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

For committee – confidential information redacted

Technology appraisal committee B [12 March 2025]

Chair: Charles Crawley

External assessment group: Kleijnen Systematic Reviews (KSR)

Technical team: Sally Lewis, Eleanor Donegan, Emily Crowe

Company: Johnson & Johnson

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

- ✓ **ACM1 recap and DG consultation responses**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Draft guidance consultation:

Daratumumab* (Darzalex, Johnson & Johnson):

- **Marketing authorisation (Nov 2024):** DAR+BOR+LEN+DEX followed by DAR+LEN maintenance for NDMM
  - **DAR:** 1,800mg/15ml fixed dose subcutaneous (SC) injection
  - **Price:** £4,320.00 (per 1,800mg vial, exl. VAT); PAS and CAA in place
- **Comparator:** DAR+BOR+THA+DEX followed by LEN maintenance – see next slide.

RECAP

Preliminary recommendation:

Daratumumab plus bortezomib, lenalidomide and dexamethasone followed by daratumumab plus lenalidomide maintenance **should not** be used for untreated multiple myeloma in adults when an autologous stem cell transplant is suitable.

Why the committee made this recommendation:

- Long-term benefits of DAR+BOR+LEN+DEX - DAR+LEN were uncertain due to no clinical evidence for the full sequence of the comparator. There was also uncertainty in the economic modelling over the appropriateness of a stopping rule and the modelled subsequent treatments. So, it was not possible to determine the most likely ICER.

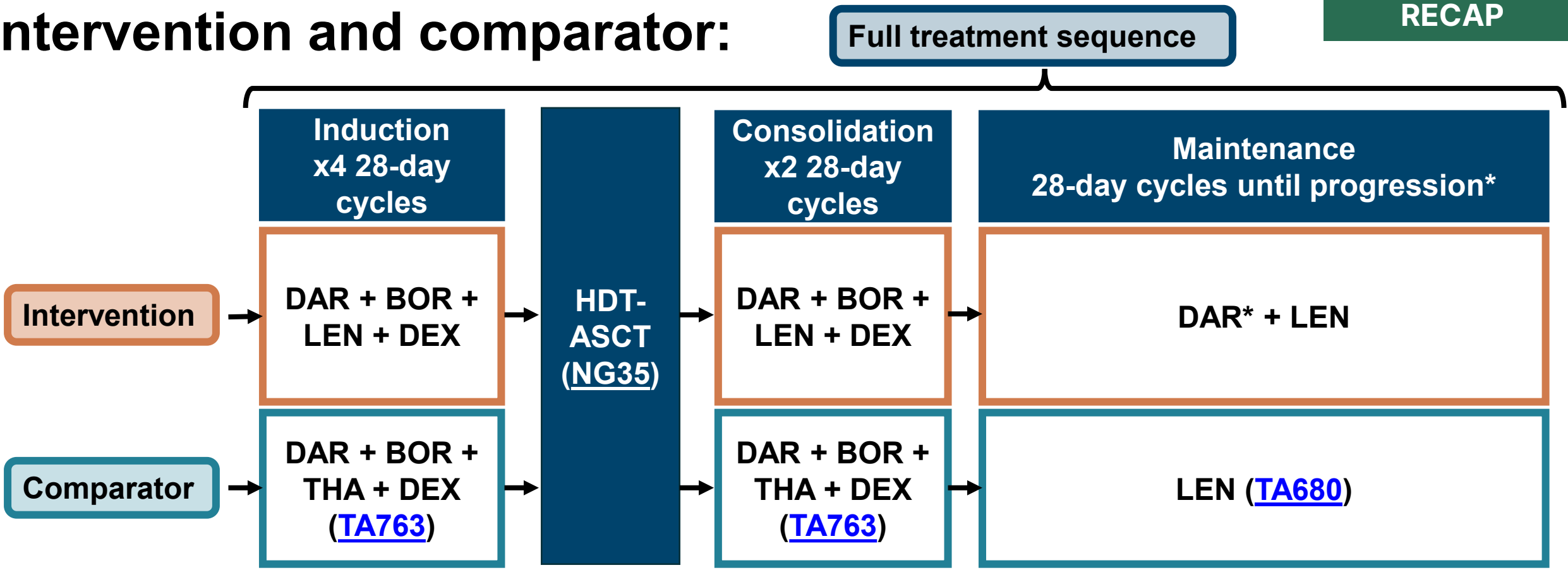
DG consultation responses:

- **Company (J&J):** new evidence and analysis, updated base case.
- **Patient organisations (Myeloma UK and The UK Myeloma Society) and NHS England**

Abbreviations: BOR, bortezomib; CAA, commercial access agreement; DAR, daratumumab; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; J&J, Johnson & Johnson; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; PAS, patient access scheme; SC, subcutaneous; THA, thalidomide.

