Daratumumab in combination for treating newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

For screen – confidential information redacted

Technology appraisal committee B [3 December 2025]

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Company: Johnson & Johnson

Daratumumab in combination for treating newly diagnosed multiple myeloma when stem cell transplant is suitable

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

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Patient perspectives

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

Submission from Myeloma UK and patient expert

- People with myeloma are aware that HDT-SCT is considered the most effective treatment.
- People receiving HDT-SCT 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."

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

Daratumumab* (Darzalex, Johnson & Johnson)

Marketing authorisation	• "in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma" • Granted November 2024, MHRA
Administration	Fixed dose subcutaneous (SC) injection (1,800mg/15ml daratumumab): • Weeks 1-8: once weekly • Weeks 9-16: every two weeks } **Induction** • Stop for HDT and ASCT • Weeks 17-24: every two weeks **- Consolidation** • Week 25 onward: every four weeks until disease progression **- Maintenance**
Price	• List price 1,800 mg (fixed-dose vial) = £4,320.00 (exl. VAT) • A patient access agreement (PAS) and commercial access agreement (CAA) is in place

*Daratumumab can be discontinued for patients who have achieved minimal residual disease (MRD) negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months.

Abbreviations: ASCT, autologous stem cell transplant; MHRA, Medicines and Health care products Regulatory Agency; HDT, high dose therapy; SC, subcutaneous; VAT, value added tax

Company positioning of DAR+BOR+LEN+DEX

NDMM transplant eligible full treatment sequence

1st Line	Induction				HDT-ASCT	Consolidation			Maintenance	
	BOR + DEX ± THA TA311	**DAR + BOR+ THA + DEX** TA763	BOR + CYC + DEX	**DAR + BOR+ LEN + DEX**	HDT-ASCT NG35	Observation	**DAR + BOR+ THA + DEX** TA763	**DAR + BOR+ LEN + DEX**	**LEN** TA680	**DAR + LEN**

EAG comment:

- Very small percentage may receive BOR+CYC+DEX at first line due to THA toxicity concerns in cases of renal impairment.

- Is DAR+BOR+THA+DEX the only relevant comparator for induction/consolidation?
- Is the intervention the full treatment sequence or induction/consolidation phases only?
- Is LEN the most appropriate comparator for maintenance treatment?

Key:

- **Company positioning**
- **Comparators**
- Unlicenced but funded by NHS
- Other options

See pathway with additional lines

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; CYC, cyclophosphamide; DAR, daratumumab; DEX, dexamethasone; HDT, high dose therapy; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; NHS, national health service; THA, thalidomide.

Key issues

Issue	ICER impact
Assuming equal efficacy during induction and consolidation	Unknown
No clinical evidence for full treatment sequence of comparator	Large
Components of the intervention	Unknown
PFS extrapolations	Moderate
Utilities for subsequent lines of therapy	Small
Subsequent treatments	Large
Daratumumab discontinuation	Large
Comparator discontinuation of lenalidomide maintenance	Small

Abbreviations: ICER, incremental cost effectiveness ratio; PFS, progression-free survival

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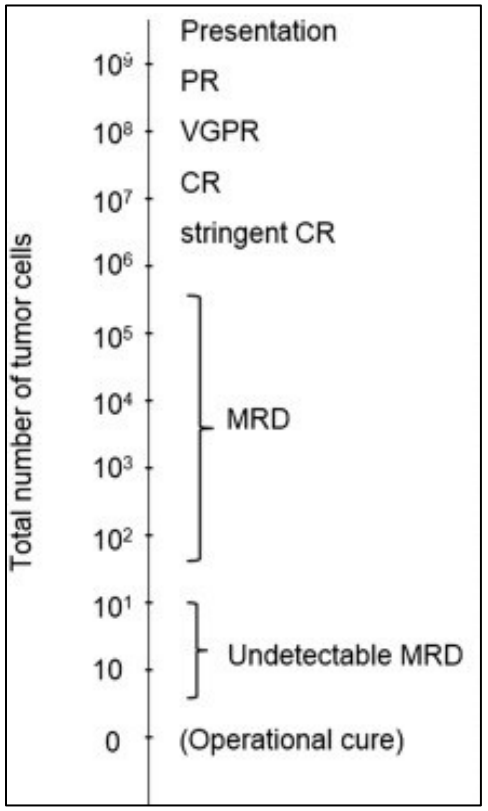
Minimal residual disease

MRD status could give indication of longer-term outcomes

Response status and number of tumour cells



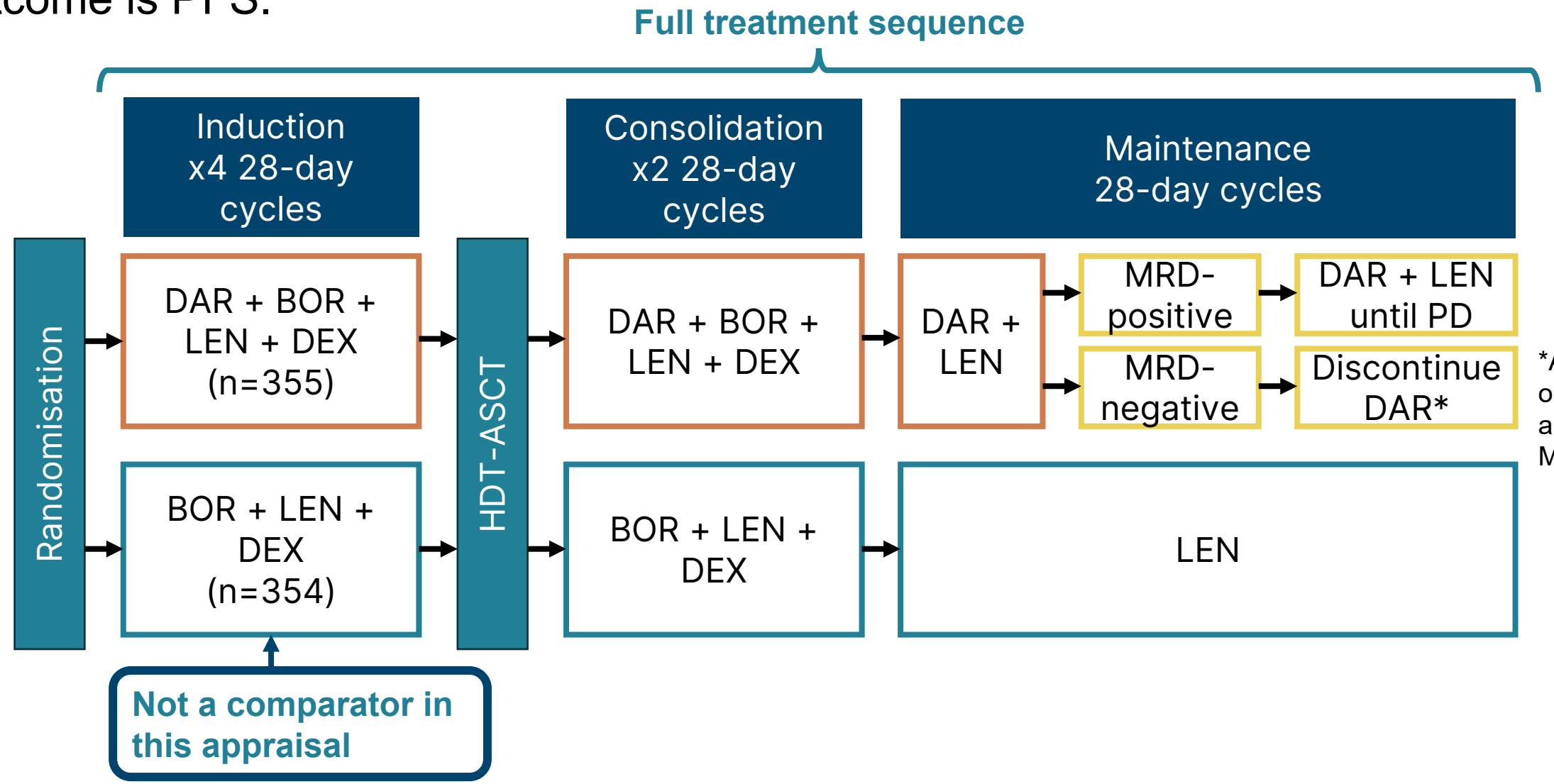
- MRD is the small number of myeloma cells remaining in the bone marrow after treatment. MRD-negativity typically refers to undetectable myeloma cells.
- Daratumumab for NDMM can be discontinued when people have achieved sustained MRD-negativity for 12-months after 24 months on maintenance treatment, as per the SmPC.
- Company and EAG base case included MRD negative stopping rule.
- Clinical experts in TA763 (2021) stated that MRD is not routinely measured and does not guide treatment choices.

Would MRD testing be done routinely to guide the discontinuation of daratumumab?

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

PERSEUS trial overview

Ongoing, randomised, open-label, multicentre phase 3 trial. Primary efficacy outcome is PFS.

