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

Technology appraisal committee B [3 December 2025]

For presentation – confidential information redacted

Chair: Charles Crawley

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Company: Johnson & Johnson

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on multiple myeloma

Multiple myeloma is a rare, complex, incurable haematological cancer

- Multiple myeloma (MM) is a rare relapsing remitting cancer that develops from bone marrow plasma cells.

- For people diagnosed with myeloma in the UK, the 5-year survival rate is 57% (up to 2021 follow up) and the 10-year survival rate is 38% (up to 2018 follow up) CRUK Cancer statistics data hub

- The multiple myeloma pathway is complex with multiple lines of therapy; choice of first-line treatment depends on suitability for HDT-ASCT.

- 74% of people diagnosed are aged over 65 years. Age, frailty and co-morbidities mean than HDT-ASCT is not suitable for many people.

- This appraisal (ID3843) focuses on ASCT-ineligible population; ID6249 focuses on the ASCT-eligible population.

Equalities considerations

- No equality issues identified for this appraisal, but previous appraisals noted that myeloma is more common in men, older people (≥75 years), and people of African and Caribbean family background.

Abbreviations: HDT, high dose chemotherapy; ASCT, autologous stem cell transplant

Patient perspectives

Treatment can halt progression and improve quality of life, but current treatments do not work for all people

Submission from Myeloma UK (for ID3843 and ID6249) and patient expert

- Myeloma complications can be severe and painful, including bone destruction, kidney damage, fatigue and a depleted immune system.
- People should get the most effective treatment option at first line; first remission is the best opportunity to get the best response, with longest time until disease progression. People with myeloma are aware that HDT-SCT is considered the most effective treatment.
- People who cannot tolerate SCT (ID3843) are generally older and/or frail; there's a clear need for treatment to deliver outcomes comparable to HDT-SCT for people with myeloma who cannot have SCT.
- People receiving HDT-SCT (ID6249) tend to be younger, more likely to be working and often have family responsibilities, so myeloma impacts on others.

"No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake…"

"The tiredness – not being tired the fatigue. It is like the plugs been pulled out. I am talking to you now, animated, focused but I know that in the afternoon I will have no energy, and it just doesn't fill back up even if I rest."

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Abbreviations: HDT, high dose chemotherapy; SCT, stem cell transplant

Daratumumab (Darzalex, Johnson & Johnson) in combination with bortezomib, lenalidomide and dexamethasone

Table. Information about daratumumab

Marketing authorisation	• Relevant MA wording: in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma. (MHRA approved)
Mechanism of action	• Daratumumab: human immunoglobulin (IgG1-kappa) monoclonal antibody that binds to CD38 and induces tumour cell death
Administration	Daratumumab 1,800 mg solution for SC injection is available as a fixed dose with each 15 mL vial
Price	• List price 1,800 mg (fixed-dose vial): £4,320.00 (excl. VAT) • A patient access scheme is in place.

Abbreviations: MA, marketing authorisation; SC, subcutaneous

Key issues

Issue	ICER impact
Comparators (EAG Issue 1b)	Unclear 
Uncertainty in the indirect comparisons for DAR+BOR+LEN+DEX versus comparators "exploratory" NMA cannot be included in the primary ITC approach used in the CS (EAG Issue 1a)	Unclear 
Uncertainty in the proportion of patients who need second-line treatment (EAG Issue 2)	Moderate 
Generalisability of baseline characteristics in the model to NHS population (EAG secondary issue 1)	Small 
Proportion of second- and third-line treatments in NHS practice (EAG secondary issue 2)	Small 

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Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; NMA, network meta analyses;

Treatment pathway

Key Issue: Comparators

Key Issue: Subsequent treatments

Newly diagnosed multiple myeloma that is ineligible for autologous stem cell transplant

First line

- THAL+ CYC+DEX (TA228)
- BOR+CYC/ MEP+DEX (TA228)
- LEN+ DEX (TA587)
- **DAR+LEN+ DEX (TA917)**
- ISA+BOR+L EN+DEX (TA1098)
- **DAR+BOR+ LEN+DEX (ID3843)**

Subsequent treatments

2L	BOR (TA129)	CAR+DEX (TA657)	DAR+BOR+ DEX (TA897)	LEN+DEX (TA586, TA171)	CAR+LEN+ DEX (TA695)		SEL+BOR+ DEX (TA974)	
3L		PAN+BOR +DEX (TA380)	IXA+LEN+ DEX (TA870)					
4L	POM+ DEX (TA427)				ISA+POM+ DEX* (TA658)	DAR (TA783)	TEC (TA1015)	ELR (TA1023)*
5L			SEL+DEX (TA970)					

KEY: **Company positioning** | **Comparator** | Other comparators included in scope | Recommended on managed access (CDF) | Other options

BOR, bortezomib; CAR, carfilzomib; CYC, cyclophosphamide; DAR, daratumumab; DEX, dexamethasone; ELR, elranatamab; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; MEL, melphalan; POM, pomalidomide; SEL, selinexor; TEC, teclistamab; THA, thalidomide.

Key issues: Comparators (1/2)

Background

- Scope comparators:
  - DAR+LEN+DEX
  - LEN+DEX
  - bortezomib combinations
  - ISA+BOR+LEN+DEX (positive recommendation received September 2025 [TA1098])
- Original CS includes DAR+LEN+DEX, LEN+DEX, and bortezomib combinations
- At/post-clarification: NMA and cost effectiveness results provided for ISA+BOR+LEN+DEX comparison, but ISA+BOR+LEN+DEX not included in company's primary ITC approach (see Key issue: NMA uncertainty).

Company

- DAR+LEN+DEX represents the current standard of care and is therefore the main comparator; company clinical expert estimates that 70-90% of treatment for ASCT-ineligible patients is DAR+LEN+DEX (company internal estimate: [redacted]);
- LEN+DEX and bortezomib combinations included in CS for completeness but not relevant comparators: LEN+DEX mainly reserved for when triplet regimen is unsuitable, or if an all-oral option is preferred. Bortezomib combinations used in small proportion of cases with renal impairment.
- ISA+BOR+LEN+DEX not relevant comparator as would not become standard of care during the short timeframe since recommendation.

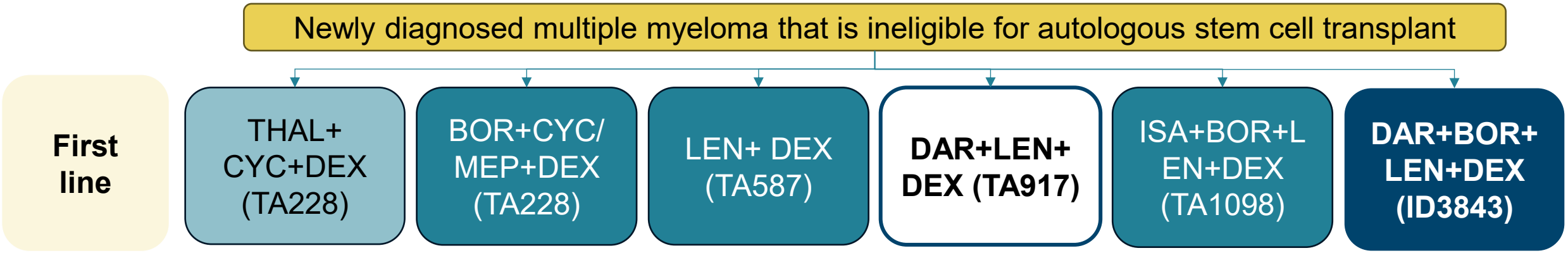
ASCT, autologous stem cell transplant; BOR, bortezomib; CS, company submission; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; ITC, indirect treatment comparison; LEN, lenalidomide; NMA, network meta analyses; TEC, teclistamab;.

Key issues: Comparators (2/2)

EAG comments

- Expert clinical advice supports that LEN+DEX and bortezomib combinations are rarely used.
- Requested ISA+BOR+LEN+DEX be included as a comparator.
- Of the other remaining comparators, (DAR+LEN+DEX, LEN+DEX, BOR+MEL+PRED and BOR+CYC+DEX), agree DAR+LEN+DEX is most relevant based on clinical expert opinion.

Figure: first line treatment for newly diagnosed MM ineligible for autologous stem cell transplant



See full treatment pathway.

What are the relevant comparators?

BOR, bortezomib; CYC, cyclophosphamide; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; LEN, lenalidomide; MEL, melphalan; THAL, thalidomide.

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CEPHEUS trial

Phase 3, randomised, multicentre trial comparing DAR+BOR+LEN+DEX versus BOR+LEN+DEX

- Trial included newly diagnosed untreated MM where HDT-ASCT was not planned as initial therapy (18-70 years and ineligible due to underlying conditions, ≥70 years, or those who decline/defer)
- Company submission: ASCT-ineligible subpopulation, i.e. excluding those who decline/defer HDT-ASCT. (age/transplant eligibility were stratified at randomisation).
    - slightly older than the overall trial population, but baseline characteristics were overall similar.
    - baseline characteristics between treatment groups were also similar, although the DAR+BOR+LEN+DEX arm had more people with ECOG 2 and a lower proportion of male participants (see appendix).

EAG comments

- More ECOG 2 participants may mean the DAR+BOR+LEN+DEX group is slightly less fit (making the results conservative/more favourable to BOR+LEN+DEX); having fewer male participants may favour DAR+BOR+LEN+DEX as male MM patients generally have worse prognosis.
- MM is more common in men, but this is not reflected in the ASCT-ineligible trial population (50.9% male)
- BOR+LEN+DEX not a regimen used in NHS → not a comparator in this appraisal.