Intervention and comparator:

RECAP



See full pathway

- Clinical evidence for DAR+BOR+LEN+DEX – DAR+LEN from PERSEUS trial; BOR+LEN+DEX with LEN maintenance is the comparator in PERSEUS and is not used in the UK.
- No clinical evidence for the full sequence of DAR+BOR+THA+DEX – LEN.
- **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.*

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HDT-ASCT, high-dose therapy with autologous stem cell transplant; LEN, lenalidomide; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; SmPC, summary of product characteristics

Key issues from ACM1 and Company's Response (1/3)

ACM1 Key Issue	Committee preference	Included in the company response
Components of the intervention	• Model the full treatment sequence	• Included in base case
Equal efficacy during induction and consolidation	• Equal efficacy (simplifying assumption)	• Included in base case
No clinical evidence for full treatment sequence of comparator	• Requested further clinical evidence for full sequence of DAR+BOR+THA+DEX followed by LEN maintenance – including RWE from SACT.	• Additional analysis on extrapolations of comparator arm with scenario analysis • SACT data presented: not included in company model but used for validation of PERSEUS
	• Reweighted HR from ITC using PERSEUS data	• Base case uses reweighted HRs from PERSEUS
	• Requested further details of ITC for reweighted PERSEUS HR and for other ITC methods to be presented	• Company to present further details on ITC • Other ITC methods presented with scenarios analysis

Abbreviations: ACM1, Appraisal Committee Meeting 1; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; ITC, indirect treatment comparison; LEN, lenalidomide; RWE, real-world evidence; SACT, Systemic Anti-Cancer Therapy dataset; THA, thalidomide.

Key: Resolved | For discussion

Key issues from ACM1 and Company's Response (2/3)

ACM1 Key Issue	Committee preference	Included in the company response
Survival extrapolations	• Requested survival analysis using the reweighted HRs from the PERSEUS data	• Analysis on OS and PFS extrapolations, including scenario analysis
Utilities for subsequent lines of therapy	• Single utility value in the progressed disease state is acceptable but a simplifying assumption	• Included in base case
Subsequent treatments	• Unclear if modelled subsequent treatment proportions represent NHS practice • Requested additional evidence	• Further evidence to inform subsequent treatments. • Scenarios varying proportions

Key: Resolved | For discussion

Abbreviations: ACM1, Appraisal Committee Meeting 1; HR, hazard ratio; NHS, National Health Service; OS, overall survival; PFS, progression-free survival.

Key issues from ACM1 and Company's Response (3/3)

ACM1 Key Issue	Committee preference	Included in the company response
Daratumumab discontinuation	• Further evidence on the appropriateness of the MRD stopping rule • Requested additional evidence on MRD testing guided DAR discontinuation.	• Base case model includes MRD stopping rule. • Scenarios assuming a fixed 2-year stopping rule incorporating data from the GRIFFIN trial.
Comparator discontinuation of lenalidomide maintenance	• Same data source should be used to model effectiveness and discontinuation	• Company base case uses extrapolations fitted to survival data from comparator arm of PERSEUS for TTD of LEN maintenance.

Key: Resolved | For discussion

Abbreviations: ACM1, Appraisal Committee Meeting 1; DAR, daratumumab; LEN, lenalidomide; MRD, minimal residual disease; TTD, time to treatment discontinuation.

Key issues for committee:

Clinical effectiveness issues

No clinical evidence for full treatment sequence of comparator — **Unknown Impact**

- Should OS data from SACT be used to assess generalisability to NHS practice?
- Is the PERSEUS data sufficiently generalisable to UK clinical practice?
- Is it appropriate to use the IPTW-ATT base case PERSEUS HRs to estimate outcomes for the comparator?

Cost-effectiveness issues

Survival extrapolations (unchanged from ACM1) — **Small Impact**

- Is the generalised gamma to extrapolate PFS plausible? Is the exponential to extrapolate OS plausible?

Subsequent treatments — **Large Impact**

- Is it appropriate to model subsequent treatments based on their estimated future use?
- Are the modelled subsequent treatments (future projections) aligned with expected NHS clinical practice?

