Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

PART 1 for PROJECTOR: contains no confidential information

Technology appraisal committee B 2nd meeting [12 March 2026]

Chair: Charles Crawley

Lead team: Mariana Bacelar, Nigel Westwood, Lisa Attrill

External assessment group: Southampton Health Technology Assessments Centre (SHTAC)

Technical team: Sharlene Ting, Nigel Gumbleton, Lauren Elston, Emily Crowe

Company: Jonhson and Johnson Innovative Medicine

Draft guidance consultation

Daratumumab (Darzalex)

- **Marketing authorisation (April 2025):** in combination with BOR, LEN and DEX for newly diagnosed MM
  - **Company narrower positioning:** untreated MM when ASCT is unsuitable
- **Relevant comparators:** DAR+LEN+DEX and ISA+BOR+LEN+DEX
- **CEPHEUS (DAR+BOR+LEN+DEX vs BOR+LEN+DEX):** company focused on ASCT-ineligible subgroup

*Link to Appendix – Treatment pathway

RECAP

Preliminary recommendation

Daratumumab with bortezomib, lenalidomide and dexamethasone should not be used for untreated multiple myeloma in adults when an autologous stem cell transplant (ASCT) is unsuitable

DG consultation responses

- **Company:** new evidence and analyses, updated base case with committee's preferred assumptions after ECM1
- **Patient organisations:** Myeloma UK, The UK Myeloma Society
- **Commentators:** Sanofi (SC admin cost for DAR, treatment duration of ISA+BOR+LEN+DEX)
- **NICE Healthcare Data Analytics team:** unable to provide SACT data on 2L and 3L treatments (insufficient post-TA917 follow-up, challenges in reliably excluding ASCT patients and identifying regimens within time frame)

Abbreviations: 2L/3L, 2nd / 3rd line; ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ECM, evaluation committee meeting; ISA, isatuximab; LEN, lenalidomide; MM, multiple myeloma; SACT, Systemic Anti-Cancer Therapy; SC, subcutaneous; TA, technology appraisal

Key issues

Issue	ICER impact
CEPHEUS analysis set: ASCT-ineligible or ITT (ASCT-ineligible and deferred) and ITCs	Large (slides 4-6)
Long-term extrapolations of OS, PFS and TTD	Unknown (slide 7)
TTD for ISA+BOR+LEN+DEX	Large (slide 8)
Subsequent treatment distributions	Moderate (slides 9-11)
Subcutaneous administration cost	Large (slide 12)
Uncaptured benefits, equality and other considerations	Unknown (slides 15-16)

NICE

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; ISA, isatuximab; ITC, indirect treatment comparison; ITT, intention to treat; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

Analysis sets and ITCs: ASCT-ineligible vs ITT

Large ICER impact

Background

- At ECM1, company provided analyses for CEPHEUS ASCT-ineligible subgroup only
- ECM1 clinical experts advised ASCT-deferred would follow ineligible pathway, with likely similar outcomes
- Committee preferred following ITCs (adjusted for COVID-19) for DAR+BOR+LEN+DEX:
  - vs DAR+LEN+DEX: IPTW using IPD from CEPHEUS and MAIA
    - Committee requested evidence supporting PH assumption for NMA [DG, 3.8]
  - vs ISA+BOR+LEN+DEX: NMA using data from CEPHEUS and IMROZ (both incl. BOR+LEN+DEX)
- Committee requested analyses using CEPHEUS ITT (ASCT-ineligible **and** deferred) [DG, 3.5]

Company: CEPHEUS ITT considerations

- Provided baseline characteristics for ASCT-ineligible (n=289, 73%) and deferred (n=106, 27%). ASCT-deferred:
  - younger and fitter → likely better outcomes
  - non-biological reasons for deferral e.g. clinician or patient choice
  - disproportionately impacted by COVID-19 (recruitment concentrated in Brazil and Poland)
  - no UK patients; experts advise deferral is rare in practice → limited UK generalisability
- Provided full details of ITC approaches to address committee's concerns about uncertainty
  - PH assessment for DAR+LEN+DEX NMAs: log-log plots suggest non-constant hazards over time
- Provided clinical and cost-effectiveness results for full CEPHEUS ITT vs comparators
  - MAIA and IMROZ enrolled ASCT-ineligible only; CEPHEUS ITT is mixed

  → violates population similarity assumptions underpinning ITCs (inclusion of ASCT-deferred introduces structural confounding in IPTW ITC)

NICE

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; DG, draft guidance; ECM, evaluation committee meeting; IPD, individual patient data; IPTW, inverse probability of treatment weighting; ISA, isatuximab; ITC, indirect treatment comparison; ITT, intention to treat; LEN, lenalidomide; n, number; NMA, network meta-analysis; PH, proportional hazards

