evidence study using PHE dataset to complement MAIC

ERG

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

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

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

⊙ *What are the committee views on the company assumptions around the relative effectiveness of the comparators? Does [redacted]?*

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

CASSIOPEIA: health-related quality of life

No difference between treatments in EQ-5D

EQ-5D score and timepoint		Change from baseline (95% CI)		Difference Mean (95% CI)	Used in model?
		DARA	No DARA		
Index score	Post-induction	0.11 (0.08, 0.13)	0.11 (0.08, 0.13)	0.0 (-0.02, 0.02)	✓*
	Post-consolidation	0.17 (0.14, 0.19)	0.16 (0.13, 0.18)	0.01 (-0.01, 0.04)	✓*

* Progression-free disease utilities based on EQ-5D-5L data from CASSIOPEIA, with utilities derived using mapping function from Van Hout et al.

CI: Confidence interval

Adverse events

Acceptable safety when adding daratumumab to BORT+THAL+DEX

Event [a]	DARA (n=536)	Control (n=538)
Any TEAE, n (%)	535 (99.8%)	536 (99.6%)
Grade 3/4 TEAE, n (%)	432 (81%)	408 (76%)
Serious TEAE, n (%)	251 (47%)	255 (47%)
TEAE leading to discontinuation, n (%)	40 (8%)	45 (8%)
TEAEs leading to death, n (%)	1 (0.2%)	9 (2%)

[a] TEAEs during induction, ASCT, or consolidation Treatment Phase; incidence reflects the number of patients experiencing at least one TEAE associated with at least one of the study treatments. Note: Adverse events emerging during ASCT phase related to the planned procedures were not reported.

Most frequent TEAEs that differ between arms	DARA (n=536)	Control (n=538)
Neutropenia	157 (29%)	89 (17%)
Thrombocytopenia	109 (20%)	73 (14%)
Lymphopenia	99 (19%)	67 (13%)
Bronchitis	102 (19%)	66 (12%)
Nausea	162 (30%)	130 (24%)
Vomiting	87 (16%)	52 (10%)
Cough	90 (17%)	49 (9%)

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Sources: Reproduction of CS Table 39; Excerpt from CS Table 40