MRD-negativity stopping rule — **Large Impact**

- Is MRD testing feasible in 100% of the eligible population across the NHS?
- If NGS testing is used, is the same sensitivity threshold used to define MRD-negativity (i.e. 10^{-6} or 10^{-5})?
- Is modelling an MRD stopping rule appropriate?
- If MRD-guided discontinuation is not feasible, is 2-year fixed discontinuation of daratumumab appropriate?

Treatment discontinuation of DAR and LEN maintenance in the intervention arm — **Large Impact**

- Is the exponential plausible to extrapolate DAR (without sustained MRD-) and LEN maintenance?

Abbreviations: ACM1, Appraisal Committee Meeting 1; ATT, average treatment effect on the treated; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HRs, hazard ratios; IPTW, inverse probability of treatment weighting; LEN, lenalidomide; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy dataset; THA, thalidomide; MRD, minimal residual disease

Consultation responses – stakeholder comments

Myeloma UK

- **DAR+BOR+LEN+DEX – DAR+LEN paves the way for a more personalised approach to myeloma treatment,** MRD-guided treatment would give people with stable myeloma an opportunity to reduce the treatment burden.
- **Reduced treatment duration is a key unmet need** - most current recommendations require continuous treatment from diagnosis to relapse; this means living with side effects and regular hospital visits.
- **Estimate that around 1,400 to 1,600 would be eligible for MRD testing.**

The UK Myeloma Society

- BOR + LEN is less likely to cause peripheral neuropathy compared to BOR + THA which can have a significant impact on quality of life.
- MRD-guided discontinuation of DAR will allow people to regain freedom from visits to day units for injections
- **MRD testing for disease monitoring is already routine** in other blood cancers.

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; MRD, minimal residual disease; SCT, stem cell transplant; THA, thalidomide.

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

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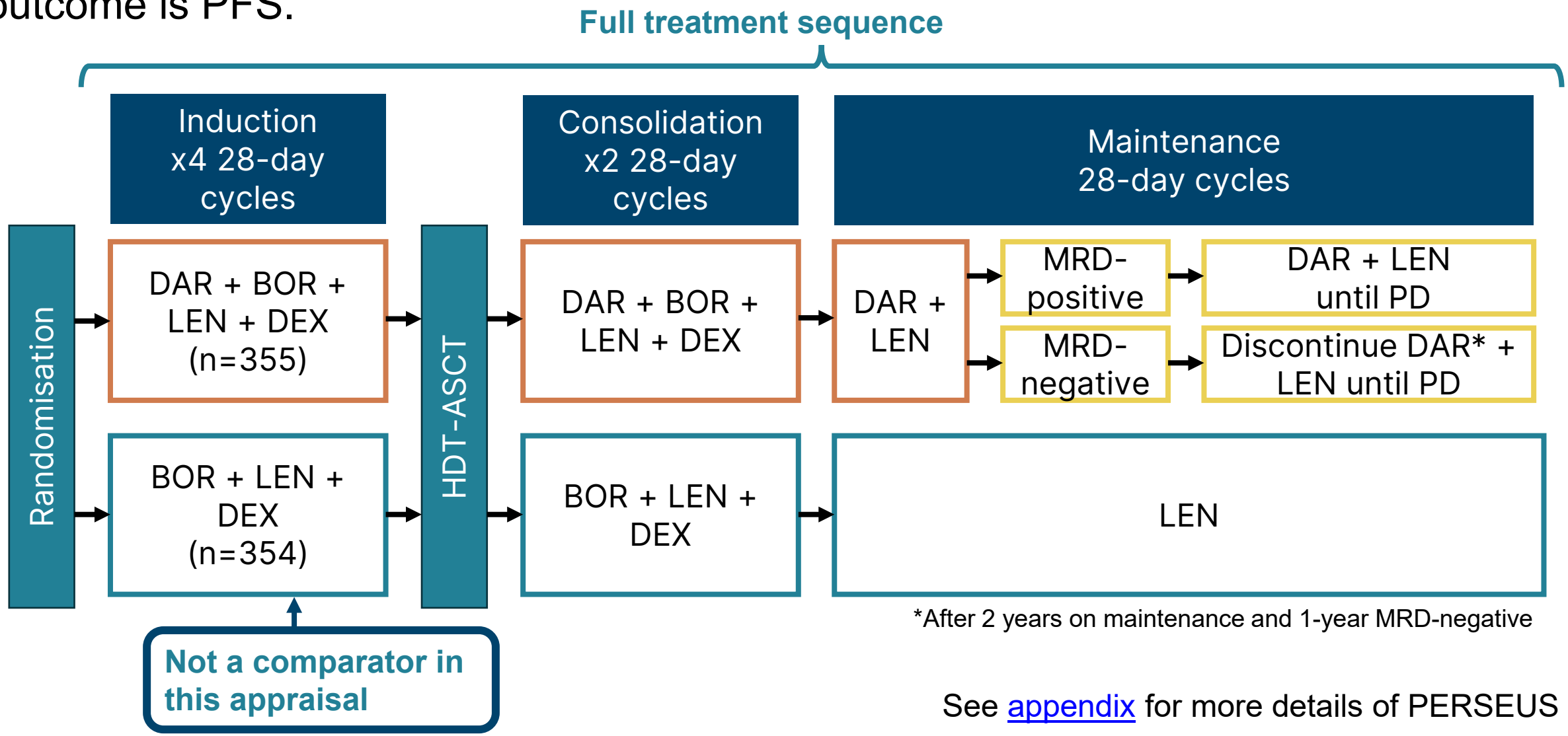
PERSEUS trial overview