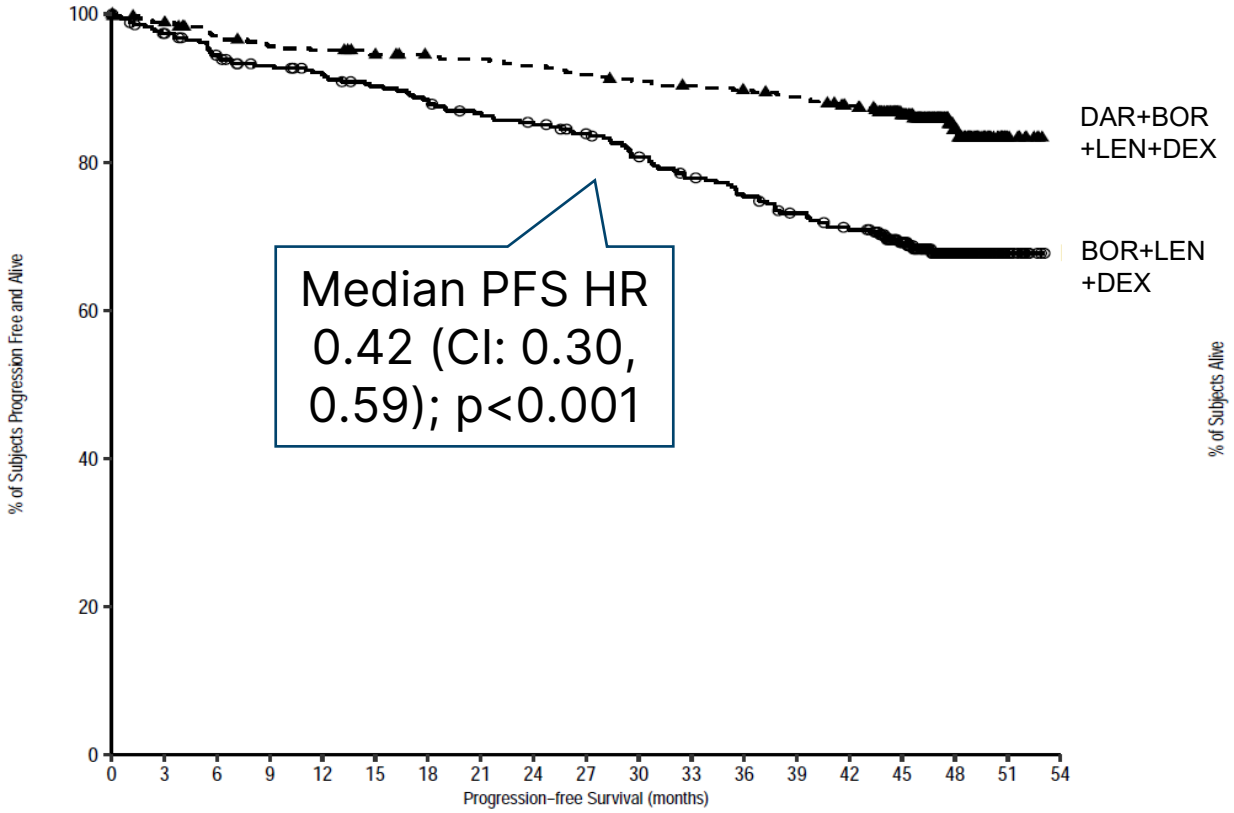


Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HDT, high-dose therapy; LEN, lenalidomide; MRD, minimal residual disease; PD, progressed disease; PFS, progression free survival

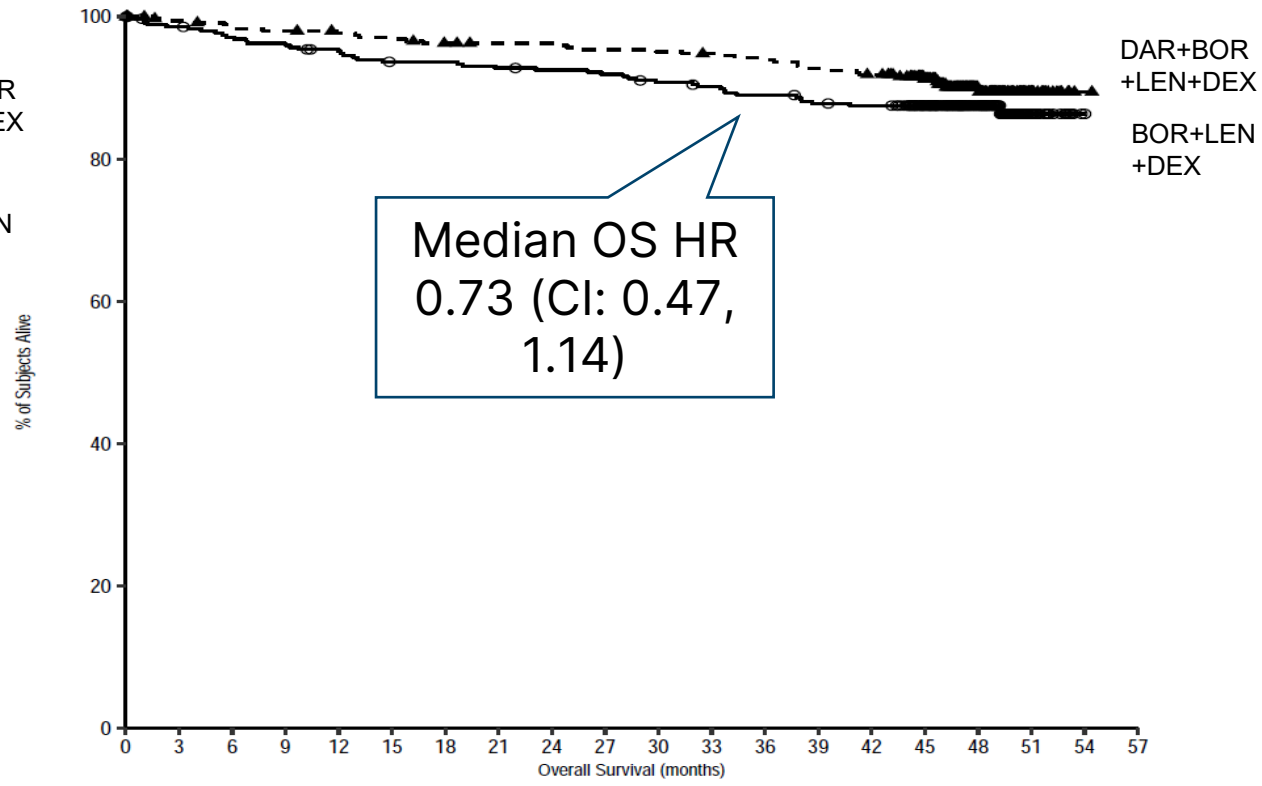
Key clinical trial results – PERSEUS (1/2)

Outcomes favour DAR + BOR + LEN + DEX over BOR + LEN + DEX and PFS showed consistent improvement, but survival data is immature with median follow-up of 47.5 months.

PFS



OS



See appendix for more detail

NICE Abbreviations: BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; PFS, progression free survival.

Key clinical trial results – PERSEUS (2/2)

DAR+BOR+LEN+DEX resulted higher MRD-negativity rates compared to BOR+LEN+DEX

- MRD-negativity defined as one tumour cell per 10^{-5} white cells in bone marrow aspirate and ≥CR.
- Overall and sustained MRD-negativity rate significantly higher compared to BOR+LEN+DEX at post-consolidation and full treatment sequence, showing an increasing benefit between the timepoints.
- Higher proportions achieving sustained MRD-negativity (17.4% vs 38.6%, p=0.0006) and higher MRD-positive (post-consolidation) to MRD-negative conversion (40.5% vs 60.2, p=0.0049) during maintenance.

Outcome	BOR + LEN + DEX	DAR + BOR + LEN + DEX
Overall MRD-negativity rate* (full treatment sequence)	47.5%	75.2%
Sustained[a] MRD-negativity rate* (full treatment sequence)	29.7%	64.8%
Sustained[a] MRD-negativity rate* (for ≥12 months during the maintenance phase)	17.4%	38.6%
MRD-positive (during maintenance phase) to MRD-negative* conversion rate	40.5%	60.2%

* at or below 10^{-5} and ≥CR [a] two consecutive MRD-negative results

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Abbreviations: BOR, bortezomib; CR, complete response; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; MRD, minimal residual disease

Key issue : ITC for induction and consolidation phase (1/2)

ICER impact: Unknown

Company ITC used to assume equal efficacy – not used for relative treatment effects.

Background

- No data for DAR+BOR+THA+DEX induction/consolidation followed by LEN maintenance. See comparator trials.
- Based on ITC (IPTW) of induction/consolidation of DAR+BOR+LEN+DEX from PERSEUS and DAR+BOR+THA +DEX from CASSIOPEIA, equal efficacy between treatments is assumed during induction/consolidation.
- Company base case IPTW adjusted for: age, sex, ECOG PS, ISS stage, baseline cytogenic risk, type of MM, haemoglobin levels.