ASCT: Autologous stem cell transplant; TEAE: Treatment-emergent adverse event

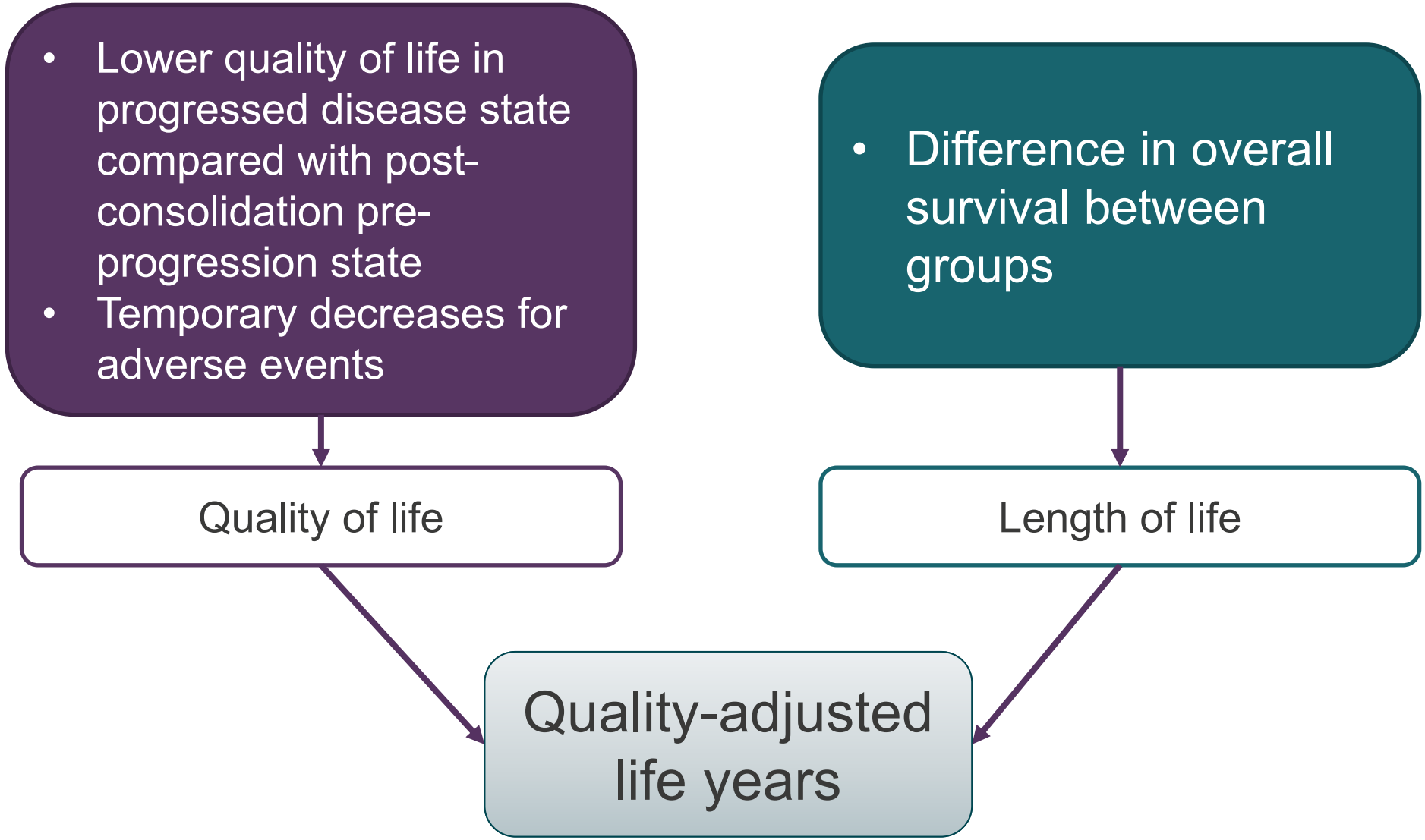
Cost effectiveness

Cost effectiveness: overview

1. Conceptual model overall QALY gains
2. Model structure
3. Comparators
4. Population
5. Modelling based on MRD status
   - Meta-analysis association between residual disease and PFS/OS
   - ‘Landmark’ analysis
6. Validity extrapolations of PFS and OS
7. Waning of treatment effect
8. Utilities
9. Costs

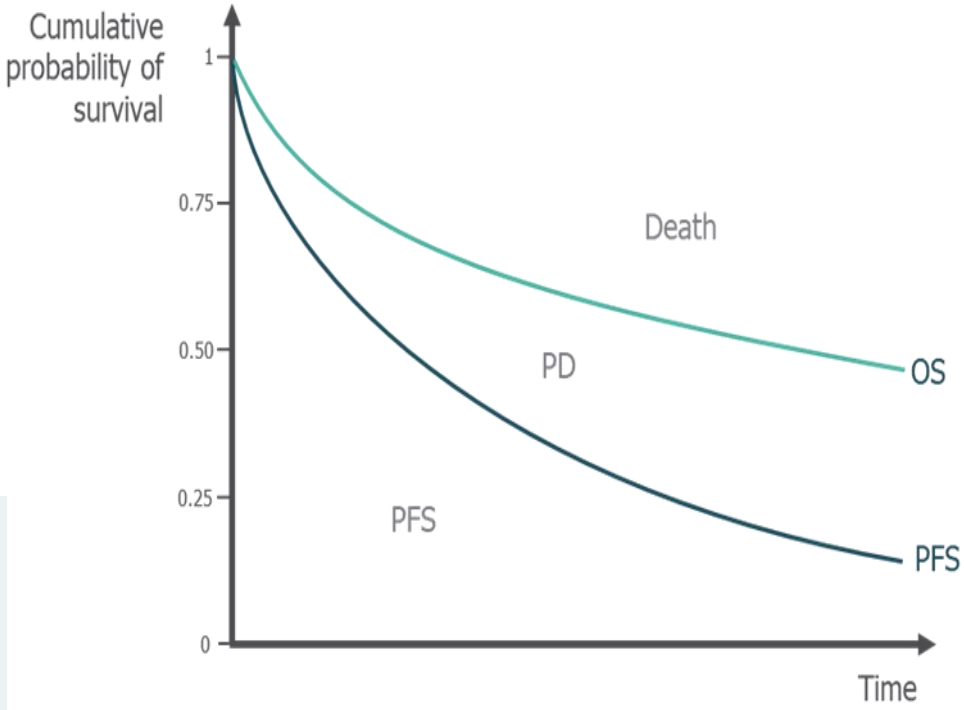
MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life year