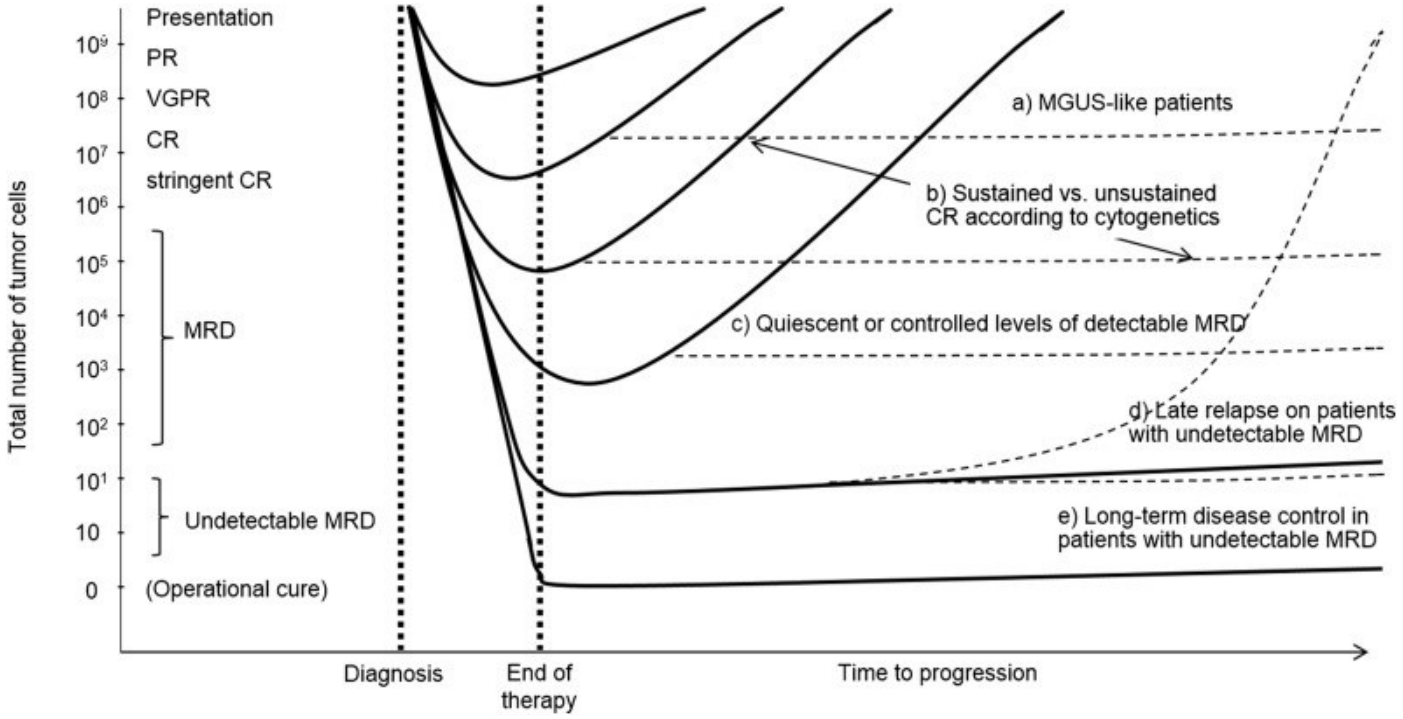
Are people who decline/defer treatment expected to have different outcomes? Is it appropriate to exclude patients who decline ASCT?

ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; HDT, high dose chemotherapy; ISA, isatuximab; LEN, lenalidomide; NMA, network meta analyses; TEC, teclistamab;.

Minimal residual disease

MRD status as an intermediate endpoint in newly diagnosed MM

Relationship between deep response and PFS



- MRD is the small number of myeloma cells remaining after CR – MRD-negativity could give indication of anti-myeloma activity that is prognostic of longer-term outcomes.
- Pooled analysis of 11 RCTs showed correlation between landmark KM PFS and OS estimates and achieving MRD-CR in people with HDT-ASCT ineligible MM (Shi et al. 2025).
- DAR for newly diagnosed MM can be discontinued when people have achieved sustained MRD-negativity for 12-months after 24 months on maintenance treatment, as per the SmPC (relevant for transplant eligible ID6249)

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; HDT, high dose therapy; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression free survival; RCT, randomised controlled trial; SmPC, summary of product characteristics.

CEPHEUS Results MRD negativity rate (primary outcome)

Table: Proportion of patients achieving MRD negativity rate 10^{-5} (CEPHEUS)

Population and timepoint	Median follow-up (months)	BOR+LEN+DEX	DAR+BOR+LEN+DEX	Difference OR (95% CI) p-value
Overall trial population (Primary outcome) Data cut off 8 April 2021	[redacted]	[redacted]	[redacted]	[redacted]
Overall trial population Data cut off 7 May 2024	58.71	39.4%	60.9%	2.37 (1.58, 3.55) p<0.0001
ASCT-ineligible Data cut off 7 May 2024	58.71	39.3%	60.4%	2.365 (1.471, 3.802) p=0.0004

- MRD negativity rate is not used within the economic model, including as a stopping criteria.

EAG comments

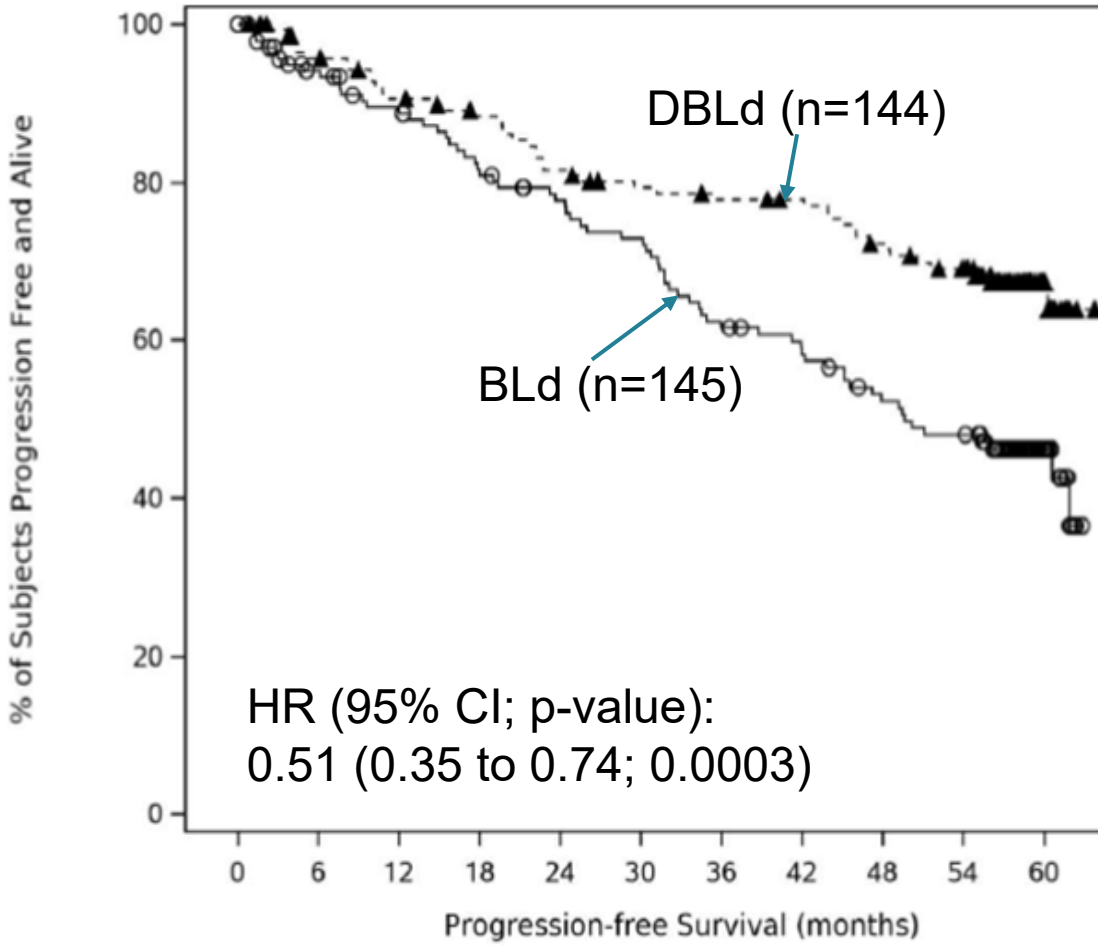
- MRD not commonly measured in clinical practice to inform treatment decisions. However, EAG's clinical expert commented that, as a measure of depth of response, these results translate into improved real-world outcomes.

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; MRD, minimal residual disease; OR, odds ratio

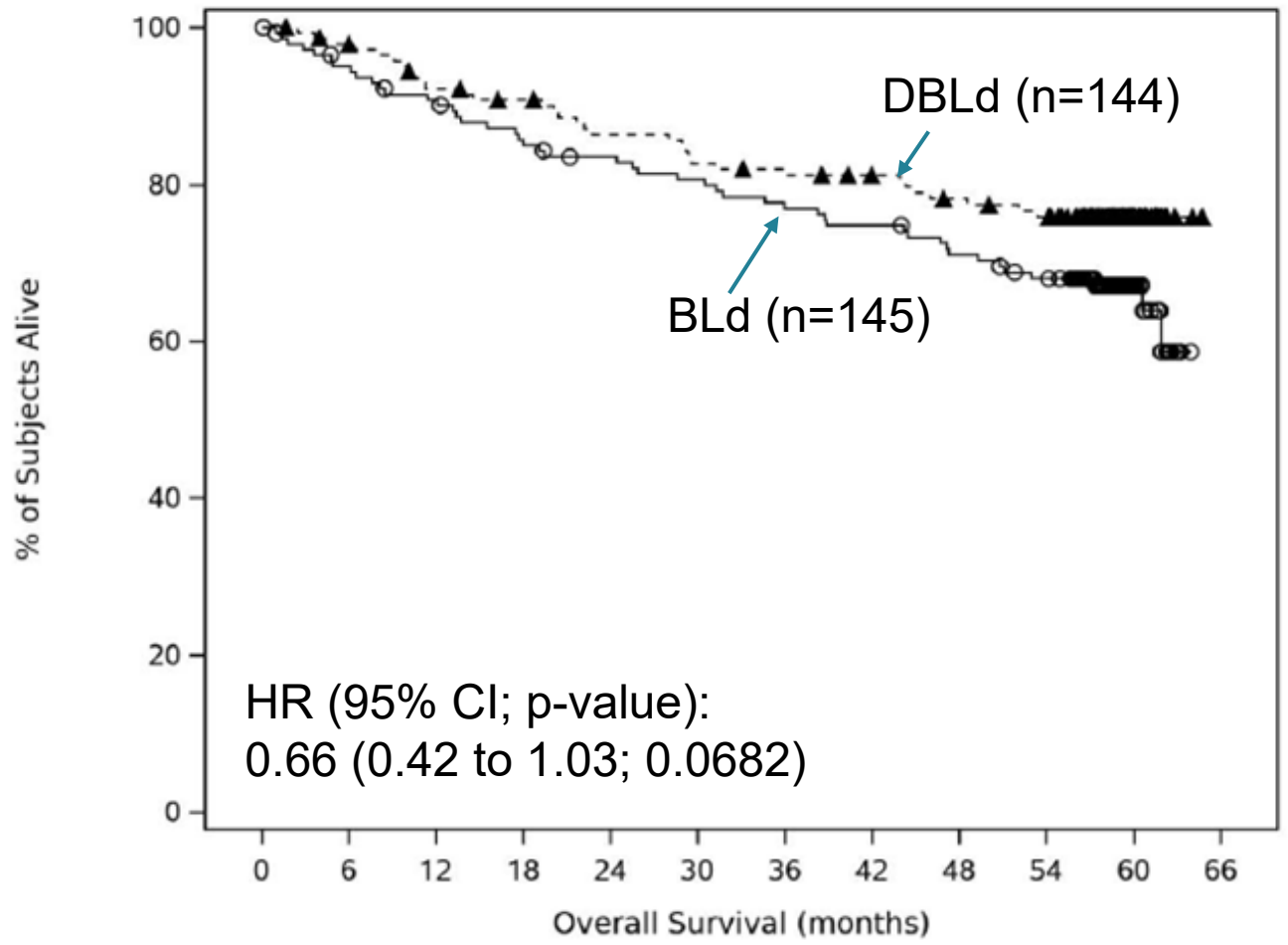
CEPHEUS Results PFS and OS

DAR+BOR+LEN+DEX improves PFS compared with BOR+LEN=DEX; OS shows trend to improvement with DAR+BOR+LEN+DEX but not statistically significant