DAR+BOR+LEN+DEX vs DAR+BOR+THA+DEX induction/consolidation

	Unadjusted	Adjusted IPTW (base case)	Adjusted IPTW (all covariates)
Outcome	**OR (95% CI; p-value)**		
≥VGPR	[redacted]	[redacted]	[redacted]
ORR	[redacted]	[redacted]	[redacted]
MRD-negativity	[redacted]	[redacted]	[redacted]
Outcome	**HR (95% CI; p-value)**		
PFS	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]

Abbreviations: BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPTW, inverse probability weighting; ITC, Indirect treatment comparison; ISS, International Staging System; LEN, lenalidomide; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OR, odds ratio; OS, overall survival; PFS, progression free survival; THA, thalidomide; VGPR, very good partial response.

Key issue : ITC for induction and consolidation phase (2/2)

ICER impact: Unknown

Company

- Company base case IPTW showed favourable outcomes for the intervention and assumption of equal efficacy is conservative [redacted]
- Survival outcomes should be interpreted with caution due to censoring at start of maintenance.

EAG comments

- Not feasible to perform ITC for the full treatment sequence due to lack of data and approach to ITC is appropriate.
- Preference for interpretation of short-term outcomes - OS and PFS should be regarded with caution due to censoring.
- Uncertainty around validity of base case ITC analysis as three priority covariates had SMDs over 0.2, suggesting poor balance after matching but results were consistent with other adjustment methods.

Given the evidence provided, does the committee believe the treatments are equally effective? Is it reasonable for induction/consolidation to be modelled this way?

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; ITC, indirect treatment comparison LEN, lenalidomide; OS, overall survival; PFS, progression free survival; SMD, standardised mean difference; THA, thalidomide

Key issue: No clinical evidence for full sequence of comparator (1/3)

ICER impact: Large

Background:

- For the maintenance phase, company estimated OS and PFS from AURIGA to estimate relative effects of DAR+LEN vs LEN maintenance because PERSEUS did not include a second randomisation after consolidation and prior to maintenance initiation.
- At clarification, the company provided unadjusted and reweighted analysis of DAR+LEN vs LEN from PERSEUS using IPTW - BOR+LEN+DEX with LEN maintenance as the comparator arm in PERSEUS.
- Base case reweights age, sex, ECOG PS, ISS stage, baseline cytogenic risk, type of MM, haemoglobin levels and LDH.
- Additional variables include MM diagnostic criteria satisfied, presence versus absence of extramedullary plasmacytomas, serum calcium, bone lesions and platelet levels.

Key Clinical Efficacy Results of DAR+LEN vs LEN:

	AURIGA	PERSEUS (unadjusted)	PERSEUS (reweighted, base case variables)	PERSEUS (reweighted, base case + additional variables)
Survival outcomes	**HR (95% CI; p-value)**			
Median PFS (Months)	0.53 (0.29, 0.97; 0.0361)	[redacted]	[redacted]	[redacted]
Median OS (Months)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPTW, inverse probability weighting; ; ISS, International Staging System; LEN, lenalidomide; LDH, lactate dehydrogenase; MM, multiple myeloma; OS, overall survival; PFS, progression free survival.

Key issue: No clinical evidence for full sequence of comparator (2/3)

ICER impact: Large

Company:

- AURIGA showed DAR+LEN led to deeper and more durable responses in MRD-negativity and improved OS/PFS compared to LEN alone. See appendix for further details.
- Different prior treatments in PERSEUS with lack of randomisation after consolidation makes it difficult to isolate the treatment effects of DAR+LEN vs LEN – AURIGA is the best data source for DAR+LEN vs LEN maintenance.
- Different prior treatments do not impact generalisability - PERSEUS and AURIGA showed similar outcomes for maintenance treatment and MRD-negativity conversion, and CASSIOPEIA trial indicates prior DAR does not notably impact DAR maintenance.
- Base case reweighted PERSEUS results in a dominant ICER in favour of DAR+BOR+LEN+DEX - DAR+LEN as people in DAR+BOR+THA+DEX – LEN arm progress quicker on to subsequent treatments which increases costs

EAG comments:

- PH assumption holds which justifies applying HR to estimate relative effects of maintenance phase.
- Generalisability - Population in AURIGA is DAR-naïve, MRD-positive, and ≥VGPR. Consolidation therapy was received by few patients [redacted]
- OS HR from AURIGA was not significant, company explored HR=1 and DAR+BOR+LEN+DEX - DAR+LEN dominated due to longer survival for DAR+BOR+THA+DEX - LEN increasing costs.
- AURIGA provides best unbiased estimate of DAR+LEN versus LEN and any estimates on unadjusted PERSEUS would be biased - reweighting PERSEUS could reduce bias but not guaranteed.

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MRD, minimal residual disease; OS, overall survival; PFS, progression free survival; PH, proportional hazards; THA, thalidomide; VGPR, very good partial response.

ICER impact: Large

Key issue: No clinical evidence for full sequence of comparator (3/3)

Summary of AURIGA vs PERSEUS for relative effects of DAR+LEN vs LEN maintenance:

	AURIGA	PERSEUS
Re-randomisation after consolidation	Yes	No – but reweighted analysis provided
Induction/consolidation for people receiving LEN maintenance	Induction treatments varied – few received consolidation, most received BOR+LEN+DEX, none received DAR.	BOR+LEN+DEX

EAG comments:

- Using the HRs from PERSEUS means [redacted] gains in LYs and QALYs occur after progression, this does not happen when using AURIGA HRs.
- [redacted] OS HR ([redacted]) and [redacted] PFS HR ([redacted] 0.53) in reweighted PERSEUS compared to AURIGA leads to more people in DAR+BOR+THA+DEX – LEN arm progressing on to expensive subsequent treatments.
- Immature data in both PERSEUS and AURIGA.

Is PERSEUS or AURIGA more appropriate to inform relative treatment effects of DAR+LEN vs LEN maintenance?

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Abbreviations: BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; LY, life years; OS, overall survival; PFS, progression free survival, QALY, quality-adjusted life year

ICER impact: Unknown

Key issue: Components of the intervention

Company provided a cost comparison of induction/consolidation only and a CEA for the full treatment sequence.

Background:

- CEA of the full treatment sequence assumes equal efficacy during induction/consolidation. Modelled differences in efficacy are due to the addition of DAR to LEN maintenance in the intervention arm, comparator arm receives LEN maintenance alone.
- Cost comparison assumes both arms receive LEN maintenance as SoC.

Company at FAC:

- Cost comparison analysis is standalone and provided to illustrate cost-savings of replacing THA with LEN for induction/consolidation – the intervention is the full treatment sequence.

EAG comments:

- ICER was very sensitive to varying HR to estimate DAR+LEN vs LEN maintenance effects in scenarios.
- Immature data in PERSEUS and AURIGA makes extrapolations uncertain with large differences between probabilistic and deterministic ICERs in EAG base case.
- No economic evaluation of maintenance only phases has been conducted.

Is the intervention the full treatment sequence, induction/consolidation only or the maintenance phase only?

Abbreviations: CEA, cost-effectiveness analysis DAR, daratumumab; EAG, external assessment group; FAC, factual accuracy check; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; SoC, standard of care; THA, thalidomide.

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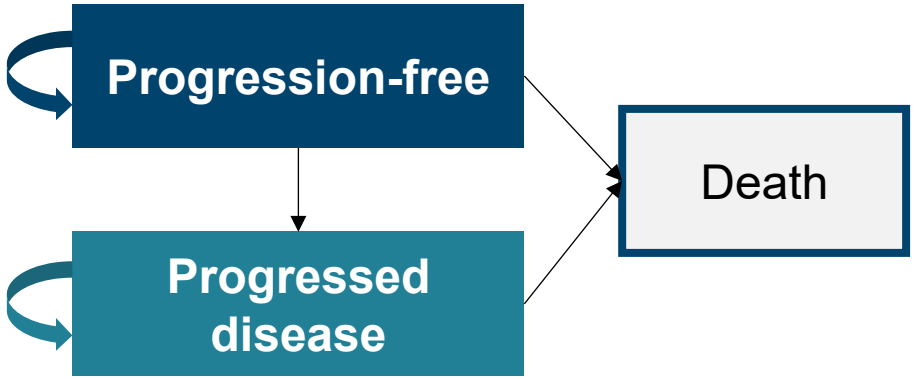
Model structure

Overview:
- Partition survival model
- Cycle length: 28 days
- Time horizon: lifetime

Induction/consolidation phase:
- Assumes equal efficacy between DAR+BOR+LEN+DEX and DAR+BOR+THA+DEX
- PFS and OS taken from PERSEUS trial

Maintenance phase:
- DAR+BOR+LEN+DEX efficacy from PERSEUS trial
- Relative efficacy for DAR+BOR+THA+DEX estimated assuming PH and applying a HR from the AURIGA trial to extrapolations from the PERSEUS trial.

See slide on comparator trials.