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



*After 2 years on maintenance and 1-year MRD-negative

See appendix for more details of PERSEUS trial

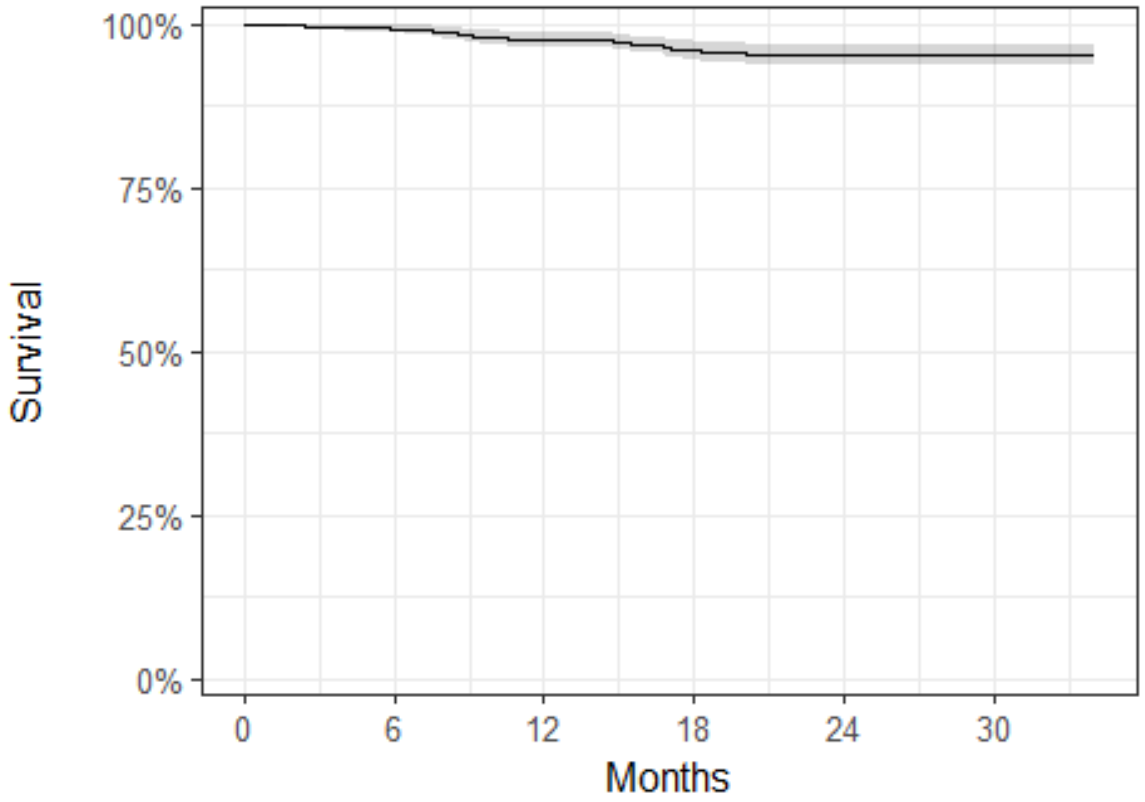
Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HDT, high-dose therapy; LEN, lenalidomide; MRD, minimal residual disease; PD, progressed disease; PFS, progression free survival

New evidence: SACT data

Background:

- At ACM1, committee requested SACT data for DAR+BOR+THA+DEX induction/consolidation followed by LEN maintenance due to the lack of direct clinical effectiveness evidence presented by the company.
- NICE provided SACT data (up to October 2025) for OS ToT, age and gender split