PFS (ASCT-ineligible)



OS (ASCT-ineligible)



NICE *see appendix for more outcomes

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; HDT, high dose therapy; OS, overall survival; PFS, progression free survival;

CEPHEUS Results - PFS, data cut off 7 May 2024

When deaths due to COVID-19 are censored, DAR+BOR+LEN+DEX improves PFS and OS compared with BOR+LEN+DEX

Table: PFS results ASCT-ineligible population

ASCT-ineligible population	Median KM estimate, months		Difference
	BOR+LEN+DEX	DAR+BOR+LEN+DEX	HR (95% CI) p-value
Unadjusted	49.61 [redacted]	[redacted]	0.51 (0.35, 0.74) p=0.0003
Adjusted for COVID-19	[redacted]	[redacted]	[redacted]

Table: PFS results overall population

Overall population	Median KM estimate, months		Difference
	BOR+LEN+DEX	DAR+BOR+LEN+DEX	HR (95% CI) p-value
Unadjusted	52.63 [redacted]	NE (NE, NE)	0.57 (0.41, 0.79)
Adjusted for COVID-19	[redacted]	[redacted]	[redacted]

Abbreviations: ASCT, autologous stem cell transplant; HDT, high dose therapy; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression free survival; RCT, randomised controlled trial; SmPC, summary of product characteristics.

CEPHEUS Results - OS, data cut off 7 May 2024

When deaths due to COVID-19 are censored, DAR+BOR+LEN+DEX improves PFS and OS compared with BOR+LEN+DEX

Table: OS results ASCT-ineligible population

ASCT-ineligible population	Median KM estimate, months		Difference HR (95% CI) p-value
	BOR+LEN+DEX	DAR+BOR+LEN +DEX	
Unadjusted	[redacted]	[redacted]	0.66 (0.42, 1.03) p=0.0682
Adjusted for COVID-19	[redacted]	[redacted]	0.55 (0.34, 0.90) p=0.0159

Table: OS results overall population

Overall population	Median KM estimate, months		Difference HR (95% CI) p-value
	BOR+LEN+DEX	DAR+BOR+LEN +DEX	
Unadjusted	[redacted]	[redacted]	0.85 (0.58, 1.24)
Adjusted for COVID-19	[redacted]	[redacted]	0.69 (0.45, 1.05)

Abbreviations: ASCT, autologous stem cell transplant; HDT, high dose therapy; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression free survival; RCT, randomised controlled trial; SmPC, summary of product characteristics.

Company approach to comparative evidence - overview

No trials compare DAR+BOR+LEN+DEX to any of the treatment comparators included in the NICE scope. So the company provided the following indirect treatment comparisons:

- **Inverse probability of treatment weighting ITC** using IPD (the company's primary approach) for DAR+BOR+LEN+DEX versus:
    - DAR+LEN+DEX (company's main comparator)
    - LEN+DEX
    - BOR+MEL+PRED.
- **A network meta-analysis (NMA)** to support the IPTW ITC, and primary results of DAR+BOR+LEN+DEX versus ISA+BOR+LEN+DEX (using the same network).
- **Anchored matched-adjusted indirect comparisons (MAIC)** to:
    - Support the NMA results for DAR+BOR+LEN+DEX versus ISA+BOR+LEN+DEX.
    - Support assumption BOR+MEL+PRED and BOR+CYC+DEX equivalent. (not discussed further: EAG considered BOR+MEL+PRED fulfils the NICE scope, and clinical expert advised BOR combinations are rarely used in the NHS)

Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; IPD, individual patient data; LEN, lenalidomide; MEL, melphalan; PRED, prednisolone;

Inverse probability of treatment weighting (IPTW)

Company's primary ITC approach for the DAR+LEN+DEX, LEN+DEX, or BOR+MEL+PRED comparisons

- MAIA participants >80 years were excluded as the oldest CEPHEUS participant was 80 years at baseline; other differences in heterogeneity were accounted for by the IPTW methods.
- 11 covariates were included in main analysis; 3 additional covariates (race, time since MM diagnosis, calcium levels) were included in a sensitivity analysis (see appendix for full list of covariates).
- Trials used:
  - CEPHEUS used for DAR+BOR+LEN+DEX.
  - MAIA trial used to inform comparisons with DAR+LEN+DEX and LEN+DEX.
  - ALCYONE trials used to inform comparison with BOR+MEL+PRED.

EAG comments

- Some concerns blinding with MAIA and ALCYONE.
- MAIA lacks clarity around the effect of treatment switching after the second interim analysis; may bias in favour of LEN+DEX, which may subsequently bias against DAR+LEN+DEX.

Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; PRED, prednisolone; ITC, indirect treatment comparison;

IPTW ITC results – PFS, OS and TTD

DAR+BOR+LEN+DEX improves PFS versus DAR+LEN+DEX, LEN+DEX, or BOR+MEL+PRED

Table: PFS, OS and TTD (adjusted for 11 covariates and COVID-19)

Analyses	DAR+BOR+LEN+DEX versus comparator HR (95% CI), p-value		
	DAR+LEN+DEX	LEN+DEX	BOR+MEL+PRED
PFS	0.55 (0.38, 0.79) p=0.001	0.30 (0.21, 0.43) p<0.0001	0.16 (0.10, 0.25) p-value not reported
OS	0.63 (0.41, 0.98) p=0.040	0.43 (0.28, 0.66) p<0.0001	0.36 (0.23, 0.57) p-value not reported
TTD	[redacted]	[redacted]	[redacted]

- Sensitivity analyses (where all 14 covariates were adjusted, or COVID-19 unadjusted) showed similar results to the base case (see appendix)

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Abbreviations: BOR, bortezomib;; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; PRED, prednisolone; ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation

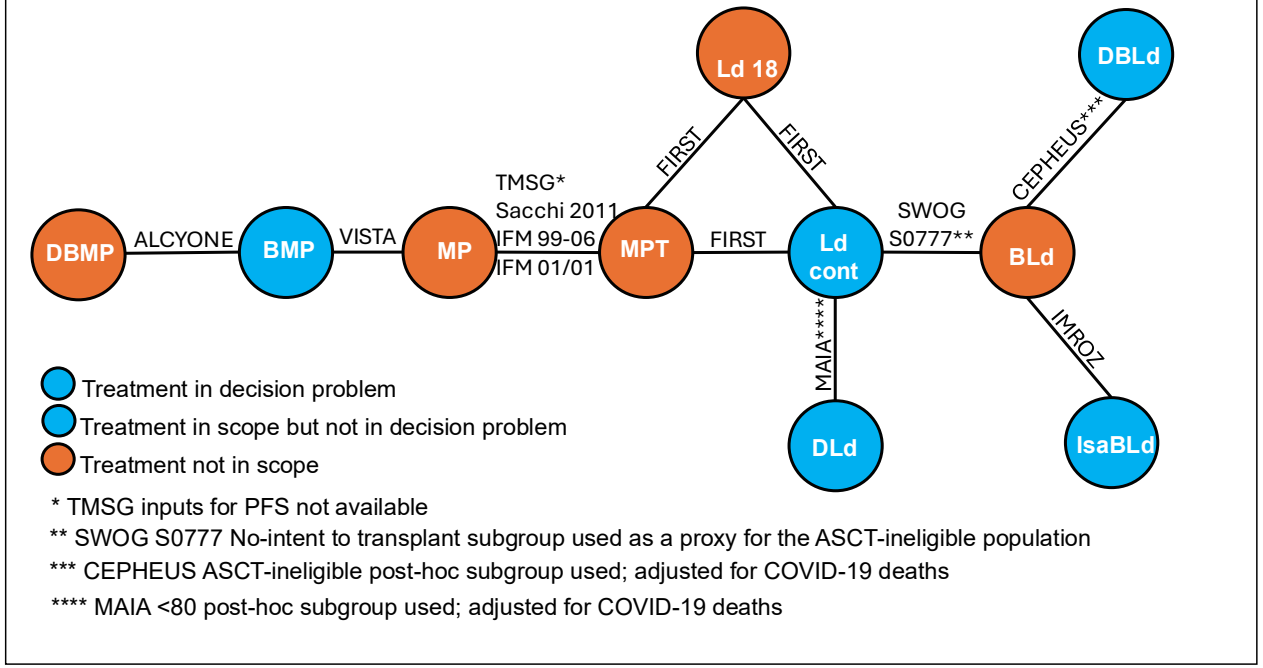
Network meta-analysis

Company's primary approach for the ISA+BOR+LEN+DEX comparison

Company

- 11 studies included (see appendix for study list and comparisons).
- IMROZ most relevant trial to inform efficacy of ISA+BOR+LEN+DEX; common comparator arm (BOR+LEN+DEX) with CEPHEUS.
- Only aggregate published data available for IMROZ; therefore, IPTW not feasible.
- NMA for ISA+BOR+LEN+DEX comparison considered the primary approach as CEPHEUS and IMROZ have similar populations and study designs; anchored MAIC included to explore potential uncertainty (see later slides).

Figure: Studies included in the NMA



Full size NMA figure available in appendix.

EAG comments

- Statistical methods for the NMAs are appropriate, and results are transparent. But heterogeneity in the network and use of subgroup data in some trials potentially increases the risk of bias, though this is offset by ASCT eligibility being a stratification factor in the randomisation to trial arms.