Large ICER impact

ITC results: CEPHEUS ASCT-ineligible and ITT

Table 1. IPTW ITC (adjusted for COVID-19): DAR+BOR+LEN+DEX vs DAR+LEN+DEX

Outcome (HR, 95% CI, p value)	ASCT-ineligible*	ITT (ASCT ineligible and deferred)
OS	**0.63**; 0.41 to 0.98; p=0.04	[redacted]
PFS	**0.55**; 0.38 to 0.79; p=0.001	[redacted]
TTD	[redacted]	[redacted]

Table 2. NMA (fixed effects models): DAR+BOR+LEN+DEX vs ISA+BOR+LEN+DEX

Outcome (HR, 95% CrI)	ASCT-ineligible		ITT (ASCT ineligible and deferred)		
	COVID-19 adjusted	COVID-19 unadjusted*	COVID-19 adjusted	COVID-19 unadjusted	COVID-19 unadjusted^ and exclude Brazil, Poland
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Results for random effects model used in company original base case (unadjusted for COVID-19) in Appendix
- Insufficient published TTD data for ISA+BOR+LEN+DEX to undertake NMA

*Company base case; ^clarified by company by email

Which NMA models should be used to inform HRs for OS and PFS for DAR+BOR+LEN+DEX vs ISA+BOR+LEN+DEX? Fixed or random effects and COVID-19 adjusted or unadjusted?

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; CI/CrI, confidence/credible intervals; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ISA, isatuximab; ITC, indirect treatment comparison; ITT, intention to treat; LEN, lenalidomide; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

ASCT-ineligible vs ITT: Comments

Large ICER impact

EAG

- Uncertain whether baseline differences between ASCT-ineligible and deferred reflect trial artefacts (e.g. eligibility criteria; disproportionately small deferred subgroup) or real-world practice
- UK patients comprised 8% of ineligible subgroup → also have limited UK generalisability
- Because ASCT-ineligible comprise 73% of CEPHEUS, baseline characteristics of ITT are closely aligned
- IPTW ITC and NMA results are broadly consistent across ASCT-ineligible and ITT populations, providing reassurance on robustness of results despite heterogeneity concerns

Patient organisations: Myeloma UK and The UK Myeloma Society

- Inappropriate to include ASCT-deferred – does not reflect NHS practice as deferral does not occur in UK; younger and fitter, not representative of ASCT-ineligible population

- Has the committee seen evidence to change its preferred ITC approaches? DAR+BOR+LEN+DEX
  - vs DAR+LEN+DEX: IPTW using IPD from CEPHEUS and MAIA (adjusted for COVID-19)
  - vs ISA+BOR+LEN+DEX: NMA using data from CEPHEUS and IMROZ (adjusted for COVID-19)
- Do the additional ITT analyses change the committee's views about the uncertainty of the ITC approaches?
- Which analysis set from CEPHEUS should be used? ASCT-ineligible or ITT?
  - Are the definitions of transplant-eligibility consistent across trials in the ITCs?

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; IPD, individual patient data; IPTW, inverse probability of treatment weighting; ISA, isatuximab; ITC, indirect treatment comparison; ITT, intention to treat; LEN, lenalidomide; NMA, network meta-analysis

Long-term extrapolations of OS, PFS and TTD

Background

- At ECM1, company extrapolated COVID-19 adjusted OS, PFS, TTD using weighted KM data from CEPHEUS ASCT-ineligible for DAR+BOR+LEN+DEX and from MAIA for DAR+LEN+DEX
  - For ISA+BOR+LEN+DEX, PFS and OS HRs from NMA were applied to baseline DAR+BOR+LEN+DEX
- Committee considered CEPHEUS data immature – median OS and PFS not reached
- Committee requested:
  - Plots of implied time-varying HRs for extrapolations
  - Scenarios using alternative baseline OS; CEPHEUS ITT data [DG, 3.9]

Company

- Provided KM COVID-19 adjusted plots for PFS, OS and TTD using CEPHEUS ITT
- CEPHEUS ~5-year follow-up (median ~58.7 months) consistent with other trials e.g. IMROZ (~59.7 months; medians not reached; considered suitable for decision making in TA1098)
- Model takes conservative calibration approach using best-fitting PFS and OS curves for DAR+BOR+LEN+DEX and DAR+LEN+DEX adjusted to match UK clinical expert survival expectations at 10, 15 and 20 years
- Provided implied HRs plots for DAR+BOR+LEN+DEX vs DAR+LEN+DEX independently fitted PFS and OS
  - Calibration leads to implied HR that varies across 5-year increments; time-varying hazard multipliers applied to each arm after Year 5 (and Year 7 for DAR+LEN+DEX OS)
  - Average implied HRs remain less favourable than ITC HRs (PFS: [redacted] vs 0.55; OS [redacted] vs 0.63)
- Provided scenario using alternative OS baseline (second best-fitting curves) – no SACT data (small ICER impact)

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; DG, draft guidance; ECM, evaluation committee meeting; HR, hazard ratio; ISA, isatuximab; ITT, intention to treat; KM, Kaplan-Meier; LEN, lenalidomide; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; SACT, Systemic Anti-Cancer Therapy; TA, technology appraisal; TTD, time to treatment discontinuation