Technology affects QALY by:
- Increasing QALYs due to people remaining longer in maintenance and shorter in post-progression phases, due to improvements in OS and PFS.
- Decreasing QALYs due to AEs

Technology affects costs by:
- A decrease in costs during induction, ASCT and consolidation phases driven mainly by differences in drug acquisition costs.
- Increasing costs during maintenance due to DAR costs. Increase in costs during maintenance is around [redacted] the reduction in cost during induction, ASCT and consolidation phases.
- Reducing costs associated with subsequent lines of treatment and terminal care.

Abbreviations: AE, adverse events; ASCT, allogenous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; PH, proportional hazards; QALY, quality-adjusted life year; THA, thalidomide

Key issue: Extrapolation of PFS (1/2)

ICER impact: Moderate

Company selected the generalised gamma. EAG prefer Gompertz.

Background

- PFS extrapolations for DAR+BOR+LEN+DEX – DAR+LEN fitted to PERSEUS. DAR+BOR+THA+DEX - LEN estimated by applying HR from AURIGA (0.53) in both company and EAG base case.
- Model applies structural constraint so PFS does not exceed OS.

Company

- Generalised gamma has the closest fit to clinician estimates and observed hazards.
- Gompertz assumes increasing hazards which is inconsistent with observed data.

EAG comments

- Given immature PERSEUS data, Gompertz should be used as a conservative option.
- Generalised gamma fits better to DAR+BOR+LEN+DEX arm according to clinician estimates but applying PFS HR from AURIGA (0.53) leads to DAR+BOR+THA+DEX PFS above clinician estimates at 10, 15 and 25 years. See next slide.
- Gompertz scores better in AIC/BIC and better aligns with clinician estimates for both arms.
- Large difference in ICER when using HR from re-weighted PERSEUS (PFS HR [redacted])

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; THA, thalidomide

Key issue: Extrapolation of PFS (2/2)

ICER impact: Moderate

Survival Model	Mean PFS (months)	Proportion (%)			
		5 Yrs	10 Yrs	15 Yrs	25 Yrs
DAR+BOR+LEN+DEX - DAR+LEN					
Generalised Gamma (Company)	193.8	81.4	65.2	49.9	22.6
Gompertz (EAG)	173.1	80.8	61.6	43.4	15.1
DAR+BOR+THA+DEX – LEN*					
Generalised Gamma (Company)	129.9	70.1	46.2	28.0	6.2
Gompertz (EAG)	104.7	68.9	41.3	14.5	0.0

*Estimated by applying PFS HR from AURIGA to DAR+BOR+LEN+DEX - DAR+LEN extrapolations

Tech team comment:

- No analysis applying reweighted PERSEUS PFS HRs on PFS extrapolations.

- What extrapolation does committee consider the most plausible?
- What proportion of people would be expected to progress on DAR+BOR+THA+DEX – LEN?

See appendix for figures and details of other extrapolations.

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; PFS, progression free survival; THA, thalidomide

Source of OS hazard ratio

ICER impact: Moderate

Exponential extrapolation has the best fit but immature survival data makes OS uncertain.

Background

- Long-term estimates of OS for DAR+BOR+LEN+DEX – DAR+LEN based on extrapolations fitted to PERSEUS trial.
- Company and EAG base case apply OS HR of DAR+LEN vs LEN maintenance ([redacted] (95% CI:[redacted]; p-value: [redacted]) from AURIGA to estimate effects for DAR+BOR+THA+DEX – LEN – see key issue.

OS HR from reweighted PERSEUS with base case variables showed [redacted] survival benefit of DAR+BOR+LEN+DEX – DAR+LEN (OS HR [redacted])

EAG comments

- No major objections to company approach of using exponential extrapolation given HRs from AURIGA are used – alternative extrapolations do not give better fit.
- Assumption of constant hazards implied by exponential may be strong as observed hazards appear to increase modestly which could lead to an overestimation of OS, but data is immature – see figure.
- Alternative extrapolations tested in scenarios – moderate impact on the ICER.
- Source of HR to inform DAR+BOR+THA+DEX arm has a large impact on the ICER – see key issue.

Which is the most appropriate source for OS HRs, AURIGA or PERSEUS?

Abbreviations: BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; THA, thalidomide

Key issue: Utilities for subsequent lines of therapy (1/2)

ICER impact: Small

Company approach to utilities generally appropriate but applying constant utility in PD state could overestimate HRQoL.

Background

- Company base case utilities from PERSEUS EQ-5D-5L data, cross-walked to UK EQ-5D-3L value set.
- Model incorporated one-off utility decrements due to adverse events, values from TA763 and TA917.

Utility values used in base case model:

Treatment Phase	Mean (SE)
PF – Induction	[redacted]
PF – ASCT	[redacted]
PF – Consolidation	[redacted]
PF – Maintenance	[redacted]
PD	[redacted]

Company at clarification:

- Higher utilities in PD state reflect the psychological impact of diagnosis.
- Utilities from PERSEUS higher than TA763 likely due to advancements in MM management.
- Applying single PD utility is a simplifying assumption.

EAG comments

- Approach to estimating utilities is reasonable but single PD value may be inappropriate and overestimate utility – see next slide.
- EAG prefers values from PERSEUS and company explanation for discrepancy in utility values plausible.
- Utilities for PF and PD used in previous daratumumab appraisal TA763 tested in scenarios – small ICER impact

Is the higher utility value in PD than PF induction, ASCT and consolidation reasonable?

Abbreviations: ASCT, autologous stem cell transplant; EQ-5D, European Quality of Life; HRQoL, health-related quality of life; MM, multiple myeloma; PD, progressed disease; PF, progression free; SE, standard error

Key issue: Utilities for subsequent lines of therapy (2/2)

ICER impact: Small

EAG comments

- Survival prognosis should be worse as patients progress to subsequent lines - LYs and QALYs may be overestimated. Less LYs for the comparator arm than in TA763 could widen this discrepancy.
- Scenario applying lower utility values for 3rd and 4th lines from TA763 to EAG base case had a small impact on the ICER.
- Assumption of constant utilities could be conservative in company base case as higher proportion in DAR+BOR+THA+DEX transition to PD state – the opposite occurs in EAG base case.
- Few people [redacted] in DAR+BOR+LEN+DEX arm in PERSEUS received one or more line of therapy while the model includes all lines, raises concerns whether PERSEUS is representative as it is immature.

Company at FAC:

- Summed proportion who progress vs are alive on subsequent treatments in model are almost identical – suggests OS and PFS in model accurately reflect survival and approach is consistent with TA917.
- Comparator accrues more QALYs post-progression than intervention in company base case - reducing utilities would reduce ICER.
- Misleading to say PERSEUS is not representative – the interventions will likely delay or negate multiple lines of therapy and additional lines have been included in the model for completeness.

Is it appropriate to assume constant utilities post-progression?

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; FAC, factual accuracy check; ICER, incremental. cost-effectiveness ratio; LEN, lenalidomide; LY, life years; OS, overall survival; PFS, progression free survival; PD, progressed disease; THA, thalidomide

Key issue: Subsequent treatments in the model (1/2)

ICER impact: Large

Background

- Distribution of subsequent line treatments based on UK clinical opinion. This has not been validated by EAG.
- Proportion receiving 2nd line treatments assumed the same for each arm.
- 3rd line proportion dependent on 2nd line treatment received and 4th line dependent on 3rd line – independent of 1st line treatment. See next slide.
- Treatment discontinuation based on median durations and progression from clinical trials.
- In the PERSEUS trial, few people received one or more subsequent lines of therapy ([redacted] in DAR+BOR+ LEN+DEX – LEN+DEX arm and [redacted] in BOR+LEN+DEX – LEN arm).

- Are the proportions progressing to subsequent line treatments representative of NHS clinical practice?
- Would the subsequent treatments be the same for both arms?
- Company/EAG: How many people in each arm are modelled to progress on to each subsequent line of therapy?
- Would subsequent treatments be different for people who are refractory to daratumumab?

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; HRQoL, health-related quality of life; NHS, national health service; LEN, lenalidomide; SEL, selinexor;

Key issue: Subsequent treatments in the model (2/2)

ICER impact: Large

Distribution of subsequent treatments:

		Distribution of treatments				
2nd-line treatments		1st-line regimen received				
		DAR+BOR+LEN+DEX-DAR+LEN		DAR+BOR+THA+DEX-LEN		
	DAR+BOR+DEX	0.00%		0.00%		
	CAR+DEX	10.00%		10.00%		
	CAR+LEN+DEX	5.00%		5.00%		
	SEL+BOR+DEX	5.00%		5.00%		
	BEL+BOR+DEX	80.00%		80.00%		
3rd-line treatments		2nd-line regimen received				
		DAR+BOR+DEX	CAR+DEX	CAR+LEN+DEX	SEL+BOR+DEX	BEL+BOR+DEX
	IXA+LEN+DEX	22.41%	14.94%	0.00%	0.00%	5.00%
	SEL+BOR+DEX	28.01%	28.01%	24.31%	0.00%	50.00%
	LEN+DEX	7.47%	3.73%	0.00%	0.00%	0.00%
	PAN+BOR+DEX	20.54%	31.75%	56.73%	81.63%	20.00%
	CYC+THA+DEX	21.57%	21.57%	18.96%	18.37%	25.00%
See 4th-line treatments		3rd-line regimen received				
		IXA+LEN+DEX	SEL+BOR+DEX	LEN+DEX	PAN+BOR+DEX	CYC+THA+DEX
	TEC	50.00%	60.00%	50.00%	56.00%	50.00%
	POM + DEX	20.00%	26.00%	20.00%	24.00%	20.00%
	DEX	20.00%	8.00%	20.00%	16.00%	20.00%
	PAN+BOR+DEX	10.00%	6.00%	10.00%	4.00%	10.00%

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CYC, cyclophosphamide; DAR, daratumumab; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; SEL, selinexor; TEC, teclistamab; THA, thalidomide.