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib;; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; PRED, prednisolone; NMA, network meta analysis; ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting; MAIC, matched adjusted indirect comparison

NMA results (1/2)

DAR+BOR+LEN+DEX was [redacted] for PFS and OS compared with DAR+LEN+DEX, LEN+DEX, BOR+MEL+PRED; [redacted] for DAR+BOR+LEN+DEX versus ISA+BOR+LEN+DEX

Table: NMA outcomes (fixed effects, adjusted for COVID-19)

Outcome	Comparison, DAR+BOR+LEN+DEX vs… HR (95% CrI)		
	DAR+LEN+DEX	LEN+DEX	BOR+MEL+PRED
PFS	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]

Table: NMA outcomes (fixed effects, unadjusted for COVID-19)

Outcome	Comparison, DAR+BOR+LEN+DEX vs… HR (95% CrI)
	ISA+BOR+LEN+DEX
PFS	[redacted]
OS	[redacted]

- Alternative analyses show similar results (see appendix)

Company

- Company base case uses FE model, highlight consistency between FE and RE results
- For comparison with DAR+LEN+DEX, LEN+DEX and BOR+MEL+PRED, data adjusted for COVID-19
- For comparison with ISA+BOR+LEN+DEX, data unadjusted for COVID-19 - could not adjust for COVID-19 in IMROZ trial for ISA+BOR+LEN+DEX comparison, not appropriate to censor in one arm but not the other
- Company consider unadjusted analysis conservative due to higher proportion of COVID-19 deaths in CEPHUS trial

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib;; DAR, daratumumab; DEX, dexamethasone; FE, fixed effects HR, hazard ratio; ISA, isatuximab; LEN, lenalidomide; MEL, melphalan; PRED, prednisolone; NMA, network meta analysis; ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting; MAIC, matched adjusted indirect comparison; RE, random effects

NMA results (2/2)

EAG comments

- EAG agree with company to use COVID-19 unadjusted results for comparison with ISA+BOR+LEN+DEX.
- Highlight difference in results for comparison of DAR+BOR+LEN+DEX with ISA+BOR+LEN+DEX and DAR+BOR+LEN+DEX with other comparators – magnitude of effect smaller compared with ISA+BOR+LEN+DEX than comparison with other comparators.
- FE and RE credible interval for comparison of DAR+BOR+LEN+DEX with ISA+BOR+LEN+DEX both [redacted]
- Company believe choice of FE or RE a minimal source of uncertainty due to consistency in estimates, EAG notes consistency but would have preferred to have seen the model fitting values for each outcome.

Tech team comments

- When company provided NMA results for ISA+BOR+LEN+DEX comparison, updated results for other comparisons not provided.
- SWOG S0777 proxy population based on no intent-to-transplant population (intent-to-transplant was a trial stratification factor; randomisation preserved).
- Note TA1098 included an NMA with a proxy population (including people ≥65 years) for SWOG S0777, a non-time-varying MAIC and an NMA with SWOG S0777 ITT population. Proxy population had concerns because randomisation was not preserved (trial did not stratify by age); ITT population also had concerns due to heterogeneity between SWOG and IMROZ.
  - Committee conclusion: non-time-varying MAIC using a constant HR because of the NMA limitations.

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib;; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; ISA, isatuxumab; LEN, lenalidomide; MEL, melphalan; PRED, prednisolone; NMA, network meta analysis; ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting; MAIC, matched adjusted indirect comparison

ITC approaches versus ISA+BOR+LEN+DEX – supportive MAIC

Company

- Possible some heterogeneity exists between CEPHEUS and IMROZ, therefore, a supportive MAIC conducted to explore potential impact of any heterogeneity on comparative efficacy results
- Given a common comparator arm (BLd) between CEPHEUS and IMROZ trial populations, anchored MAIC using IPD from CEPHEUS was considered to represent the next best approach
- Data for CEPHEUS in MAIC was informed by ASCT-ineligible ITT analysis set.
- IPD available from CEPHEUS trial; only aggregate data available from IMROZ trial.
- Almost all baseline characteristics in CEPHEUS trial (ASCT-ineligible population) and IMROZ trial fell within an SMD threshold ±0.2 prior to adjustment, indicating high level of alignment between trial populations.

Summary of MAIC results for DAR+BOR+LEN+DEX versus ISA+BOR+LEN+DEX

	PFS, HR (95% CI)	OS, HR (95% CI)
Unadjusted	[redacted]	[redacted]
Company-preferred MAIC*	[redacted]	[redacted]
Sensitivity analysis MAIC*	[redacted]	[redacted]

*See appendix for variables adjusted for in company-preferred and sensitivity analysis MAICs

EAG comments

- Selection of covariates for MAIC aligned to covariate selection used in IPTW – consider reasonable
- Limited detail on other statistical characteristics of MAIC → No comparison of patient characteristics before and after matching and effective sample size not stated so degree of lost data is unknown
- Notes MAIC results broadly consistent with NMA results, albeit with slightly higher HRs
- Without further information on methods, EAG unable to fully appraise MAIC and regard the results uncertain

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib;; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; LEN, lenalidomide; MEL, melphalan; PRED, prednisolone; ITC, indirect treatment comparison; IPD, individual patient data; ITT, intention to treat; IPTW, inverse probability of treatment weighting; MAIC, matched adjusted indirect comparison

Key issues: Uncertainty in the indirect comparisons

Background

- Company-preferred ITC in the CS uses IPTW approach with independent data for DAR+LEN+DEX, LEN+DEX and BOR+MEL+PRED; NMA provided to support IPTW ITC.
- ISA+BOR+LEN+DEX was not included in the original CS; company say it is not a relevant comparator (see Key issue: Comparators).
- At/post-clarification, company presented NMA comparing DAR+BOR+LEN+DEX with ISA+BOR+LEN+DEX, along with a supportive MAIC

EAG comments

- Despite some limitations (e.g. a sparse network, use of subgroups) the EAG deem NMA is of a reasonable standard
- The company's MAIC comparing DAR+BOR+LEN+DEX with ISA+BOR+LEN+DEX shows some consistency with NMA in the relative effect estimates → suggests robustness in estimates based on the NMA
- EAG urge caution in interpretation of MAIC results as limited details provided on its methodology

Which ITC results should be used to inform decision making?

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib;CS, company submission; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; LEN, lenalidomide; MEL, melphalan; PRED, prednisolone; NMA, network meta analysis; ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting; MAIC, matched adjusted indirect comparison

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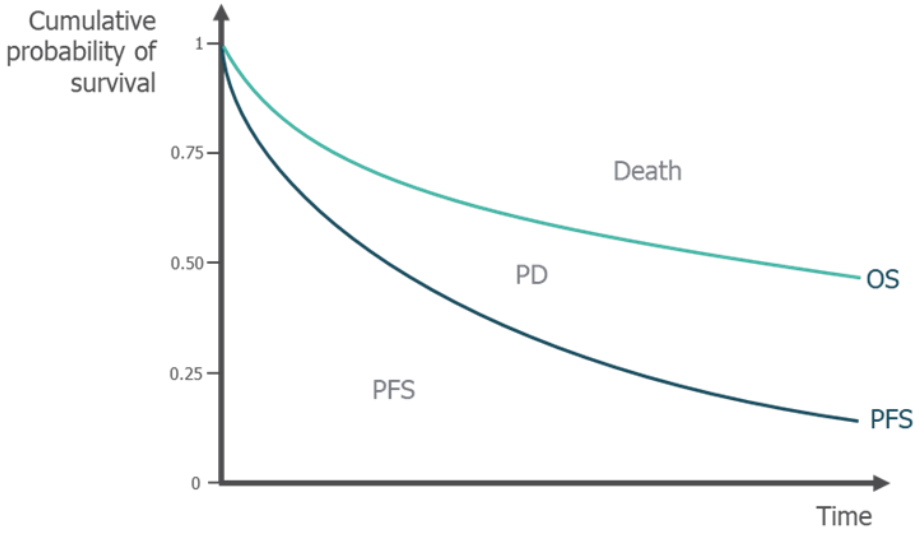
Company's model overview

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;

Key Issue: Proportion who have second-line treatment

Background

- Rate of second-line treatment is lower in DAR+BOR+LEN+DEX arm ([redacted] sourced from CEPHEUS, ASCT-ineligible population) compared with DAR+LEN+DEX arm (81.25%; sourced from MAIA) and ISA+BOR+LEN+DEX (72%; sourced from IMROZ).
- Company explains this by:
  - PFS benefit of DAR+BOR+LEN+DEX
  - Those receiving DAR+BOR+LEN+DEX would be much older following disease progression and therefore less likely to receive further subsequent treatments

EAG comments

- Clinical expert: unlikely that improvements with DAR+BOR+LEN+DEX would reduce the proportion of people needing second-line treatment by [redacted]
- Median OS and PFS in CEPHEUS not been reached; expect proportion needed second-line would increase with time; later data cut-off would provide more certainty (final data cut expected [redacted])
- Prefer to assume that 75% of people need second-line treatment in the DAR+BOR+LEN+DEX and ISA+BOR+LEN+DEX arms (informed by clinical expert that proportion likely to be higher than [redacted]%, but DAR+BOR+LEN+DEX proportion would still be expected to be lower than DAR+LEN+DEX); increases costs for DAR+BOR+LEN+DEX

What second-line treatment rate for DAR+BOR+LEN+DEX should be used?

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; PFS, progression free survival; OS, overall survival;

Key issue: Model characteristics may not reflect NHS practice

Background

- Baseline characteristics in the modelled population are based on the CEPHEUS ASCT-ineligible population: mean age [redacted] years, [redacted] male.
- TA1098 (ISA+BOR+LEN+DEX): starting age in model was initially 71.6 (IMROZ), but updated to 75 years based on Djebbari et al. (SACT data for ASCT-ineligible population was not available).

EAG comments

- Clinical advice: people with newly diagnosed MM in the NHS likely to be slightly older than CEPHEUS, with higher proportion of males.
- RWD from England (NCRAS, Jan 2015 – Dec 2022): cohort was [redacted] years and [redacted] male
- EAG base case: mean age 75 years and 55% male (informed by clinical advice).

What age and proportion of male/female should be used in the model?

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; RWD, real world data

Key issue: Second and third-line treatment distributions may not reflect NHS practice

Table: Distribution of subsequent treatments in company model (with EAG-preferred values in brackets)

2nd line, %							
Subsequent therapy:	LEN+DEX	CAR+DEX	DAR+BOR +DEX	BOR	CAR+LEN +DEX	SEL+BOR+ DEX	BEL+BOR+ DEX
DAR+BOR+LEN+DEX*	0.00	9.38	0.00	0.00	0.00	3.13	87.50
DAR+LEN+DEX	0.00	9.38	0.00	**0.00 (10)**	**0.00 (4)**	3.13	**87.50 (74)**

3rd line, %						
Subsequent therapy:	LEN+DEX	PAN+BOR+ DEX	IXA+LEN+DE X	SEL+BOR+ DEX	CYC	CAR+LEN+DE X
DAR+BOR+LEN+DEX*	0.00	**17.65 (26.86)**	0.00	**41.18 (10)**	**41.18 (62.67)**	0.00
DAR+LEN+DEX	0.00	**17.65 (26.86)**	0.00	**41.18 (10)**	**41.18 (62.67)**	0.00

Differences between EAG and company

EAG comments

- *Company assume DAR+BOR+LEN+DEX and ISA+BOR+LEN+DEX distribution to be the same
- BEL+BOR+DEX (ID6212) recommended June 2025; expert says difficult to predict uptake but considered the company assumption too high (toxicity of BEL+BOR+DEX may prevent some people from taking it).
- Availability of SEL+BOR+DEX is currently limited; likely to be used less for both arms

What subsequent treatment distribution is plausible for decision making?