Extrapolation of TTD for ISA+BOR+LEN+DEX

Large ICER impact

Company

- Insufficient published TTD data for ISA+BOR+LEN+DEX → ITC vs DAR+BOR+LEN+DEX not feasible
- **Company base case**: assumes equal TTD to DAR+BOR+LEN+DEX (reasonable → both are anti-CD38 quadruplets with BOR+LEN+DEX)
- **Additional scenario (conservative):** applied PFS HR for DAR+BOR+LEN+DEX and ISA+BOR+LEN+DEX ([redacted]) to DAR+BOR+LEN+DEX TTD curve to derive shorter ISA+BOR+LEN+DEX TTD
  - Ensures consistency between PFS and TTD
  - Rationale for shorter ISA+BOR+LEN+DEX TTD: Inconvenience of administration and greater AE burden – hours for ISA IV vs 3-5 min SC injection for DAR and 15 additional hospital visits in first 2 years for ISA

Other stakeholders: Sanofi (Data confidential and will be presented in Part 2a)

- In TA1098, MAIC showed ISA+BOR+LEN+DEX and DAR+LEN+DEX TTD curves overlapped across follow-up
  - Committee concluded equal duration between ISA+BOR+LEN+DEX and DAR+LEN+DEX acceptable
  - Implies shorter treatment duration for ISA+BOR+LEN+DEX vs DAR+BOR+LEN+DEX
    - ISA+BOR+LEN+DEX TTD can be modelled using DAR+LEN+DEX TTD curve

EAG

- Agrees TTD KM curves for ISA+BOR+LEN+DEX and DAR+LEN+DEX overlap
  - Scenario: ISA+BOR+LEN+DEX TTD equal to DAR+LEN+DEX TTD

How should TTD of ISA+BOR+LEN+DEX be modelled? Equal to DAR+LEN+DEX or equal to DAR+BOR+LEN+DEX or company's PFS HR scenario?

NICE

Abbreviations: AE, adverse event; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; ISA, isatuximab; ITC, indirect treatment comparison; IV, intravenous; KM, Kaplan-Meier; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; SC, subcutaneous; TA, technology appraisal; TTD, time to treatment discontinuation

Subsequent treatment distributions

Moderate ICER impact

Background: committee considerations

- Uncertainty in 2L and 3L subsequent treatment distributions
- Requested more evidence to validate NHS subsequent treatment patterns including SACT data to inform proportions (DG, 3.12)

Company

- Company base case informed by UK clinical expert advisory board of 5 haematologists (May 2025)
  - Clinical expert opinion most credible and current: long 1L PFS and rapidly evolving MM landscape limits availability of robust real-world data
- Limitations of alternative sources
  - **NHS pharmacy/ePrescribing datasets (VSTx):** reflects prevalent, not new patients; does not link 2L use to prior 1L regimen; no 3L splits after DAR+LEN+DEX. Limited 2L data to options allowed after DAR+LEN+DEX
  - **IQVIA market research** (2025 online surveys): BEL+BOR+DEX use continually increasing per quarter
  - No robust dataset currently available for post-DAR+LEN+DEX or DAR+BOR+LEN+DEX sequencing
  - Small patient numbers prevent meaningful 3L distribution estimates (little impact on ICER)
- **EAG preferred 2L distribution:** not clinically plausible or allowed per NICE guidance
- Model applies same 2L and3L distributions across arms (UK clinical experts consider appropriate): no differential relative effects expected
- Provided 2 scenarios:
  - **Scenario 1:** 2L BEL+BOR+DEX at 50%, remaining treatments reweighted
  - **Scenario 2:** 2L distribution aligned with VSTx dataset

Abbreviations: 1L/2L/3L, 1st / 2nd / 3rd line; BEL, belantamab mafodotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; DG, draft guidance; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MM, multiple myeloma; PFS, progression free survival; SACT, Systemic Anti-Cancer Therapy

Moderate ICER impact

Subsequent treatment distributions

NICE technical team

- In its DGC response, company submitted reference pack with full VSTx dataset (see table below)
- Company's truncated dataset of options permitted after DAR+LEN+DEX included BOR+DEX/BOR combinations, not present in full dataset and only used September data to derive its proportions
- NICE technical team used complete dataset (4 months of data) and redistributed non-applicable options to derive 2 alternative scenarios

Table 3. NICE technical team subsequent treatment distribution scenarios using VSTx dataset