How quality-adjusted life years accrue



Company's model structure

- Partitioned survival model
- 3 health states: pre-progression, progressed disease, and death
- Cycle length: 4 weeks
- Time horizon: lifetime
- Extrapolating OS and PFS: 'MRD-based' modelling
- Only comparator considered is BORT+THAL+DEX



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- CASSIOPEIA OS data too immature for parametric extrapolations
- High uncertainty also over parametric extrapolations of PFS
- ERG agrees with modelling based on residual disease status

MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival

Comparators in model

BORT+THAL+DEX is only comparator considered in economic modelling

Company

- Results from matching adjusted indirect comparison (MAIC):
  - [redacted]
  - [redacted]
  - [redacted]
- If DARA+BORT+THAL+DEX is cost-effective versus BORT+THAL+DEX, then it will also be cost-effective versus BORT+CYC+DEX and BORT+DEX

ERG

- Agree: treatment effect and costs similar for BORT+THAL+DEX and BORT+CYC+DEX based on company's MAIC analysis and clinical opinion

Clinical experts

- BORT+THAL+DEX and BORT+CYC+DEX comparable
- Response rate slightly better with BORT+THAL+DEX
- Cyclophosphamide is associated with increased toxicity

NICE ⊙ *What comparators should be included in the economic model?*

Population in the model

Choice of baseline characteristics in the model impacts on cost effectiveness

CASSIOPEIA:

- Adults newly diagnosed myeloma transplant-eligible, mean age 56.6 years
- Company uses this age in base-case

Public health England:

- Newly-diagnosed and transplant-eligible diagnosed between 1 January 2015 and 31st Dec 2018 - mean age [redacted] years at diagnosis

ERG

- CASSIOPEIA does not reflect UK NHS
- ERG base case, mean age of [redacted] years reflecting UK NHS

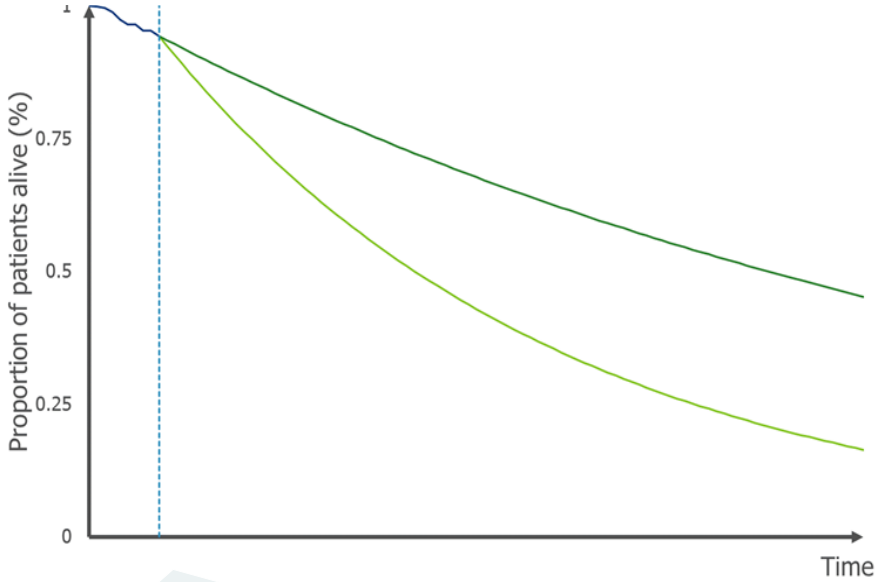
Company: adjustment inappropriate because all other efficacy inputs come from the trial population