Abbreviaitons: BOR, bortezomib; CAR, carfilzomib; CYC, cyclophosphamide; DAR, daratumumab; DEX, dexamethasone; ELR, elranatamab; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; SEL, Selinexor.

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Choice of ITC for ISA+BOR+LEN+DEX	NMA	NMA
Proportion of second-line treatment	DAR+BOR+LEN+DEX = [redacted]%; DAR+LEN+DEX = 81.25; ISA+BOR+LEN+DEX = 72%	DAR+BOR+LEN+DEX and ISA+BOR+LEN+DEX = 75%
Mean age	[redacted] years	75 years
Proportion male	[redacted] male	55%
Distribution of subsequent treatments	**Second line:** **DAR+LEN+DEX arm:** 0% bortezomib 0% CAR+LEN+DEX 87.5% BEL+BOR+DEX **Third line:** **All arms:** 41.18% SEL+BOR+DEX 17.65% PAN+BOR+DEX 41.18% cyclophosphamide	**Second line:** **DAR+LEN+DEX arm:** 10% bortezomib 4% CAR+LEN+DEX 73.5% BEL+BOR+DEX **Third line:** **All arms:** 10% SEL+BOR+DEX 26.8% PAN+BOR+DEX 62.67% cyclophosphomide

Note: EAG aligned with company on OS, PFS and TTD extrapolations. Related scenarios explored by EAG (see appendix).

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; ITC, indirect treatment comparison; LEN, lenalidomide; NMA, network meta analysis; SEL, selinexor; PAN, panobinostat; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation

Cost-effectiveness results

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

When using confidential prices, both the company and EAG base cases are above the range normally considered an acceptable use of NHS resources (over £20,000-£30,000 per QALY)

All company and EAG scenarios (including those varying OS, PFS, TTD, utilities, subsequent treatments) are above the range normally considered an acceptable use of NHS resources (over £20,000-£30,000 per QALY)

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Severity modifier

- Does not meet severity weighting threshold.

Uncaptured benefits

- No uncaptured benefits raised by stakeholders

Equality considerations

- No potential issues raised by stakeholders.
- But, previous appraisals have noted that MM is more common in men, older people (≥75 years) and people of African and Caribbean family background.

Managed access

- Company has not submitted a managed access proposal.

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues recap

Issue	ICER impact
Comparators (EAG Issue 1b)	Unclear 
Uncertainty in the indirect comparisons for DAR+BOR+LEN+DEX versus comparators "exploratory" NMA cannot be included in the primary ITC approach used in the CS (EAG Issue 1a)	Unclear 
Uncertainty in the proportion of patients who need second-line treatment (EAG Issue 2)	Moderate 
Generalisability of baseline characteristics in the model to NHS population (EAG secondary issue 1)	Small 
Proportion of second- and third-line treatments in NHS practice (EAG secondary issue 2)	Small 

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; NMA, network meta analyses;

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

Supplementary appendix

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Overall survival extrapolations (COVID-19 adjusted)

DAR+BOR+LEN+DEX

DAR+LEN+DEX

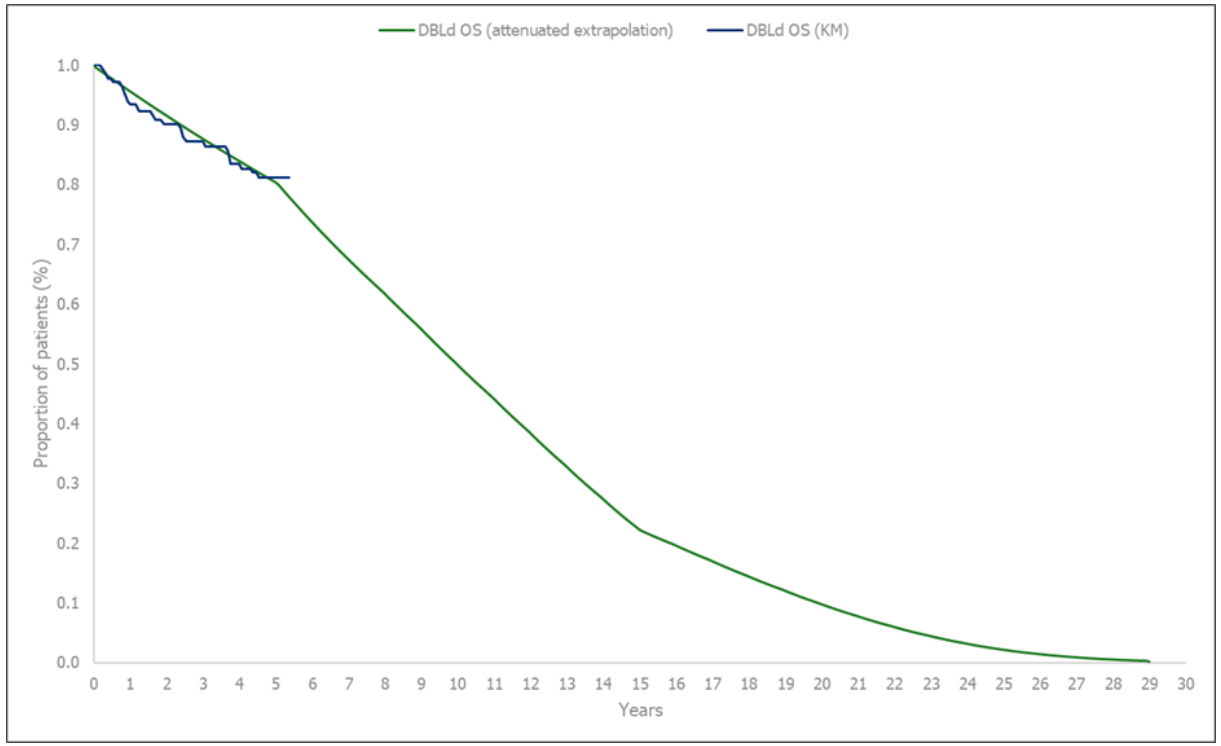
EAG comments

- EAG agrees with company that exponential has best fit based on AIC/BIC for both arms (closely followed by all other distributions for DAR+BOR+LEN+DEX and Weibull and log-logistic for DAR+LEN+DEX)

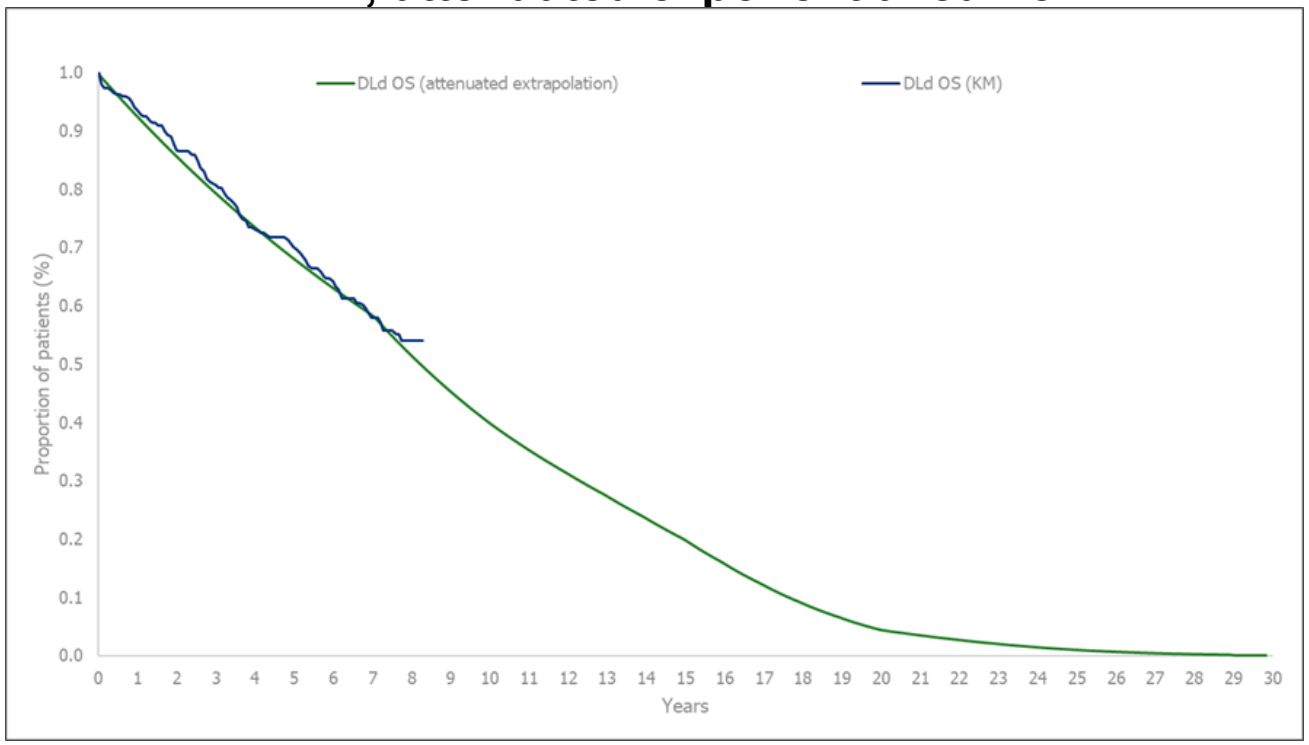
Overall survival extrapolations - attenuations

Company attenuated the curves at 10, 15 and 20 years to align with UK clinical experts advisory board.