2L regimens	Jun 25	Jul 25	Aug 25	Sep 25	Jun to Sep 25 n (%)	NICE technical team scenarios
CAR+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SEL+BOR+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BEL+BOR+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Redistributed across CAR+DEX ([redacted]%) and SEL+BOR+DEX ([redacted]%)
DAR+BOR+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Exclude **Scenario 3:** all move to BEL+BOR+DEX **Scenario 4:** all redistributed to other 2L options
CAR+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Exclude (removed from dataset)
LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Exclude (removed from dataset)

consultation; LEN, lenalidomide; SEL, selinexor

Moderate ICER impact

Subsequent treatment distributions: 2L and 3L

Table 4. Subsequent treatment 2L and 3L distributions

	Treatment	Proportion of patients (%)						
		Company base case	IQVIA	VSTx	Scenario 1	Scenario 2	EAG scenarios requested by NICE	
							Scenario 3	Scenario 4
2L	CAR+DEX	9.38	[redacted]	[redacted]	37.6	[redacted]	[redacted]	[redacted]
	SEL+BOR+DEX	3.13	[redacted]	[redacted]	12.4	[redacted]	[redacted]	[redacted]
	BEL+BOR+DEX	87.5	[redacted]	[redacted]	50	[redacted]	[redacted]	[redacted]
	BOR+DEX or BOR	0	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
3L	Cyclophosphamide	41.18	NA	NA	49.05	56.1	41.18	41.18
	PAN+BOR+DEX	17.65	NA	NA	20.95	23.9	17.65	17.65
	SEL+BOR+DEX	41.18	NA	NA	30	20	41.18	41.18

- Company original base case: distributions differed depending on 1L treatment, DAR+BOR+LEN+DEX or DAR+LEN+DEX. Company assumed same distributions for DAR+BOR+LEN+DEX and ISA+BOR+LEN+DEX
- Company updated base case: assumes distributions are same regardless of 1L treatment
- NICE requested **scenarios 3 and 4** using VSTx data. **Scenario 3**: everyone who had DAR+BOR+DEX moved to BEL+BOR+DEX at 2L. **Scenario 4**: everyone who had DAR+BOR+DEX redistributed across other 2L options

- Is it clinically plausible that the subsequent treatment distributions at 2L and 3L would be the same regardless of 1L DAR+BOR+LEN+DEX, ISA+BOR+LEN+DEX or DAR+LEN+DEX?
- Which 2L and 3L distributions are most clinically plausible?

NICE

Abbreviations: 1L/2L/3L, 1st / 2nd / 3rd line; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; LEN, lenalidomide; PAN, panobinostat; SEL, selinexor

Subcutaneous administration cost

Large ICER impact

Company

- Company base case used cost code for subcutaneous administration that includes nurse time only
  - N10AF (£115.36); Specialist nursing, cancer related, adult, face to face; National Schedule of NHS Costs 2023/24

Other stakeholders: Sanofi

- Section 3.12 of TA1098 states "SB12Z [cost code] included nurse time (30 minutes) and chair time (up to 60 minutes), as per NHS guidelines. The chair time included time to observe people having the treatment and to administer the subcutaneous treatment. N10AF factors in the nurse time, but not chair time."
  - TA1098's committee concluded that SB12Z applied in TA1098's model was acceptable

EAG

- Provided scenario using SB12Z (£152) National Schedule of NHS Costs 2023/24 applied to subcutaneous administrations in company updated base case

Which subcutaneous administration cost should be used? N10AF (£115.36) excluding or SB12Z (£152) including chair time?

Summary of committee's preferred assumptions after ECM1 and company's updated base case

Table 5. Committee's preferred assumptions after ECM1 and company's updated base case

Parameter	Committee's preferred assumption after ECM1	Company updated base case
ITCs	DAR+LEN+DEX: IPTW and ISA+BOR+LEN+DEX: NMA	
Baseline characteristics	Mean age 75 years and 55% male	
% having 2L after DAR or ISA +BOR+LEN+DEX	75%	
Distribution of 2L and 3L treatments	Uncertain	**All arms have same 2L and 3L distribution** • **2L:** 87.5% BEL+BOR+DEX, 3.13% SEL+BOR+DEX, 9.38% CAR+DEX • **3L:** 41.18% cyclophosphamide, 41.18% SEL+BOR+DEX, 17.65% PAN+BOR+DEX

Abbreviations: 2L/3L, 2nd / 3rd line; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; ECM, evaluation committee meeting; ISA, isatuximab; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; LEN, lenalidomide; NMA, network meta-analysis; PAN, panobinostat; SEL, selinexor

Cost-effectiveness results

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

When using confidential prices, the company updated base case, scenarios and EAG scenarios are above the range normally considered an acceptable use of NHS resources (£20,000 to £30,000 per QALY)

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Other considerations: feedback from patient organisations