Key issue: Daratumumab discontinuation

ICER impact: Large

Background:

- Treatment discontinuation modelled as per the SmPC. DAR maintenance administered until progression but can be discontinued if MRD-negativity is sustained for 1 year after receiving maintenance treatment for at least 2 years – Company and EAG model DAR maintenance discontinuation according to MRD status in PERSEUS.

DAR maintenance discontinuation:

Subgroups	DAR+BOR+LEN+DEX
2 years on treatment + MRD-negative for 1 year	PERSEUS TTD (Mature KM)
People without MRD-negativity*	PERSEUS TTD (Extrapolated)

* Receive DAR until progression

Company:

- DAR discontinuation should be modelled as per the SmPC – MRD testing is expected in clinical practice in the UK.
- Two thirds of the people in PERSEUS stopped DAR maintenance and mature TTD KM available.
- Scenario assuming DAR maintenance discontinuation at 2 years had minimal impact on the ICER.

EAG comments

- EAG base case includes MRD stopping rule but exploratory scenario treating with DAR until progression increased costs and led to large ICERs.
- ICERs were sensitive to extrapolation curve fitted for group without MRD-negativity but company approach appropriate.

Is modelling MRD as a stopping rule appropriate?

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LEN, lenalidomide; MRD, minimal residual disease; SmPC, summary of product characteristics; TTD, time to treatment discontinuation

Key issue: Comparator discontinuation of lenalidomide maintenance

ICER impact: Small

Company used PERSEUS to model LEN discontinuation - EAG base case uses AURIGA.

Background

- LEN maintenance discontinuation in DAR+BOR+THA+DEX arm modelled using LEN TTD from BOR+LEN+DEX arm of PERSEUS - EAG argue using TTD from LEN arm in AURIGA is more appropriate.

EAG comments

- PERSEUS used for TTD but AURIGA might be more appropriate as already used for relative treatment effects of DAR+LEN vs LEN maintenance.
- Company approach assumes LEN discontinuation is not impacted by prior DAR or whether BOR+LEN+DEX or DAR+BOR+THA+DEX is received for induction/consolidation.
- Shorter LEN duration expected after THA as THA-based therapies have worse tolerance compared to LEN.
- Heterogeneous induction regimens in LEN arm in AURIGA ([redacted] received BOR+LEN+DEX) may better capture the impact of DAR+BOR+THA+DEX on LEN maintenance.
- People were DAR-naïve in both AURIGA and PERSEUS – assumes prior DAR has no impact on LEN duration.

Company

- Scenario using AURIGA had minimal impact on the ICER and most pessimistic extrapolation was chosen.

Is AURIGA or PERSEUS the most appropriate source to model LEN maintenance treatment discontinuation in the DAR+BOR+THA+DEX – LEN arm?

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; TTD, time to treatment discontinuation; THA, thalidomide.

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
PFS Extrapolation Distribution	Generalised Gamma	Gompertz
Source for LEN maintenance discontinuation	TTD from PERSEUS	TTD from AURIGA

Abbreviations: PFS, progression free survival; TTD, time to treatment discontinuation; LEN, lenalidomide.

Cost-effectiveness results summary

Cost effectiveness results cannot be reported here because of confidential discounts for included technologies.

All results are presented in Part 2 slides for committee:

- Company base case - ICER within the threshold usually considered an acceptable use of NHS resources.
- EAG base case* - ICER is above the threshold usually considered an acceptable use of NHS resources.

*Probabilistic ICER is significantly lower than the deterministic ICER. The EAG was unable to determine the cause of this discrepancy.

Daratumumab in combination for treating newly diagnosed multiple myeloma when stem cell transplant is suitable

- ❑ 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.

Abbreviations: MM, multiple myeloma.

Daratumumab in combination for treating newly diagnosed multiple myeloma when stem cell transplant is suitable

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

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Key issues

Key issue	ICER impact	Slide
Assuming equal efficacy during induction and consolidation	Unknown	12
No clinical evidence for full treatment sequence of comparator	Large	14
Components of the intervention	Unknown	17
PFS extrapolations	Moderate	20
Utilities for subsequent lines of therapy	Small	23
Subsequent treatments	Large	25
Daratumumab discontinuation	Large	27
Comparator discontinuation of lenalidomide maintenance	Small	28

NICE Abbreviations: PFS, progression free survival

Daratumumab in combination for treating newly diagnosed multiple myeloma when stem cell transplant is suitable

Supplementary appendix

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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, which is assessed based on age, frailty and performance status.

- 74% of people diagnosed are aged over 65 years, as a result, many are not considered suitable for HDT-ASCT.

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

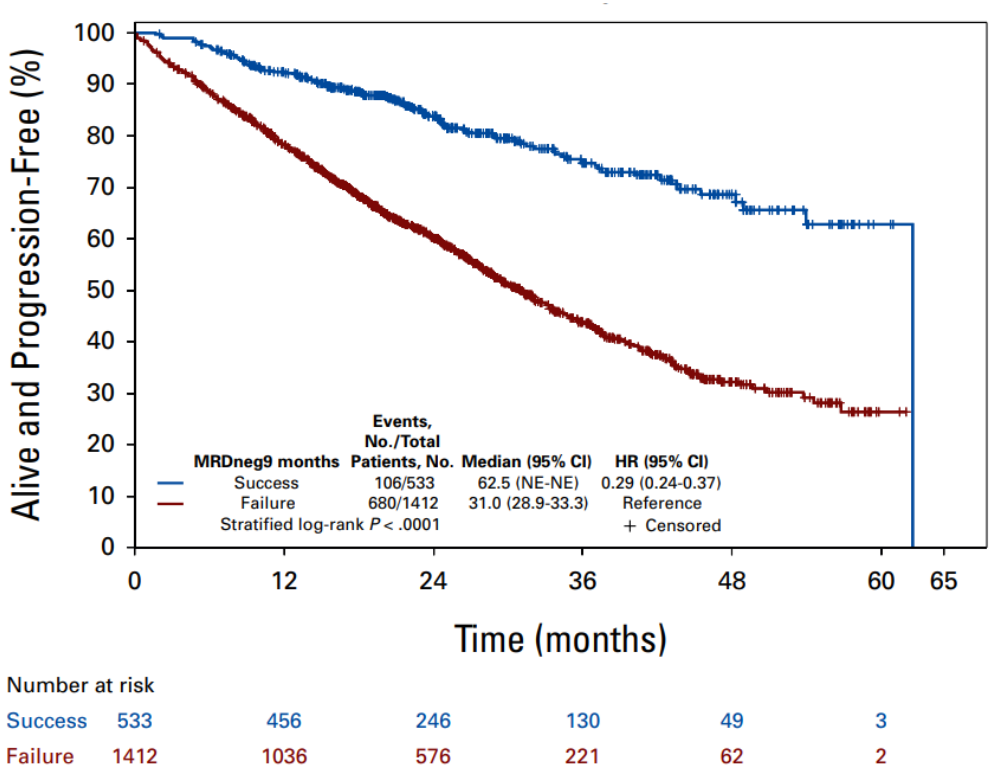
Equalities considerations

- 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.

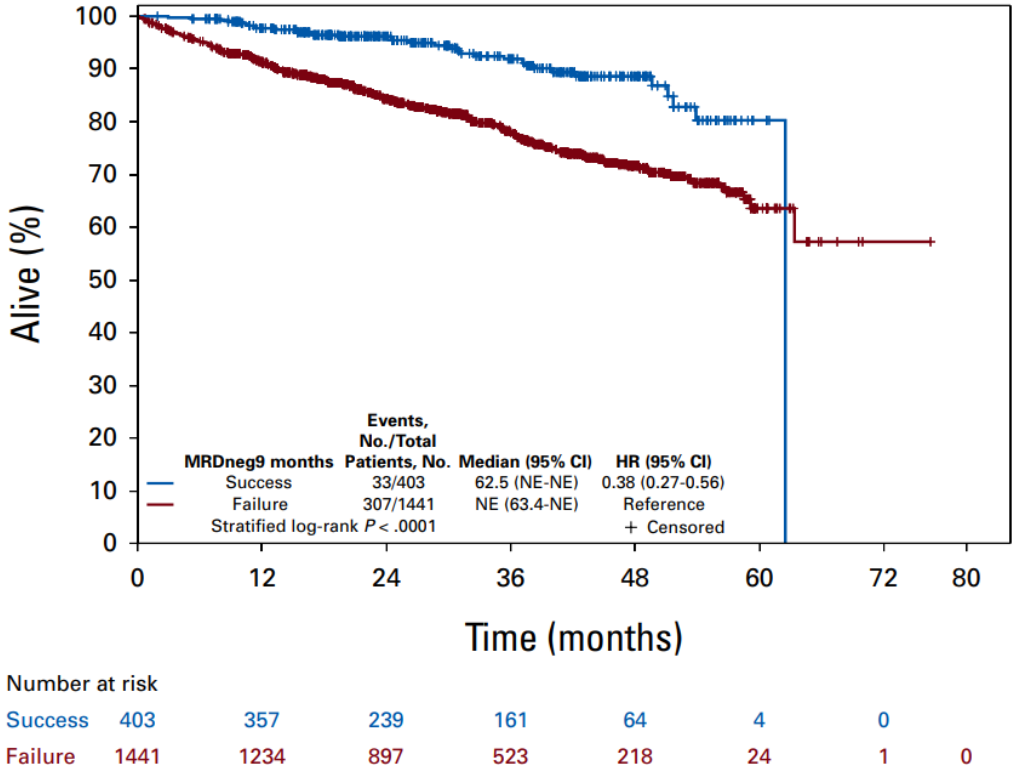
Abbreviations: HDT, high dose chemotherapy; ASCT, autologous stem cell transplant