DAR+BOR+LEN+DEX, attenuated exponential curve



DAR+LEN+DEX, attenuated exponential curve



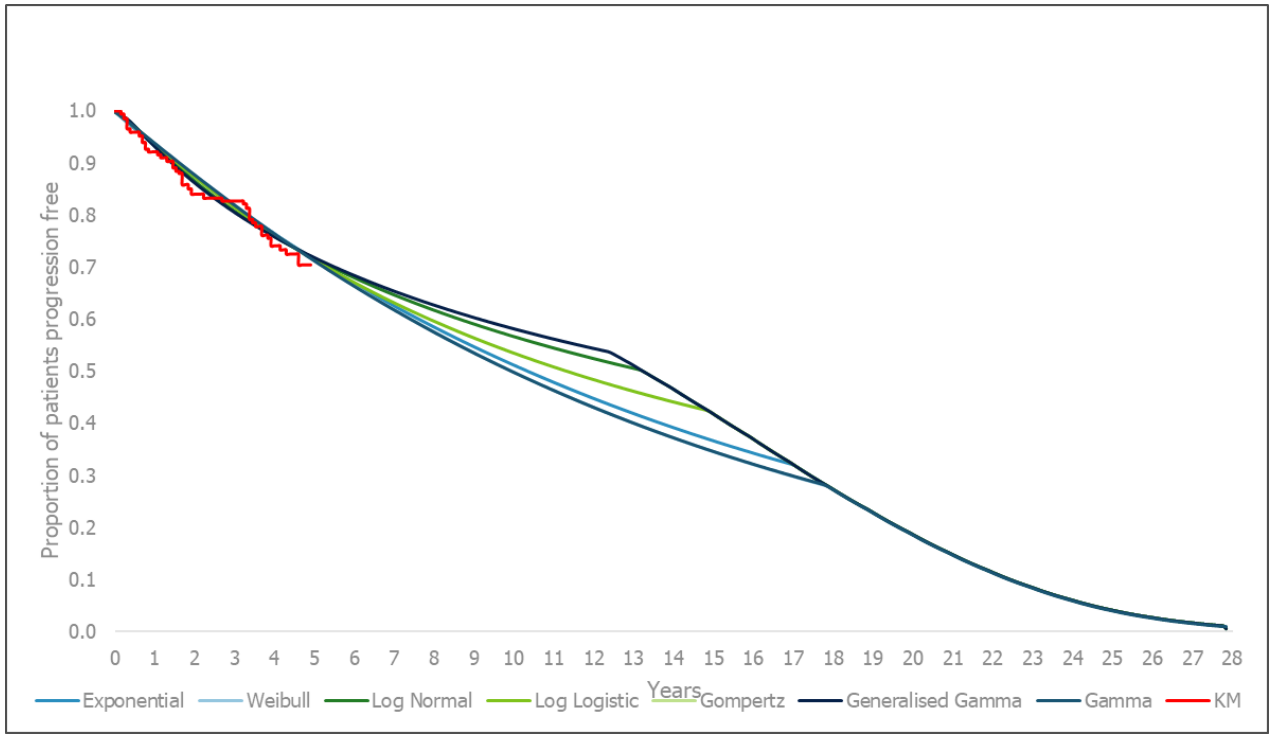
EAG scenarios:

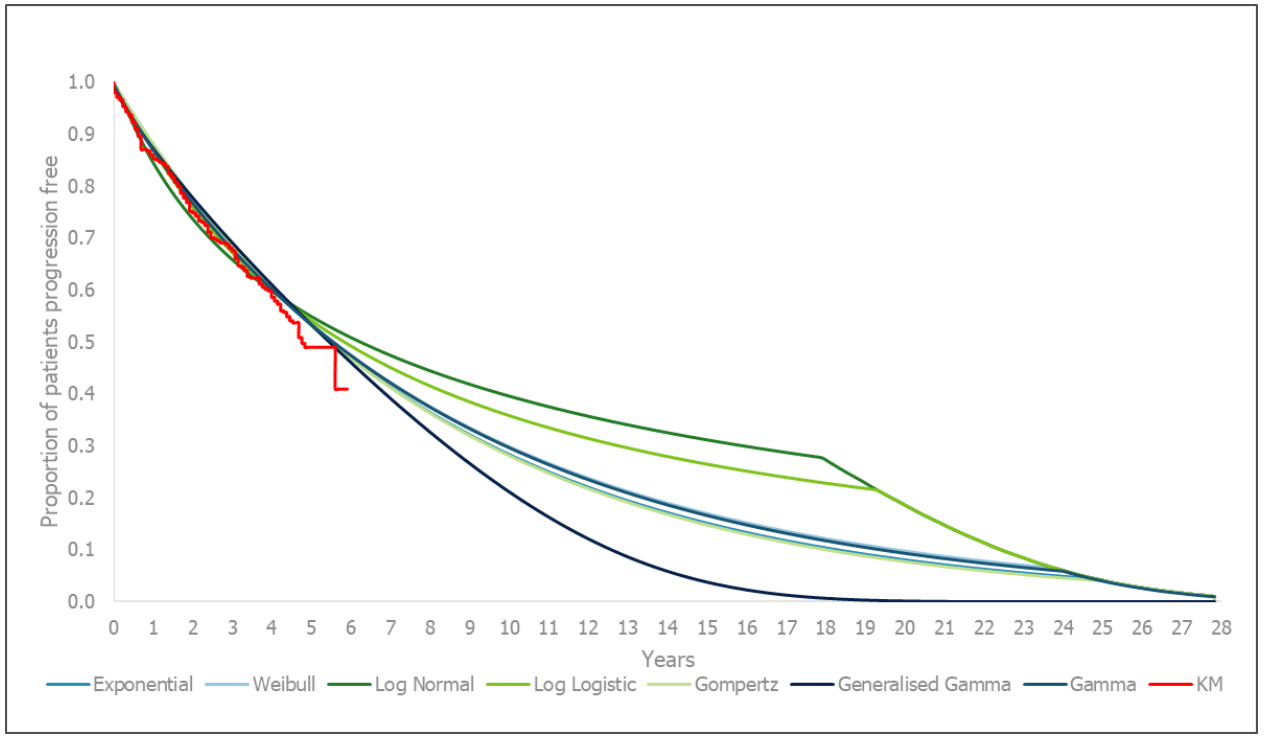
- Reduce OS (and PFS) estimates by 10% at 10 years and 5% at 15 years for both DAR+BOR+LEN+DEX and DAR+LEN+DEX; Clinical advice to EAG was that the DAR+LEN+DEX survival estimates were optimistic and that it is expected that DAR+BOR+LEN+DEX would offer a survival benefit over DAR+LEN+DEX.
- DAR+LEN+DEX attenuation point at 5 years for OS (to match OS attenuation for DAR+BOR+LEN-DEX)

Company OS estimates

	Estimated survival		
Parametric function	**5 years**	**10 years**	**20 years**
DBLd			
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
DLd			
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Progression-free survival extrapolations (COVID-19 adjusted)