- **Uncaptured benefit: impact on quality of life of administration and dosing of subcutaneous DAR vs intravenous ISA**
  - More convenient delivery with DAR – no cannulation, shorter time in clinic; potential for community or home administration vs hospital attendance for ISA IV infusion
  - Less intense dosing (monthly after 24 weeks) with DAR vs 80 weeks with ISA
  - Improved quality of life: reduced physical and psychological burden; less disruption to work, family and daily life; lower travel and financial costs; greater independence and normality
  - QoL tools may underestimate impact: do not fully capture cyclical relapse anxiety; emotional burden on carers and families
- **Immature CEPHEUS data [NICE corrected figures based on company submission]**
- DAR+BOR+LEN+DEX: longer remission (PFS) 69% still in remission at 4.5 years vs 48% with BOR+LEN+DEX; high rates of sustained MRD negativity at 3 years [redacted] vs [redacted] with BOR+LEN+DEX
- **Quadruplet vs triplet: DAR+BOR+LEN+DEX vs DAR+LEN+DEX**
  - Greater efficacy potential: quadruplets target MM subclones through complementary mechanisms
  - More flexibility: 4 drugs allow dose adjustment to manage side effects
  - Lower risk of stopping treatment: fewer-drug regimens likely lead to stopping if side effects occur

Are there any uncaptured benefits?

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; IV, intravenous; LEN, lenalidomide; MM, multiple myeloma; MRD, minimal residual disease; PFS, progression free survival; QoL, quality of life

Other considerations

Company: considers ICER threshold should be at high end rather than lower end of range (£20k-£30k)

- Limited decision uncertainty: robust evidence across company submission, addendum and DGC response, including ~5 years' follow-up from CEPHEUS
- Conservative modelling: OS and PFS extrapolations are more conservative than ITC estimates, reducing long-term uncertainty
- Robust comparative methods: rigorous ITCs and extensive scenario analyses address key areas of concern
- High unmet need and inequality: need for more effective options in transplant-ineligible MM and to reduce disparities in remission outcomes

- **Severity modifier:** does not meet severity weighting threshold
- **Equality considerations:** no other issues raised by stakeholders
- **Managed access:** company has not submitted managed access proposal

- Has the committee seen any evidence to change its views about the immaturity of CEPHEUS data and related uncertainty?
- Are there any equality issues to consider?
- What are the uncertainties and can they be resolved with further data collection?

Abbreviations: DGC, draft guidance consultation; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MM, multiple myeloma; OS, overall survival; PFS, progression free survival

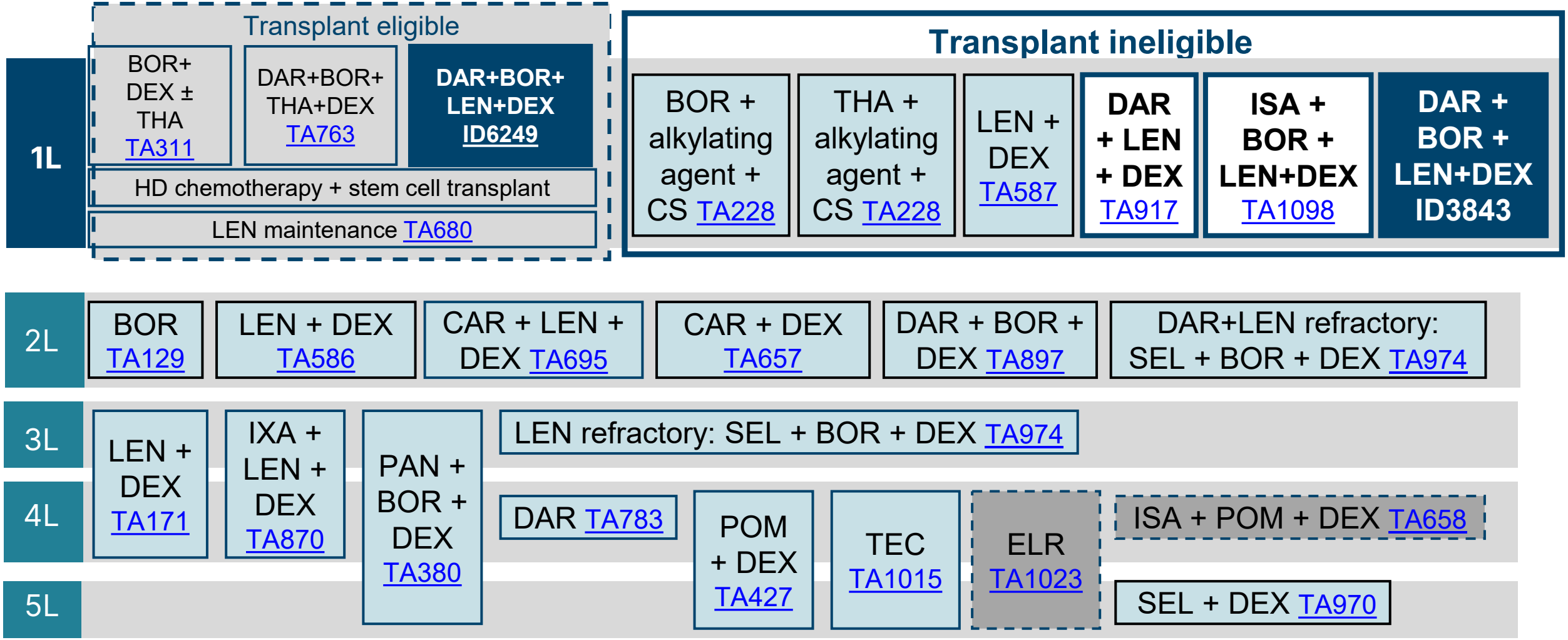
Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Treatment pathway and company positioning of DAR+BOR+LEN+DEX