⊙ *What baseline age should be used in the economic model?*

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

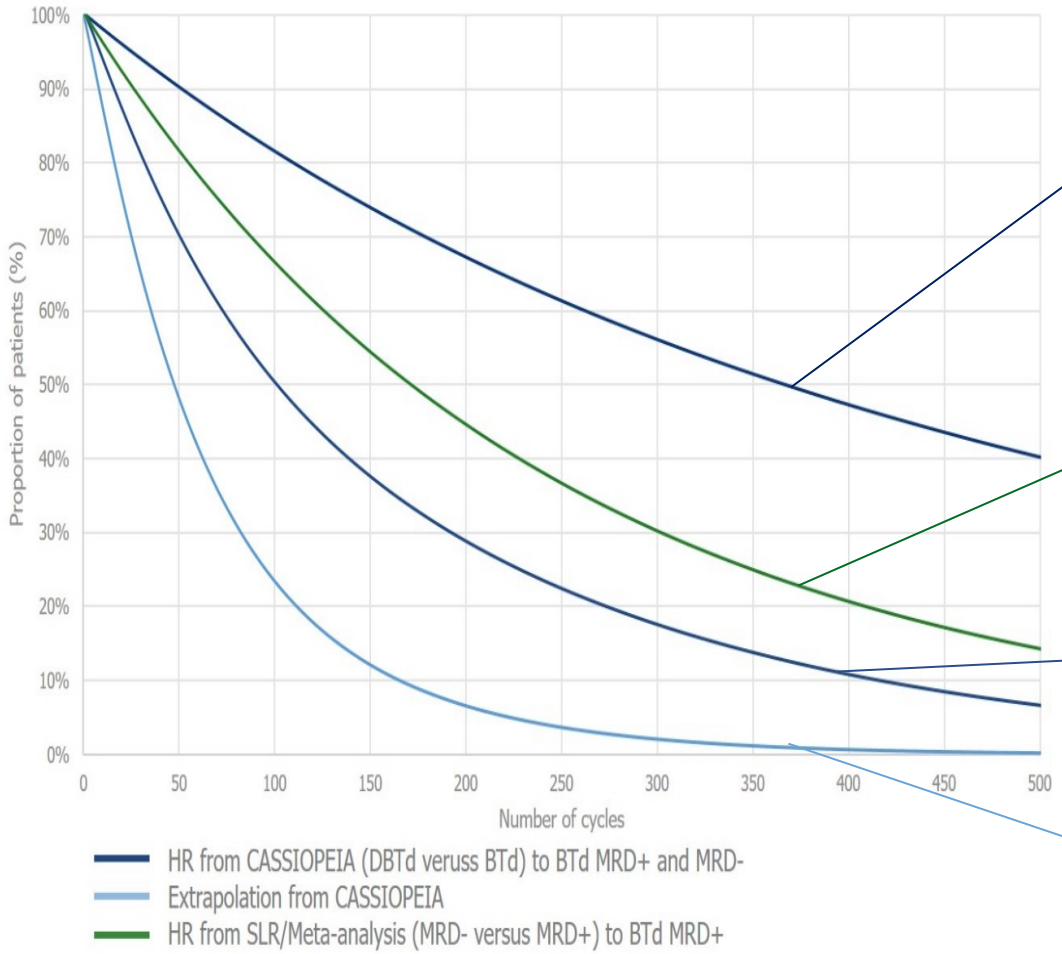
MRD status	DARA+BORT+THAL+DEX	BORT+THAL+DEX
MRD-negative	64% (95% CI: 60%, 68%)	44% (95% CI: 39%, 48%)
MRD-positive	36%	56%