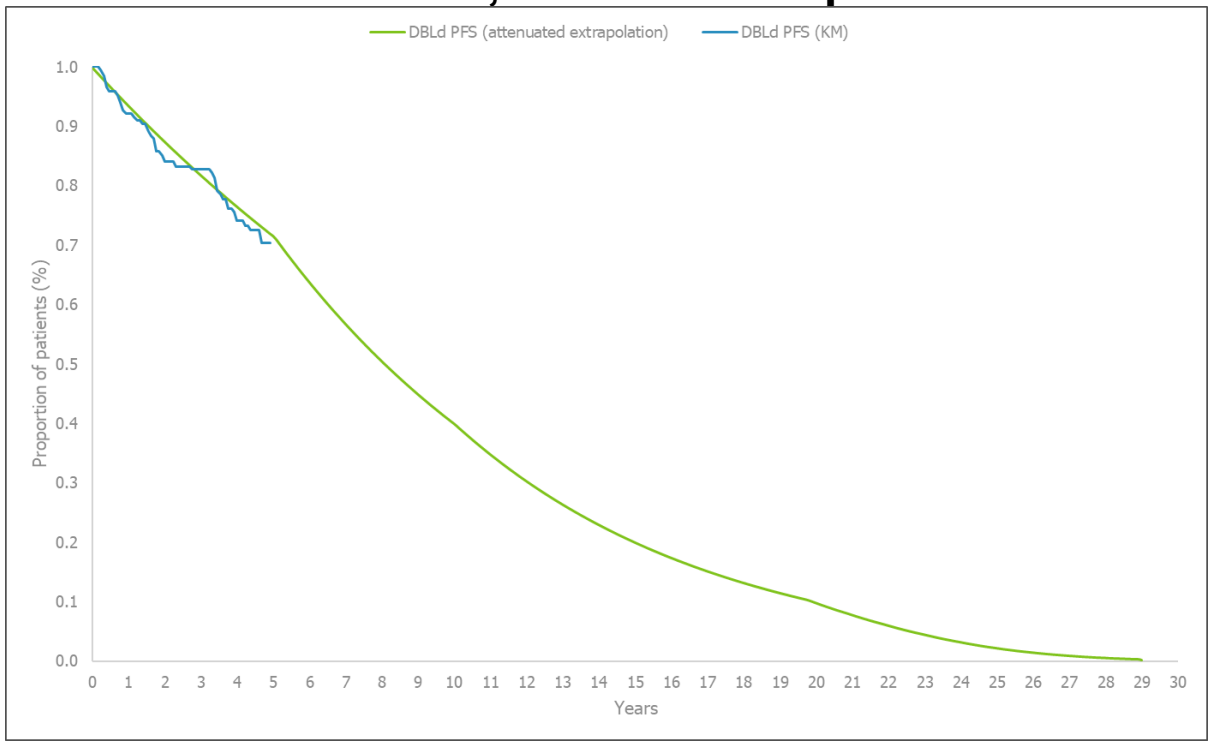


EAG comments

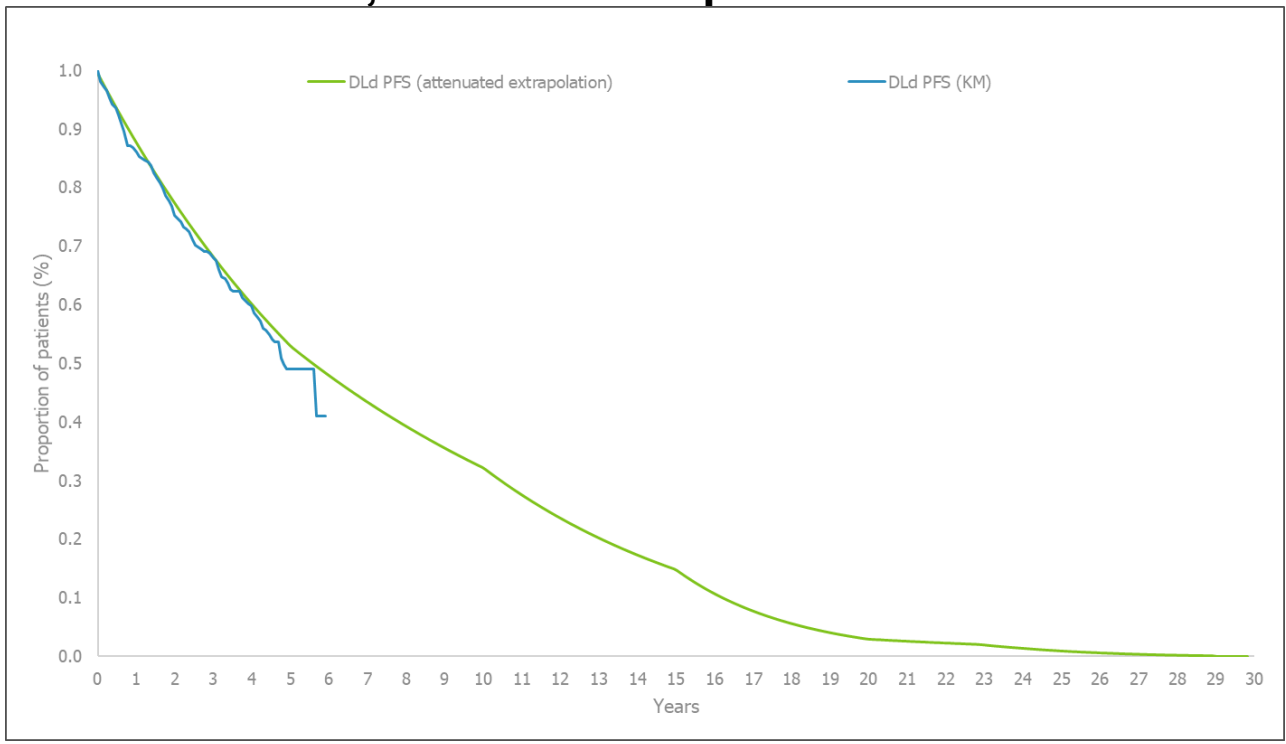
- Agree with company that best-fitting curve for both is exponential, but CEPHEUS data is immature (median PFS not yet met for DAR+BOR+LEN+DEX).
- Proportional hazards assumption holds for PFS, but company model the treatment arms independently to be consistent with OS; EAG views this as a reasonable adjustment.

Progression-free survival - attenuations

DAR+BOR+LEN+DEX, attenuated exponential curve



DAR+LEN+DEX, attenuated exponential curve



EAG scenarios:

- DAR+LEN+DEX attenuation point at 7 years for PFS; the DAR+LEN+DEX OS attenuation point is 7 years.

Company PFS estimates

	Estimated survival		
Parametric function	**5 years**	**10 years**	**20 years**
DBLd			
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
DLd			
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Time to treatment discontinuation

DAR+BOR+LEN+DEX

[redacted]

DAR+LEN+DEX

[redacted]

EAG scenarios:

- TTD: exponential distribution for DBLd (without attenuation) and the Gompertz distribution for DLd (without attenuation); The exponential and Gompertz are the best-fitting curves according to AIC/BIC scores
- TTD: Gompertz distribution for DBLd (without attenuation) and the Gompertz distribution for DLd (without attenuation); Exploratory analysis based on clinical advice to the EAG
- TTD: Gompertz distribution for DBLd (without attenuation) and the generalised gamma distribution for DLd (without attenuation); Exploratory analysis based on clinical advice to the EAG

Company PFS estimates

	Estimated survival		
Parametric function	**5 years**	**10 years**	**20 years**
DBLd			
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
DLd			
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

CEPHEUS trial characteristics

Clinical trial design and outcomes

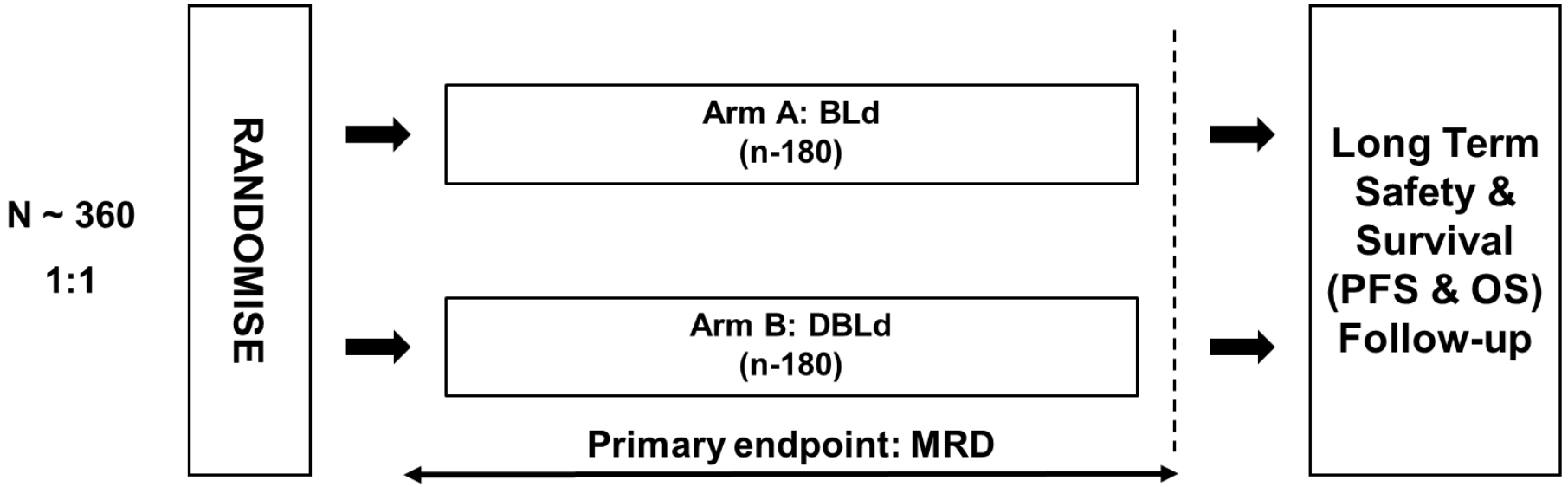
	CEPHEUS
Design	Phase 3, randomised, open label
Population	Newly diagnosed (untreated) MM, considered ineligible for or deferred (refused) ASCT.
Intervention	DAR+BOR+LEN+DEX
Comparator(s)	BOR+LEN+DEX
Duration	Latest data cut May 2024; duration of follow-up for PFS 58.7 months (range 0.1-64.7 months)
Primary outcome	Overall MRD negativity rate
Key secondary outcomes	≥CR rate, PFS, sustained MRD negativity rate (OS included as other secondary outcome)
Locations	Multicentre across North & South America, Europe, Israel and Japan; 9 UK sites (n=25 participants)

CEPHEUS baseline characteristics

Table: Baseline characteristics for the ASCT-ineligible ITT group (full characteristics in CS Table 6)

Characteristics	ASCT-ineligible ITT analysis set		
	BLd (N=145)	DBLd (N=144)	Total (N=289)
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	72.0 (51, 80)	72.0 (58, 79)	72.0 (51, 80)
Overall age group, n (%)			
<65	[redacted]	[redacted]	[redacted]
≥65 to <70			
≥70			
Stratification factor age/transplant			
<70 ineligible	35 (24.1%)	35 (24.3%)	70 (24.2%)
≥70	110 (75.9%)	[redacted]	[redacted]
Sex, n (%)			
Female	63 (43.4%)	79 (54.9%)	142 (49.1%)
Male	82 (56.6%)	65 (45.1%)	147 (50.9%)
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Other			
Missing			
Baseline ECOG, n (%)			
0	57 (39.3%)	52 (36.1%)	109 (37.7%)
1	78 (53.8%)	75 (52.1%)	153 (52.9%)
2	10 (6.9%)	17 (11.8%)	27 (9.3%)

CEPHEUS trial schematic



- **Arm A:** BOR+LEN+DEX alone for eight cycles followed by Ld alone until disease progression or unacceptable toxicity
- **Arm B:** DAR+BOR+LEN+DEX for eight cycles followed by DAR+LEN+DEX therapy until disease progression or unacceptable toxicity

IPTW covariates

Table: Treatment effect modifiers and prognostic factors included as covariates in IPTW

Variable	Base case	Sensitivity analysis (all covariates adjusted)
Age	✓	✓
Sex	✓	✓
Race		✓
ECOG PS	✓	✓
MM stage per ISS	✓	✓
Cytogenetic risk	✓	✓
EMD	✓	✓
Time since initial MM diagnosis		✓
Frailty (based on simplified IMWG frailty score)	✓	✓
Type of MM (IgG versus other)	✓	✓
Anaemia, haemoglobin (< versus ≥ 100mg/L)	✓	✓
Creatinine clearance (≥ versus < 60mL/min/1.73 m^2)	✓	✓
LDH (> versus ≤ 280 U/L)	✓	✓
Calcium levels (> versus ≤ 2.75 mmol/L)		✓

ECOG PS: Eastern Cooperative Oncology Group performance score; EMD: extramedullary plasmacytoma; GFR: estimated glomerular filtration rate; IMWG: International Myeloma Working Group; IPTW: inverse probability of treatment weighting; ISS: International Staging System; L: litre; LDH: lactate dehydrogenase; MM: multiple myeloma

IPTW ITC results - PFS

DAR+BOR+LEN+DEX improves PFS versus DAR+LEN+DEX, LEN+DEX, or BOR+MEL+PRED

Analyses		DAR+BOR+LEN+DEX versus comparator HR (95% CI), p-value		
		DAR+LEN+DEX	LEN+DEX	BOR+MEL+PRED
IPTW **Base case**	11/14 covariates adjusted; adjusted for COVID-19	0.55 (0.38, 0.79) p=0.001	0.30 (0.21, 0.43) p<0.0001	0.16 (0.10, 0.25) p-value not reported
IPTW sensitivity analysis	All covariates adjusted; adjusted for COVID-19	0.54 (0.37, 0.79) p=0.001	0.31 (0.21, 0.45) p<0.0001	0.16 (0.10, 0.25) p-value not reported
IPTW **sensitivity analysis**	11/14 covariates adjusted; unadjusted for COVID-19	0.62 (0.44, 0.88) p=0.007	[redacted]	[redacted]

IPTW ITC results - OS

DAR+BOR+LEN+DEX improves OS versus DAR+LEN+DEX, LEN+DEX, or BOR+MEL+PRED

Analyses		Comparison, DAR+BOR+LEN+DEX versus… HR (95% CI) p-value		
		DAR+LEN+DEX	LEN+DEX	BOR+MEL+PRED
IPTW **Base case**	11/14 covariates adjusted; adjusted for COVID-19	0.63 (0.41, 0.98) p=0.040	0.43 (0.28, 0.66) p<0.0001	0.36 (0.23, 0.57) p-value not reported
IPTW sensitivity analysis	All covariates adjusted; adjusted for COVID-19	0.65 (0.41, 1.02) p=0.060	0.44 (0.29, 0.69) p<0.0001	0.39 (0.24, 0.62) p-value not reported
IPTW sensitivity analysis	11/14 covariates adjusted; unadjusted for COVID-19	0.80 (0.53, 1.19) p=0.262	[redacted]	[redacted]