RECAP



Company positioning of DAR+BOR+LEN+DEX | **Comparators** | Other options | Recommended on managed access | ***Link to Draft guidance consultation**

Abbreviations: 1/2/3/4/5L, 1st /2nd/3rd/4th/5th line; BCMA, B-cell maturation antigen; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CS, corticosteroid; DAR, daratumumab (**anti-CD38**); DEX, dexamethasone; ELR, elranatamab; HD, high dose; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; SEL, selinexor; TEC, teclistamab; THA, thalidomide

CEPHEUS ITT (all randomised): ASCT-ineligible and ASCT-deferred

Table A1. CEPHEUS baseline characteristics for ASCT-ineligible and deferred

Characteristic	ASCT-ineligible (n=289)	ASCT-deferred (n=106)
Mean age (SD), years	[redacted]	[redacted]
Female, n (%)	142 (49.1%)	[redacted]
White, n (%)	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander, n (%)	[redacted]	[redacted]
Baseline ECOG PS 0	109 (37.7%)	[redacted]
Baseline ECOG PS 1	153 (52.8%)	[redacted]
ISS Stage I	98 (33.9%)	[redacted]
ISS Stage II	111 (38.4%)	[redacted]
ISS Stage III	80 (27.7%)	[redacted]
Cytogenetic Risk: standard	216 (74.7%)	[redacted]
Cytogenetic Risk: high	38 (13.1%)	[redacted]

*Link to Analysis sets and ITCs: ASCT-ineligible vs ITT

DAR+LEN+DEX NMA proportional hazards: OS

Figure A2. MAIA OS log-log plot

Figure A3. MAIA OS Schoenfeld residuals plot

Figure A4. SWOG OS log-log plot

Figure A5. SWOG OS Schoenfeld residuals plot

*Link to Analysis sets and ITCs: ASCT-ineligible vs ITT

DAR+LEN+DEX NMA proportional hazards: PFS

Figure A6. MAIA PFS log-log plot

Figure A7. MAIA PFS Schoenfeld residuals plot

Figure A8. SWOG PFS log-log plot

Figure A9. SWOG PFS Schoenfeld residuals plot

[Link to Analysis sets and TCs: ASCT-ineligible vs ITT]