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

Company's MRD-based modelling

MRD-positive or -negative post-consolidation determines PFS, OS extrapolations

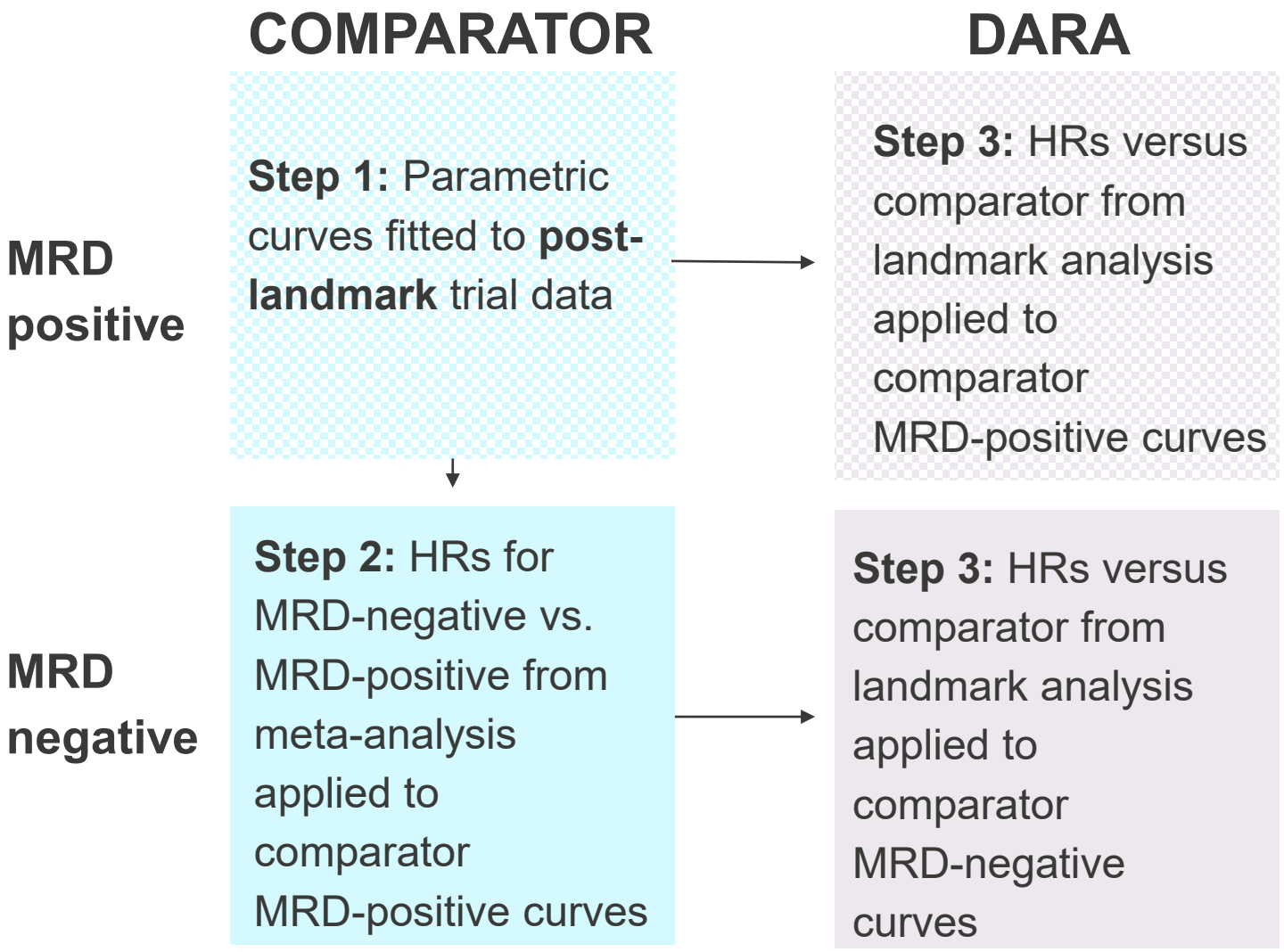


Clinical status	Source of extrapolated data
MRD- DARA	HRs from Landmark analysis applied to MRD-negative control survival curves
MRD- control	HR (MRD neg versus MRD+) from meta-analysis applied to control MRD-positive survival curve
MRD+ DARA	HRs from Landmark analysis applied to MRD+ control survival curves
MRD+ control	OS and PFS extrapolated directly from CASSIOPEIA

Source: modified, company document B, Figure 28

HR: Hazard ratio; MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival

MRD-based modelling of survival outcomes in post-landmark period model cycle 9+



HR: Hazard ratio; MRD: Minimal residual disease

Company performed meta-analysis on association of MRD on survival outcomes

Results of meta-analysis show improved survival for people with MRD-negative status

Comparison	PFS - HR (95% CI)	OS - HR (95% CI)
Control group MRD-negative vs MRD-positive	[redacted]	[redacted]

ERG

- Meta-analysis methodology has been correctly applied
- Some uncertainty in HRs remains due to heterogeneity of the included studies
- Results depend on the timing of the survival assessment
- Later timepoints likely provide less favourable HRs for the effect of MRD negativity on survival
- Economic model results not sensitive to HRs for the effect of MRD negativity on survival

⊙ *What is committee's view on using a secondary endpoint as a surrogate for another secondary endpoint?*

HR: Hazard ratio; MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival

CASSIOPEIA: ‘Landmark’ analysis survival by MRD status

Exploratory analysis to assess survival outcomes by MRD response status

Landmark analysis:

- Company chose a time point during follow-up period known as ‘landmark’
- Analysis includes only those who have survived until landmark time

CASSIOPEIA: Landmark analysis

- Exploratory analysis
- Compared survival for people with MRD-negative vs positive status 100 days post transplant
- Impact of MRD negative status on survival outcomes for people who had DARA treatment compared to control treatment
- Association between MRD-positive versus negative and both PFS and OS HRs using Cox proportional hazard model
- Updated analysis (median follow-up 44.5 months) censored on maintenance daratumumab to adjust for 2nd randomisation