IPTW ITC results - TTD

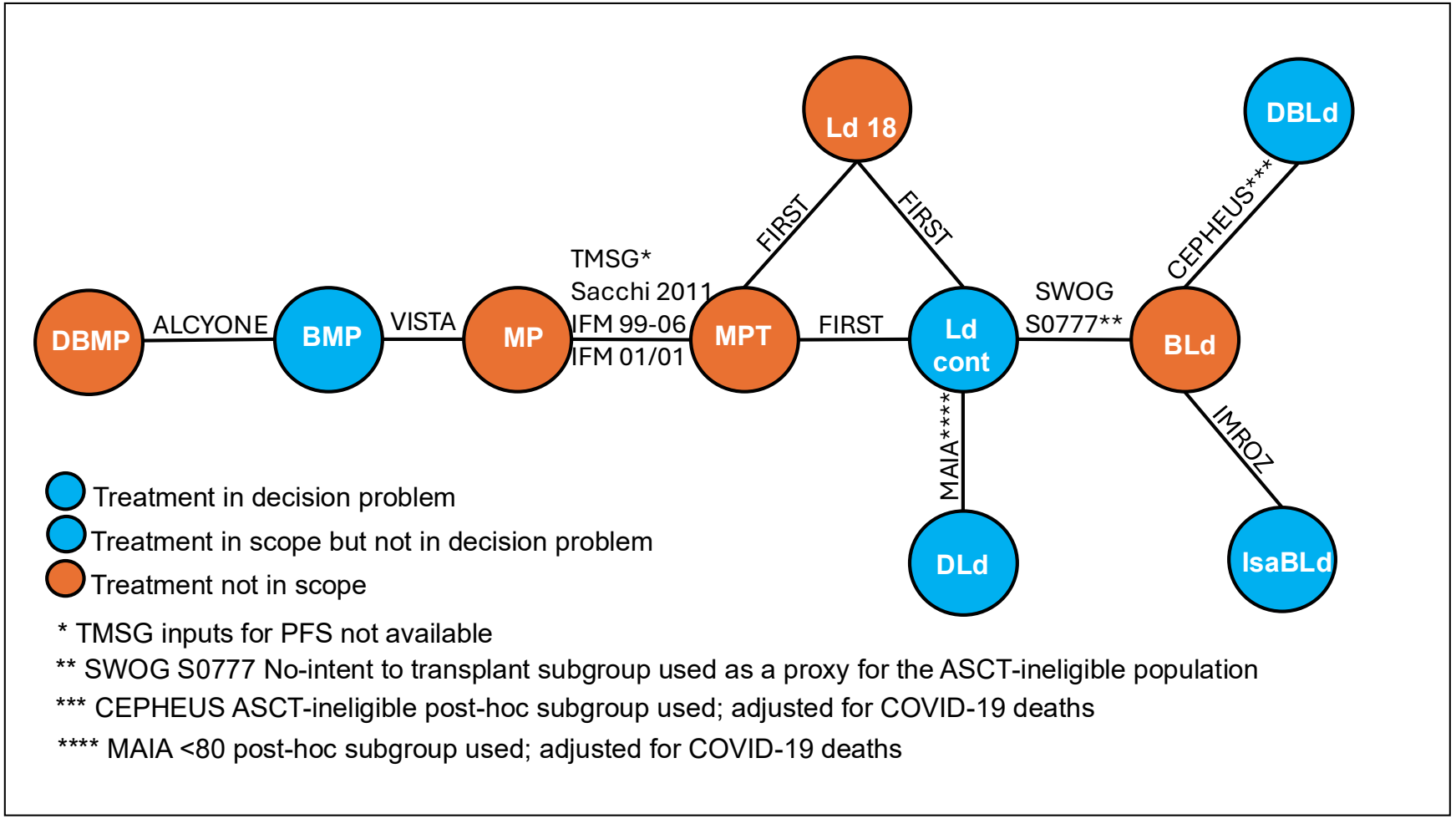
DAR+BOR+LEN+DEX reduces the risk of TTD versus DAR+LEN+DEX, LEN+DEX, or BOR+MEL+PRED

Analyses		Comparison, DBLd versus… HR (95% CI) p-value		
		DAR+LEN+DEX	LEN+DEX	BOR+MEL+PRED
IPTW **Base case**	11/14 covariates adjusted; adjusted for COVID-19	[redacted]	[redacted]	[redacted]
IPTW sensitivity analysis	All covariates adjusted; adjusted for COVID-19	[redacted]	[redacted]	[redacted]
IPTW sensitivity analysis	11/14 covariates adjusted; unadjusted for COVID-19	[redacted]	[redacted]	[redacted]

NMA approach

NMA network - provided as supportive evidence for the IPTW ITC and main evidence for the ISA+BOR+LEN+DEX comparison

Figure: Studies included in the NMA



Network meta-analysis – included studies

Table: Studies used to inform NMA

Trial	Intervention	Comparator
VISTA	BOR+MEL+PRED	MEL+PRED
ALCYONE	DAR+BOR+MEL+PRED	BOR+MEL+PRED
MAIA	DAR+LEN+DEX	LEN+DEX (Ldcont in figure)
Sacchi 2011	MEL+PRED	MEL+PRED+THAL
IFM 01/01	MEL+PRED	MEL+PRED+THAL
SWOG S0777 no intent to transplant	BOR+LEN+DEX	LEN+DEX (LdCont in figure)
IFM 99–06	MEL+PRED	MEL+PRED+THAL
TMSD (OS only)	MEL+PRED+THAL	MEL+PRED
FIRST	MEL+PRED+THAL	LEN+DEX (Ldcont in figure)
FIRST	LEN+DEX (Ld18 in figure)	LEN+DEX (Ldcont in figure)
IMROZ	ISA+BOR+LEN+DEX	BOR+LEN+DEX
CEPHEUS ASCT-ineligible	DAR+BOR+LEN+DEX	BOR+LEN+DEX

NMA results - PFS

NMA provided as “supportive” evidence to the IPTW

Outcome	Comparison, DAR+BOR+LEN+DEX versus… OR (95% CrI)			
	DAR+LEN+DEX	LEN+DEX	BOR+MEL+PRED	ISA+BOR+LEN+DEX
PFS (Fixed effect; adjusted for COVID-19; base case)	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Random effects; adjusted for COVID-19)	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Fixed effect; unadjusted)	Not reported	Not reported	Not reported	[redacted] (company base case)
PFS (Random effects; unadjusted)	Not reported	Not reported	Not reported	[redacted]

NMA results - OS

NMA provided as “supportive” evidence to the IPTW

Outcome	Comparison, DAR+BOR+LEN+DEX vs… HR (95% CrI)			
	DAR+LEN+DEX	LEN+DEX	BOR+MEL+PRED	ISA+BOR+LEN+DEX
OS (Fixed effect; adjusted for COVID-19; base case)	[redacted]	[redacted]	[redacted]	[redacted]
OS (Random effects; adjusted for COVID-19)	[redacted]	[redacted]	[redacted]	[redacted]
OS (Fixed effect; unadjusted)	Not reported	Not reported	Not reported	[redacted] (company base case)
OS (Random effects; unadjusted)	Not reported	Not reported	Not reported	[redacted]

Variables adjusted for in the base and sensitivity MAICs

	Covariate	
Base model	R-ISS	• Stage I or II • Stage III • Not classified
	Cytogenetic risk	• Standard • High • Unknown/missing
	Age	• <65 yr • 65-69 yr • 70-74 yr • 75-80 yr
	ECOG PS	• 0 • 1 • 2+
	Myeloma type	• IgG • Non-IgG
	Frailty	
	EMD	
	Sex	
	eGFR <60 ml per minute per 1.73 m^2	

	Covariate
Full model (Sensitivity)	Median duration since initial Dx with MM
	Race

Subsequent treatments in CEPHEUS

Table: Subsequent treatment regimens received as a first subsequent treatment (ASCT-ineligible)

Subsequent treatment, n (%)	BOR+LEN+DEX [redacted] who received subsequent treatment	DAR+BOR+LEN+DEX [redacted] who received subsequent treatment
Carfilzomib plus dexamethasone	[redacted]	[redacted]
Carfilzomib, pomalidomide and dexamethasone	[redacted]	[redacted]
Daratumumab, bortezomib and dexamethasone	[redacted]	[redacted]
Daratumumab, carfilzomib and dexamethasone	[redacted]	[redacted]
Daratumumab, lenalidomide and dexamethasone	[redacted]	[redacted]
Daratumumab, pomalidomide and dexamethasone	[redacted]	[redacted]
Investigational drugs	[redacted]	[redacted]
Isatuximab, pomalidomide and dexamethasone	[redacted]	[redacted]
Lenalidomide and dexamethasone	[redacted]	[redacted]
Pomalidomide and dexamethasone	[redacted]	[redacted]
Other	[redacted]	[redacted]

"Other" comprised 32 other treatments/treatment combinations, including CAR+LEN+DEX ([redacted] in the BOR+LEN+DEX arm, [redacted] in the DAR+BOR+LEN+DEX arm); for full table see clarification response A2.

Key issue: Subsequent treatments after second line

Distribution of patients to subsequent therapies used in company model

Line:	2nd line (%)						
Subsequent therapy:	LEN+DEX	CAR+DEX	DAR+BOR+DEX	BOR	CAR+LEN+DEX	SEL+BOR+DEX	BEL+BOR+DEX
DAR+BOR+LEN+DEX	0.00	9.38	0.00	0.00	0.00	3.13	87.50
DAR+LEN+DEX	0.00	9.38	0.00	0.00	0.00	3.13	87.50
Line:	3rd line (%)						
Subsequent therapy:	LEN+DEX	PAN+BOR+DEX	IXA+LEN+DEX	SEL+BOR+DEX	Cyclo	CAR+LEN+DEX	-
DAR+BOR+LEN+DEX	0.00	17.65	0.00	41.18	41.18	0.00	-
DAR+LEN+DEX	0.00	17.65	0.00	41.18	41.18	0.00	-
Line:	4th line (%)						
Subsequent therapy:	PomDex	Teclistamab	-	-	-	-	-
All treatments	[redacted]	[redacted]	-	-	-	-	-