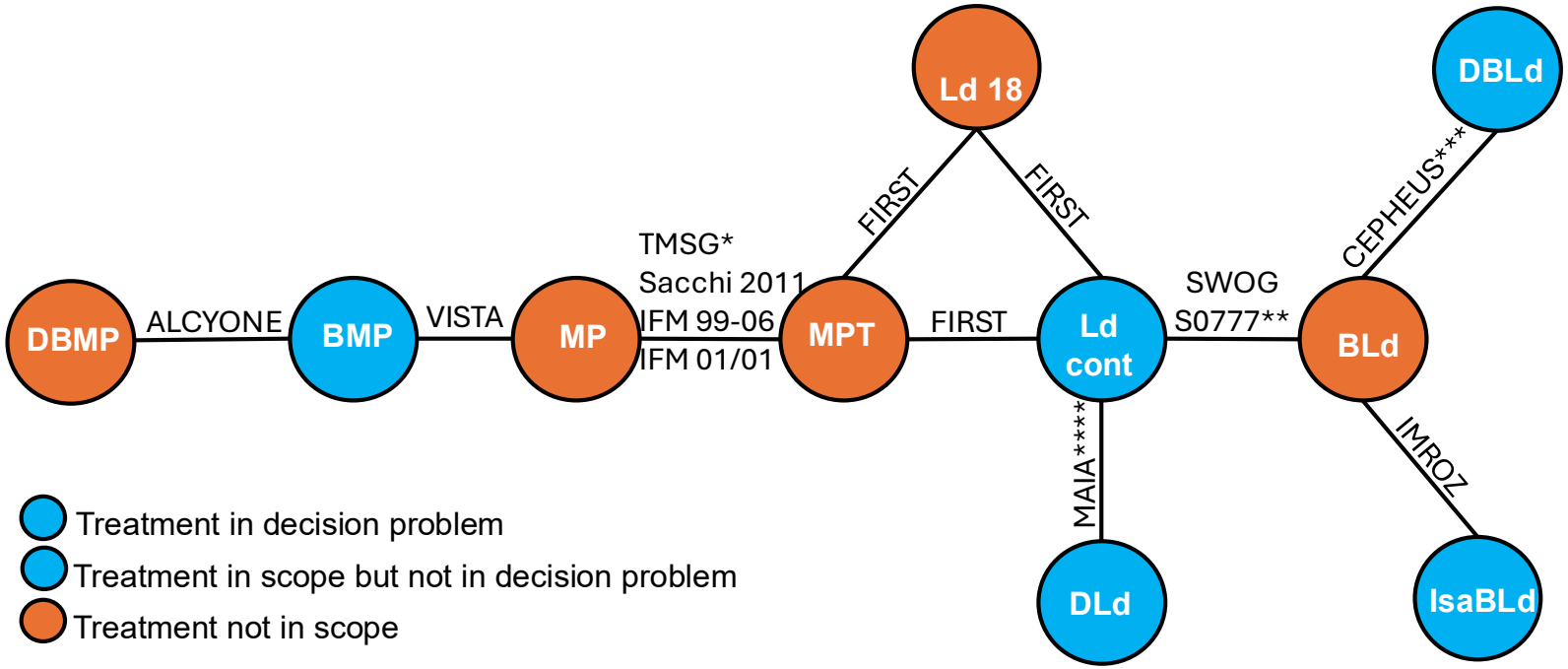
Abbrev

N

NMA: DAR+BOR+LEN+DEX vs ISA+BOR+LEN+DEX

RECAP

Figure A1. Studies included in NMA



* TMSG inputs for PFS not available

** SWOG S0777 No-intent to transplant subgroup used as a proxy for the ASCT-ineligible population

*** CEPHEUS ASCT-ineligible post-hoc subgroup used; adjusted for COVID-19 deaths

**** MAIA <80 post-hoc subgroup used; adjusted for COVID-19 deaths

***Link to ITC results: CEPHEUS ASCT-ineligible and ITT**

NMA results DAR+BOR+LEN+DEX vs ISA+BOR+LEN+DEX: CEPHEUS ASCT-ineligible and ITT

Table A2. NMA (random and fixed effects model): DAR+BOR+LEN+DEX vs ISA+BOR+LEN+DEX (insufficient TTD data)

Outcome (HR, 95% CrI)	ASCT-ineligible				ITT (ASCT ineligible and deferred)					
	COVID-19 adjusted		COVID-19 unadjusted		COVID-19 adjusted		COVID-19 unadjusted		COVID-19 unadjusted^ and exclude Brazil, Poland	
	FE	RE	FE*	RE	FE	RE	FE	RE	FE	RE
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*company base case; ^clarified by company by email

*Link to ITC results: CEPHEUS ASCT-ineligible and ITT

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; CI/CrI, confidence/credible intervals; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ISA, isatuximab; ITC, indirect treatment comparison; ITT, intention to treat; LEN, lenalidomide; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

Kaplan-Meier plots for COVID-19 adjusted PFS, OS and TTD: CEPHEUS ITT

Figure A10. KM plot of PFS

Figure A11. KM plot of OS

Figure A12. KM plot of TTD

*Link to Long-term extrapolations of OS, PFS and TTD

Implied HRs between DAR+BOR+LEN+DEX and DAR+LEN+DEX: PFS and OS

Figure A13. Implied HR (DAR+BOR+LEN+DEX vs DAR+LEN+DEX) – modelled PFS extrapolations (calibrated)

Figure A14. Implied HR (DAR+BOR+LEN+DEX vs DAR+LEN+DEX) – modelled OS extrapolations (calibrated)

*Link to Long-term extrapolations of OS, PFS and TTD

Modelling OS: alternative baseline curves

Small ICER impact

Company

- SACT data unavailable (see slide 2). But, even if available, only ~2 years follow-up since TA917 (Sept 2023)
  - Too immature to meaningfully inform long-term OS
  - Would introduce additional, unquantifiable RWE uncertainty
- Unable to explore alternative baseline OS curve for DAR+LEN+DEX
  - Inappropriate to apply HR to DAR+LEN+DEX baseline OS: violation of PH between DAR+BOR+LEN+DEX and DAR+LEN+DEX
- Additional analyses
  - Compared DAR+LEN+DEX modelled OS and PFS extrapolations with TA917 preferred assumptions:
    - Beyond 10 years, model more optimistic than TA917 → may overpredict DAR+LEN+DEX survival
  - OS scenario using second-best fitting curves: lognormal DAR+BOR+LEN+DEX, Gompertz DAR+LEN+DEX
- Base case using mature MAIA DAR+LEN+DEX OS data: ~8 years follow-up (median 89.3 months) → more robust for long-term survival modelling

EAG

- Little impact on choice of OS curve for DAR+BOR+LEN+DEX
- For DAR+LEN+DEX extrapolated OS, Gompertz matches KM data in first 7 years, worse long-term prediction than exponential

Has the committee seen any evidence to change its views on how OS should be modelled?