HR: Hazard ratio; MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival

Landmark analysis: OS and PFS by treatment arm and MRD status median follow-up = 44.5 months

Improved OS and PFS for MRD- compared to MRD+ in both treatment arms

Progression-free survival

Overall survival

BTd: Bortezomib, thalidomide and dexamethasone; DBTd: Daratumumab, bortezomib, thalidomide and dexamethasone; MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival

CASSIOPEIA: Landmark analysis of survival by MRD status

DARA appears to improve OS and PFS regardless of MRD response status

DARA vs Control	Original landmark analysis (median follow-up = 29.2 months)	Updated landmark analysis (median follow-up = 44.5 months, censoring for maintenance)
PFS		
MRD+ HR (95% CI)	[redacted]	[redacted]
MRD- HR (95% CI)	[redacted]	[redacted]
OS		
MRD+ HR (95% CI)	[redacted]	[redacted]
MRD- HR (95% CI)	[redacted]	[redacted]

ERG

- Results exploratory and not powered statistically for this comparison
- Analysis supports the treatment effect on PFS
- Despite additional follow-up, [redacted]
- Landmark analysis adjusted for re-randomisation more appropriate

- *Is the censored landmark analysis acceptable?*
- *Should adjustment methods not sensitive to the proportional hazards assumption be used?*

NICE

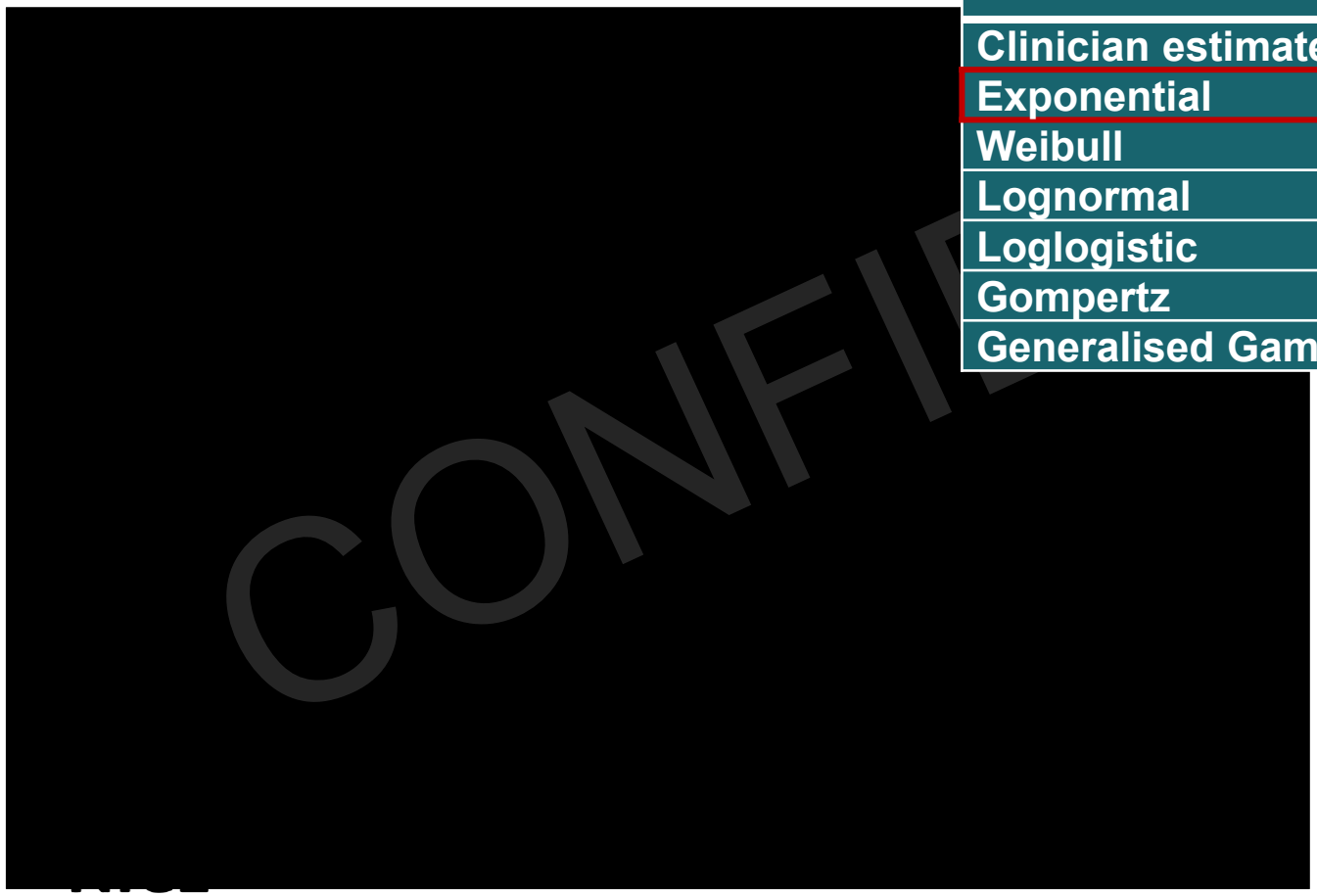
CI: Confidence interval; HR: Hazard ratio; MRD: Minimal residual disease; OS: Overall survival; PFS: Progression-free survival