Landmark analyses assessing prognostic values of 9-month MRD-CR status regarding PFS and OS in HDT-ASCT eligible patients with NDMM

9-month MRD-CR status regarding PFS



9-month MRD-CR status regarding OS



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.

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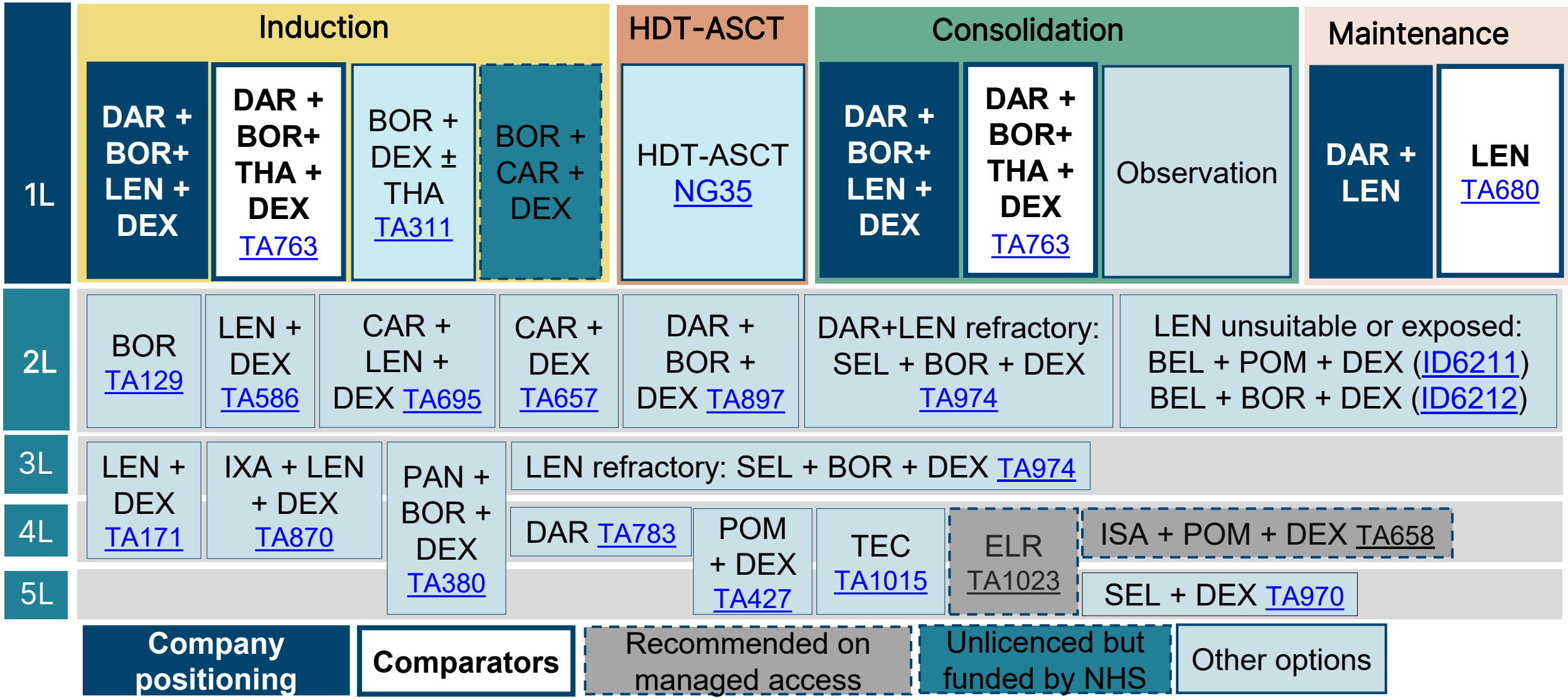
Treatment pathway and company positioning of DAR+BOR+LEN+DEX



Abbreviations: 1/2/3/4/5L, 1st /2nd/3rd/4th/5th line; ASCT, autologous stem cell transplant; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; ELR, elranatamab; HDT, high dose therapy; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; NHS, national health service; POM, pomalidomide; SEL, selinexor; TEC, teclistamab; THA, thalidomide.

PERSEUS - PFS and OS outcomes

Outcome	BOR + LEN + DEX	DAR + BOR + LEN + DEX
Full Treatment Sequence* PFS (% people (95% CI))		
12-Month	[redacted]	[redacted]
24-Month	[redacted]	[redacted]
36-Month	[redacted]	[redacted]
48-Month	67.7 (62.2, 72.6)	84.3 (79.5, 88.1)
Full Treatment Sequence* OS (% people (95% CI))		
12-Month	[redacted]	[redacted]
24-Month	[redacted]	[redacted]
36-Month	[redacted]	[redacted]
48-Month	[redacted]	[redacted]

*Full treatment sequence: Induction, consolidation, and maintenance

NICE Abbreviations: BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; NE, not evaluable; OS, overall survival; PFS, progression free survival.

Comparator trials

Clinical trial designs and use in model

	CASSIOPEIA	AURIGA
Design	Randomised phase 3 trial	Ongoing, randomised, phase 3 trial
Population	People with untreated MM eligible for HDT-ASCT	People with NDMM after prior induction therapy and HDT-ASCT who are anti-CD38-naïve and MRD-positive.
Intervention	Induction/consolidation: DAR+BOR+THA+DEX Maintenance (after re-randomisation): DAR or Observation	DAR+LEN
Comparator(s)	Induction/consolidation: BOR+THA+DEX Maintenance (after re-randomisation): DAR or Observation	LEN
Duration	Median follow-up: [redacted]	Median follow-up: 32.3 months
Used in model?	In ITC to assess relative efficacy of DAR+BOR+LEN+DEX and DAR+BOR+THA+DEX during induction/consolidation.	To derive a HR to inform relative efficacy of DAR+LEN vs LEN as a maintenance treatment.

Abbreviations: ASCT, allogenous stem cell transplant; BOR, bortezomib; CD38, cluster of differentiation 38 antigen; DAR, daratumumab; DEX, dexamethasone; HDT, high dose therapy; HR, hazard ratio; ITC, indirect treatment comparison; LEN, lenalidomide; OS, overall survival; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PFS, progression free survival; THA, thalidomide

AURIGA – Key clinical results

Median follow up of 32.3 months

	DAR+LEN vs LEN maintenance
Survival outcomes	**HR (95% CI)**
Median PFS (Months)	0.53 (0.29, 0.97); 0.0361
Median OS (Months)	[redacted]
Response outcomes	**OR (95% CI)**
12-month MRD-negativity conversion [a]	4.51 (2.37, 8,57); p<0.0001
Overall MRD-negativity conversion [b]	4.12 (2.26, 7.52); p<0.0001
Sustained MRD-negativity rate [c]	4.08 (1.43, 11.62); p=0.0065

[a] Defined as the proportion of patients who achieved MRD-negative status (threshold 10^{-5}) by 12 months after the initiation of maintenance treatment and before progressive disease or subsequent antimyeloma therapy. [b] Defined as the proportion of patients who achieved MRD-negative status any time after the date of randomisations. [c] Defined as patients who achieved MRD-negative status (at 10^{-5}) in two bone marrow aspirate assessments with a minimum of 12 months apart, without any assessment showing MRD-positive status in between assessments.

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Abbreviations: BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; DCO, data cut off; HR, hazard ratio; LEN, lenalidomide; NE, not evaluable; OS, overall survival; PFS, progression free survival.