***Link to Long-term extrapolations of OS, PFS and TTD**

Modelled OS and PFS for DAR+LEN+DEX: CEPHEUS vs TA917

Table A3. Comparison of OS and PFS extrapolations for DAR+LEN+DEX: TA917 Committee-preferred assumptions vs updated base case

Year	DAR+LEN+DEX	
	Committee-preferred assumptions from TA917	CEPHEUS (updated base case with age = 75)
OS		
10	[redacted]	39.5%
15	[redacted]	19.9%
20	[redacted]	4.3%
PFS		
10	[redacted]	32.3%
15	[redacted]	14.9%
20	[redacted]	3.0%

*Link to Modelling OS: alternative baseline curves

Extrapolations of PFS, OS and TTD: DAR+BOR+LEN+DEX vs ISA+BOR+LEN+DEX

Figure A15. Comparison of extrapolated PFS, OS and TTD curves for DAR+BOR+LEN+DEX vs ISA+BOR+LEN+DEX

*Link to Extrapolation of TTD for ISA+BOR+LEN+DEX

RECAP

Subsequent treatment distributions: 2L and 3L

Table A4. Subsequent treatment 2L and 3L distributions

	Treatment	Proportion of patients (%)	
		Company base case	EAG base case at ECM1
2L	CAR+DEX	9.38	9.38
	SEL+BOR+DEX	3.13	3.13
	BEL+BOR+DEX	87.5	87.5*
	BOR+DEX or BOR	0	10
	CAR+LEN+DEX	0	4
3L	Cyclophosphamide	41.18	62.67
	PAN+BOR+DEX	17.65	26.86
	SEL+BOR+DEX	41.18	10

- Company original base case: distributions differed depending on 1L treatment, DAR+BOR+LEN+DEX or DAR+LEN+DEX. Company assumed same distributions for DAR+BOR+LEN+DEX and ISA+BOR+LEN+DEX
- Unless otherwise stated, proportions are same for different 1L treatments. *EAG assumed 74% on DAR+LEN+DEX would have BEL+BOR+DEX at 2L
- Company updated base case: assumes distributions are same regardless of 1L treatment

*Link to ITC results: Subsequent treatment distributions

Abbreviations: 1L/2L/3L, 1st / 2nd / 3rd line; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; LEN, lenalidomide; PAN, panobinostat; SEL, selinexor

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

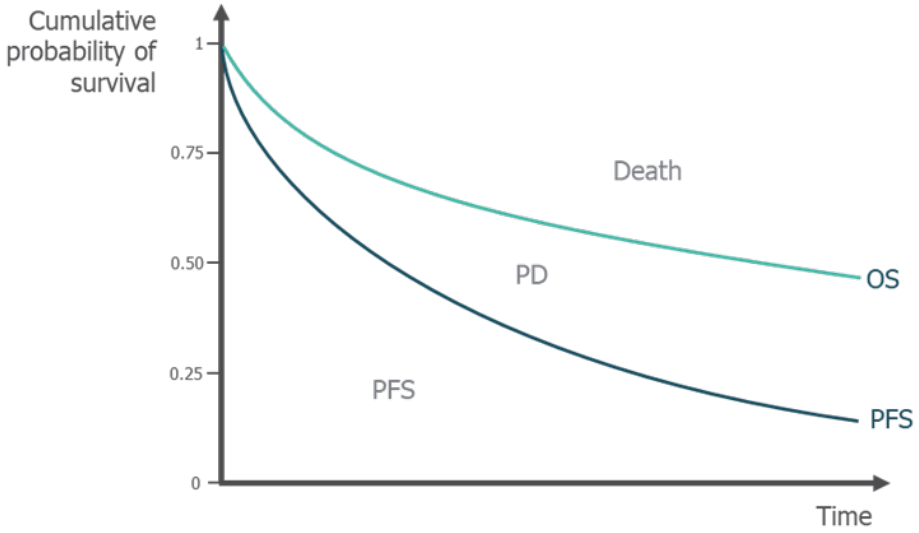
*Link to Other considerations

RECAP

Company's model overview

Company model is a partitioned survival model, with a time horizon of 28 years and cycle length of 4 weeks

Model structure



Proportion of people occupying health state calculated as:

- **Pre-progression:** proportion alive (based on OS) and progression free (based on PFS).
- **Post-progression:** proportion alive (based on OS extrapolations) minus proportion who are alive AND progression free (based on PFS extrapolations).
- **Death:** proportion who have died (OS extrapolations).

- Technology affects **costs** by:
  - Increasing total drug costs associated with DAR+BOR+LEN+DEX compared with DAR+LEN+DEX.
  - Reducing the proportion of patients progressing to subsequent treatment.

- Technology affects **QALYs** by:
  - Increasing overall survival.
  - Increasing progression free survival.

- Assumptions with greatest ICER effect:
  - The average subsequent treatment acquisition cost per model cycle (for both arms).
  - The treatment acquisition cost of daratumumab (for both arms).
  - The proportion of patients receiving subsequent treatment second-line, after having received DAR+BOR+LEN+DEX first-line.

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PFS, progression free survival;