Overall survival extrapolating MRD+ comparator group

Uncertainty in extrapolations due to censoring

Company fitted curves to the landmark analysis using censored data from August 2020 data cut (median follow-up = 44.5 months)

Extrapolation of OS for comparator MRD+



Survival model	OS survival rates			
	5 years	10 years	20 years	30 years
Clinician estimate	≤70%	44%	-	-
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]

ERG: Survival curves for extrapolation of OS may be susceptible to selection bias due to censoring of patients who were randomised to daratumumab maintenance

MRD: Minimal residual disease; OS: Overall survival

Plausibility long-term survival extrapolations standard care

Comparing OS for comparator predicted by model versus CASSIOPEIA (MRD+ and MRD- combined), censoring for maintenance therapy

MRD: Minimal residual disease; OS: Overall survival

Plausibility of long-term survival extrapolations

Company chose exponential but not best visual fit to trial data

[redacted]

Survival model	Progression-free survival rates		
	5 years	10 years	20 years
Clinician estimate	20–30%	<10%	<1%
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]

ERG: Gompertz and Weibull clearly have a better visual fit than the exponential

NICE

⊙ *What curve should be used to extrapolate progression-free survival in MRD+ population on standard care?*

Plausibility long-term survival extrapolations standard care

Comparing PFS for comparator predicted by model versus CASSIOPEIA (MRD+ and MRD- combined), censoring for maintenance therapy

MRD: Minimal residual disease; PFS: Progression-free survival

Plausibility long-term survival extrapolations standard care

Survival rates predicted by the model compared to other sources

Data source	Progression-free survival			Overall survival		
	3-Yr	5-Yr	10-Yr	3-Yr	5-Yr	10-Yr
Revised company model	52%	33%	12%	86%	76%	57%
CASSIOPEIA (censored for daratumumab maintenance)	[redacted]	-	-	[redacted]	-	-
GIMEMA study	68%	50%	34%	86%	79%*	60%
PHE cohort	[redacted]	-	-	[redacted]	-	-
US RWE (SEER/OPTUM)	-	-	-	-	74%	68%
ONS (55-64 years old) **	-	-	-	-	64%	43%

*Janssen estimate based on visual inspection of the published Kaplan-Meier curves from Tacchetti et al. 2020

** All patient estimate for newly diagnosed MM including mixed population of transplant-eligible and ineligible patients

Additional evidence:

- GIMEMA: RCT of BORT+THAL+DEX vs THAL+DEX (median follow-up 124.1 months)
- US real-world evidence (SEER/OPTUM): US claims and EMR data sources
- PHE cohort: real-world evidence study using multiple linked datasets including HES, SACT
- ONS: Cancer survival in England (2013-2017) dataset, multiple myeloma 55-64 age group

NICE

HES: Hospital Episode Statistics; ONS: Office of National Statistics; PHE: Public Health England; RCT: Randomised controlled trial; RWE: Real-world evidence; SACT: Systemic Anti-Cancer Therapy Dataset

Plausibility long-term survival extrapolations standard care

Results uncertain: trial included maintenance and license does not

ERG

- US RWE and ONS data less useful
  - US RWE only 51 patients with 1st line BORT+THAL+DEX induction prior to ASCT
  - ONS data not relevant (includes transplant-ineligible patients)

Overall survival

- Data immature
- Exponential extrapolation is reasonable
- Fitted survival curves may be biased due to censoring
- OS estimates are broadly similar to GIMEMA

Progression-free survival

- Exponential model does not fit trial data
- Modelled PFS considerably lower at 3, 5 and 10 years than in GIMEMA, maybe due to differences in the trial protocols or patient characteristics
- Weibull PFS extrapolations fit better
- Weibull more appropriate for PFS in MRD