Decision problem

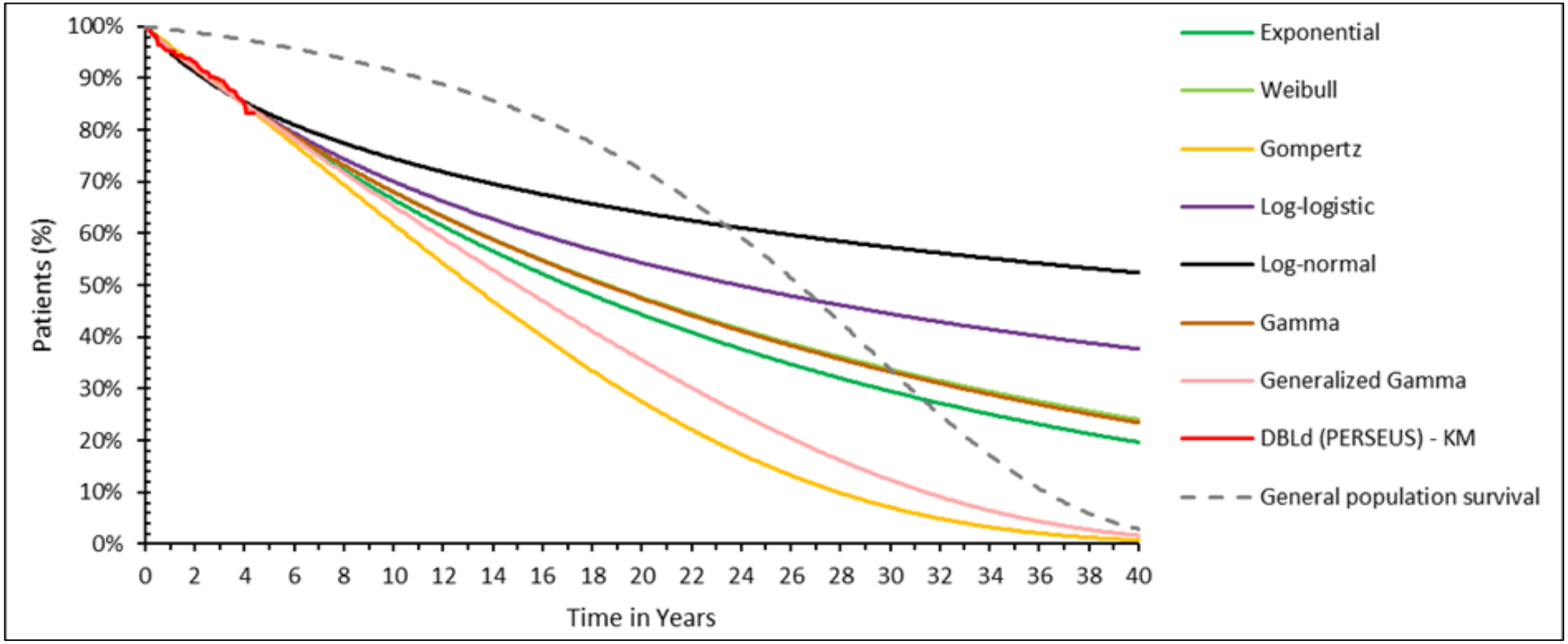
Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with NDMM who are eligible for HDT-ASCT		-
Intervention	Induction/consolidation: DAR+BOR+LEN+DEX Maintenance: DAR+LEN		Company provided a cost comparison for induction/consolidation and a CEA for induction/consolidation/maintenance.
Comparators	Induction/consolidation: • BOR+DEX • BOR+THA+DEX • BOR+CYC+DEX • DAR+BOR+THA+DEX Maintenance: • LEN	Induction/consolidation: • DAR+BOR+THA+DEX Maintenance: • LEN	EAG clinical expert supported DAR+BOR+THA+DEX as SoC but company highlighted a very small percentage of people may receive BOR+CYC+DEX in some cases of renal impairment due to THA toxicity.
Outcomes	• PFS, OS, response rates, MRD negativity status, proportion undergoing HDT-ASCT, HRQoL and AEs		-

Abbreviations: AE, adverse event; ASCT, allogenous stem cell transplant; BOR, bortezomib; CD38, cluster of differentiation 38 antigen; CEA, cost-effectiveness analysis; CYC, cyclophosphamide; DAR, daratumumab; DEX, dexamethasone; HDT, high dose therapy; HRQoL, health-related quality of life; LEN, lenalidomide; OS, overall survival; MM, multiple myeloma; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression free survival; SoC, standard of care; THA, thalidomide

PFS extrapolations

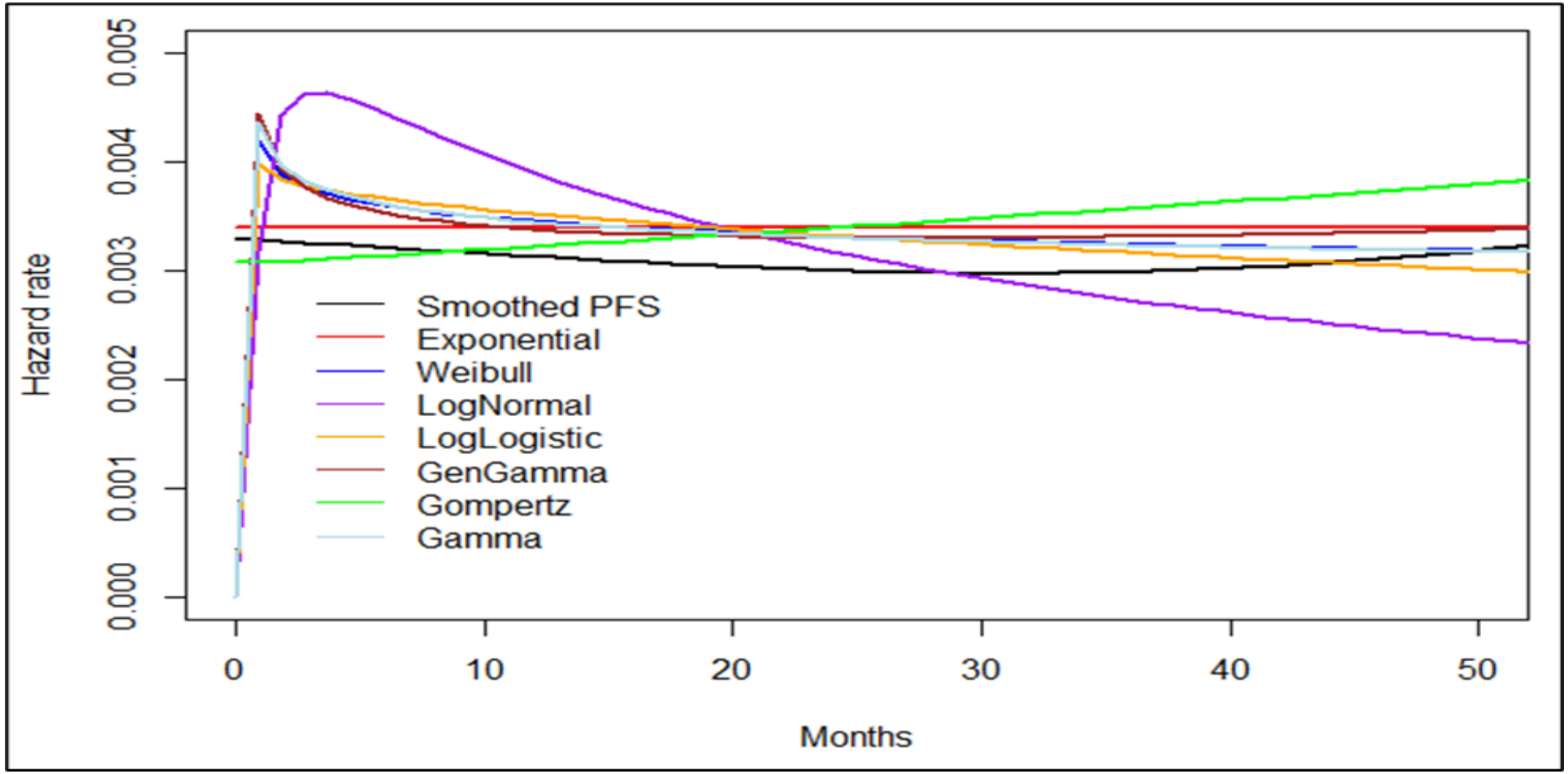
PFS extrapolations for DAR+BOR+LEN+DEX – DAR+LEN from the PERSEUS trial



Abbreviations: BOR, bortezomib; DAR, daratumumab; DBLd, DAR+BOR+LEN+DEX; DEX, dexamethasone; LEN, lenalidomide; PFS, progression-free survival

PFS hazards

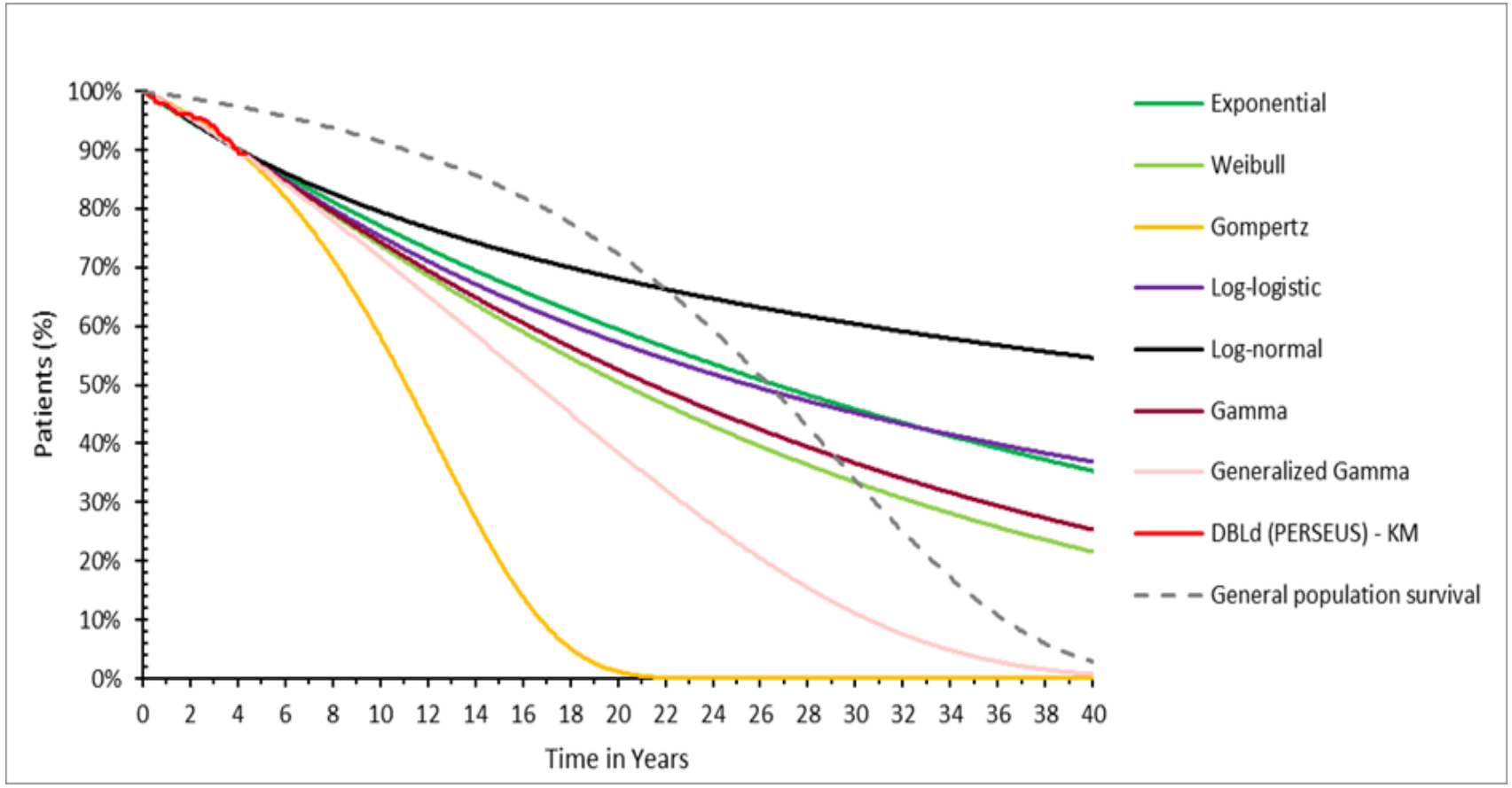
PFS hazards for DAR+BOR+LEN+DEX – DAR+LEN from the PERSEUS trial



Abbreviations: BOR, bortezomib; DAR, daratumumab; DBLd, DAR+BOR+LEN+DEX; DEX, dexamethasone; LEN, lenalidomide; PFS, progression-free survival

OS extrapolations

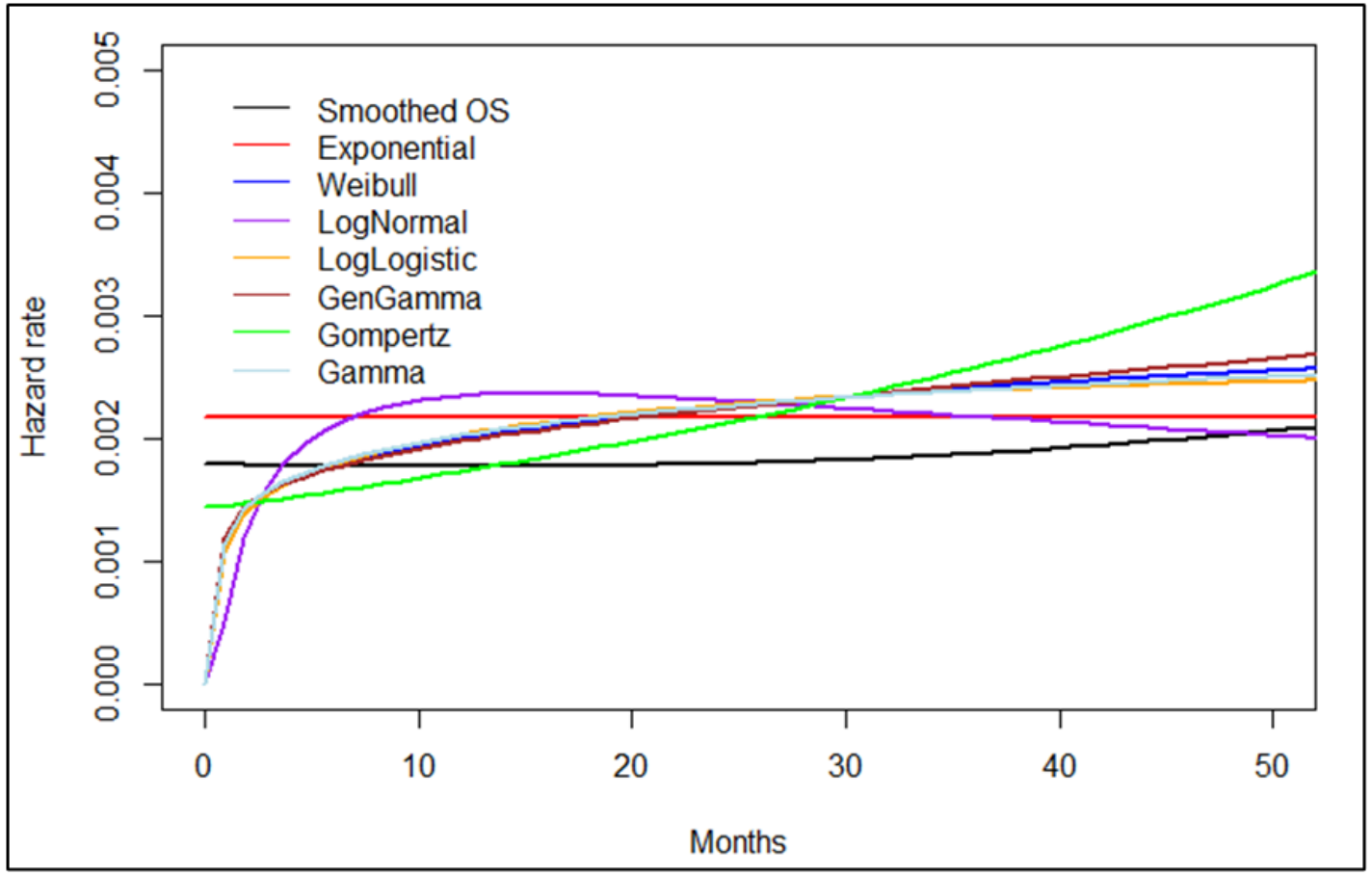
OS extrapolations for DAR+BOR+LEN+DEX – DAR+LEN from the PERSEUS trial



Abbreviations: BOR, bortezomib; DAR, daratumumab; DBLd, DAR+BOR+LEN+DEX; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival

OS hazards

OS hazards for DAR+BOR+LEN+DEX – DAR+LEN from the PERSEUS trial



NICE Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival

PFS extrapolations

*Estimated by applying PFS HR from AURIGA to DAR+BOR+LEN+DEX - DAR+LEN extrapolations

Survival Model	Mean PFS (Months)	Proportion (%)			
		5 Yrs	10 Yrs	15 Yrs	25 Yrs
DAR+BOR+LEN+DEX with DAR+LEN maintenance					
Exponential	193.8	223.1	81.4	66.5	54.3
Weibull	173.1	230.3	81.7	68.0	56.8
Gompertz	223.1	173.1	80.8	61.6	43.4
Log-logistic	230.3	240.9	82.0	70.0	61.1
Log-normal	240.9	249.9	82.9	74.4	68.5
Gamma	249.9	229.9	81.7	67.9	56.7
Generalised Gamma	229.9	193.8	81.4	65.2	49.9
DAR+BOR+THA+DEX with LEN maintenance*					
Exponential	150.1	70.0	47.8	32.6	15.0
Weibull	159.1	70.6	49.9	35.7	18.3
Gompertz	104.7	68.9	41.3	14.5	0.0
Log-logistic	176.2	71.1	52.8	40.9	24.9
Log-normal	203.4	73.0	59.5	51.0	33.4
Gamma	158.6	70.7	49.9	35.5	18.0
Generalised Gamma	129.9	70.1	46.2	28.0	6.2