ASCT: Autologous stem-cell transplant; MRD: Minimal residual disease; ONS: Office of National Statistics; RWE: Real-world evidence

Waning of daratumumab treatment effect

Large impact on the cost effectiveness results

Company

- Relative treatment effects persist over model time horizon of ~ 40 years
- Data from August 2020 data cut (median follow-up approaching 4 years) demonstrates relative benefit
- Additional evidence presented: sustained MRD negativity, increasing response without maintenance therapy and MRD-negative conversion from Part 2 of CASSIOPEIA over 2 years of follow-up and PFS2 from Part 1 of CASSIOPEIA with follow-up approaching 4 years
- GIMEMA study demonstrates a persistent relative benefit of BTd versus Td for PFS (median follow-up of 10-years)

Clinical experts

- Treatment probably wanes, definitely does not persist over lifetime horizon
- No long-term data (> 5 years) with daratumumab in 1st line therapy

ERG

- No data to support absence of waning
- Difficult to draw conclusions from updated landmark analysis, because of problems with censoring
- ERG base case has loss of treatment effect 5 years after consolidation (HR=1 for PFS and OS in both MRD+ and MRD-)

BTd: Bortezomib, thalidomide and dexamethasone; HR: Hazard ratio; MRD: Minimal residual disease; PFS: Progression-free survival; Td: Thalidomide and dexamethasone

Waning of daratumumab treatment effect

Survival curves extrapolations no waning

Survival curves with waning
HR = 1 @ 5 years – ERG preferred assumption

- *Is the clinical evidence adequate to support a continued daratumumab treatment effect over the model time horizon?*
- *How should the waning of treatment effect be modelled?*

HR: Hazard ratio

Company base case model: utilities

Sources and implementation overall appropriate

- CASSIOPEIA EQ-5D-5L data at 3 timepoints:

  Baseline; Cycle 4 day 28 = end induction, Day 100 post-ASCT = end consolidation

- Alternative utility values in scenario analyses – do not influence cost effectiveness

ERG

- Modified age adjustment
- Utilities reasonable

Health state		Model cycle	Utility Mean (SD)	Source
Progression free	Induction therapy	0-3	0.57 (0.31)	CASSIOPEIA Baseline
	Post-induction to post-consolidation response	4-8	0.68 (0.22)	End of induction
	Post-consolidation	9+	0.73 (0.17)	Response assessment
Progressed disease			0.69 (-)	Van Agthoven et al. (2004), TA311

Source: CS Table 60

ASCT: Autologous stem-cell transplant

Company base case model: costs

Treatment costs differ between company and ERG

Company

- Systematic literature review conducted to identify resource use, costs
- Costs: drug acquisition and administration for induction/consolidation and subsequent therapies; concomitant medication for induction/ consolidation therapies; transplant; monitoring; and management of adverse events

ERG

- ERG overall agrees with sources and implementation except:
  - Cost of subsequent treatments
    - ERG and NICE clinical experts: PAN+BORT+DEX regimen is not currently used at third or fourth line
    - Cost of PAN+BORT+DEX excluded from ERG analyses
  - Daratumumab acquisition costs (next slide)

Daratumumab acquisition costs in model

Do not reflect costs of formulation used in the trial

- In CASSIOPEIA daratumumab administered as a weight-based intravenous (IV) formulation - 16 mg/kg
- In company base case analysis, daratumumab costed as fixed-dose subcutaneous (SC) formulation 1800 mg

ERG

- Evidence that SC formulation is non-inferior (COLUMBIA trial), and patients and clinicians likely prefer it
- But, divorcing costs and effects may bias cost effectiveness estimates

⊙ *What costs should be used in the economic model for daratumumab?*

Innovation

Company considers daratumumab is innovative

- 1st in class therapy, targeting CD38
- Targets tumour and modulates immune system
- Daratumumab is effective irrespective of clonal heterogeneity and increases the depth and durability of response

Equalities

- Treatment should not be limited to patients aged under 65
- Myeloma more common in men than women and the incidence is also reported to be higher in people of African American family origin (TA 510)
- No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts

Summary of model survival estimates

Mean survival estimates differ between company and ERG base case

Mean survival estimates

DARA+BORT+THAL+DEX
- Company
- ERG

BORT+THAL+DEX
- Company
- ERG

[redacted]

Cost-effectiveness results

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