Overall Survival - SACT Cohort 2:



	SACT Cohort 2 (Subset of cohort 1, n=759)
Definition	People receiving first line LEN maintenance after ASCT and induction/consolidation with DAR
Median follow-up	22.7 months
Median survival	Not reached
Restricted mean survival	32.93 months

Abbreviations: ACM1, Appraisal Committee Meeting 1; ASCT, autologous stem cell transplant; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; SACT, Systemic Anti-Cancer Therapy dataset; THA, thalidomide

Key Issues: No clinical evidence for full treatment sequence of comparator (1/4)

ICER impact: Unknown

Background:

- SACT data not incorporated into company model but cohort 2 used to validate PERSEUS data.

Company comments:

- Comparisons of SACT cohort 2 vs modelled OS highly susceptible to bias:
  - Cohort definition includes Myelomatosis, Plasma cell myeloma and myeloma (NOS)
  - No Target Trial Emulation approach
  - Lack of important prognostic patient characteristics - not possible to adjust for confounding factors
- Shorter median OS follow-up in SACT (22.7m vs [redacted]m in PERSEUS) to inform long term projections.
- SACT does not collect PFS and this cannot be robustly estimated; RWE from the Royal Marsden of people treated with DAR+BOR+THA+DEX where 98% received subsequent LEN maintenance showed 24m PFS rates broadly consistent with PERSEUS (89.7% vs [redacted]).

EAG comments:

- Acknowledge company concerns about SACT data; agrees some comparability with PERSEUS (next slide)
- Comparisons between SACT and PERSEUS for other statistics, time points and outputs might be valuable.

Given the concerns raised, is it reasonable to use the SACT data to assess the generalisability of PERSEUS rather than use SACT to inform effectiveness of DAR+BOR+THA+DEX – LEN ?

Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; NOS, not otherwise specified; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset; THA, thalidomide

Key Issues: No clinical evidence for full treatment sequence of comparator (2/4)

ICER impact: Unknown

Company comments:

- SACT cohort 2 supports generalisability of PERSEUS:
  - Similar mean age and proportion of males
  - Overlay of SACT and reweighted PERSEUS OS shows LEN maintenance outcomes are aligned.
- Long-term extrapolations fitted to SACT with best AIC/BIC broadly align with company base case (see appendix for other extrapolations) and lower estimates using PERSEUS are likely because extrapolations were fitted from randomisation.

Extrapolation	10-year survival
SACT cohort 2 (Exponential)	79.3%
SACT cohort 2 (Gen. Gamma)	87.5%
PERSEUS (Base Case)*	[redacted]%

*Applies reweighted HR to exponential distribution fitted to intervention

Is the PERSEUS data sufficiently generalisable to UK clinical practice?

Naïve comparison of OS from maintenance:

Summary of data:

Data	Mean Age	Male
SACT cohort 2	63 (at start of maintenance)	59.3%
PERSEUS	60 (at randomisation)	58.7%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset.

Key Issues: No clinical evidence for full treatment sequence of comparator (3/4)

ICER impact: Unknown

ACM1 considerations

- Committee requested details of the IPTW to generate reweighted HRs from PERSEUS data of DAR+LEN vs LEN maintenance and for other ITC methods to be conducted and presented.

Company

- Base case IPTW-ATT reweights LEN maintenance arm to resemble DAR+LEN arm in PERSEUS for post-consolidation MRD negativity status and base case variable set. Scenarios presented using additional variables and other ITC methods:
  - **Base case variables:** age, sex, ECOG PS, ISS stage, baseline cytogenic risk, type of MM, haemoglobin levels
  - **Additional variables**: LDH, creatinine clearance, MM diagnostic criteria, presence of extramedullary plasmacytomas, serum calcium, bone lesions and platelet levels

ITC of DAR+LEN vs LEN from PERSEUS:

Company/EAG base case

	Unweighted	IPTW-ATT (base case)	IPTW-ATT (additional variables)
Outcomes	**HR (95% CI; p-value)**		
Median PFS (Months)	[redacted]	[redacted]	[redacted]
Median OS (Months)	[redacted]	[redacted]	[redacted]

Abbreviations: ACM1, Appraisal Committee Meeting 1; ATT, average treatment effect on the treated; CI, confidence interval; DAR, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ISS, International Staging System; LEN, lenalidomide; LDH, lactate dehydrogenase; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival

Key Issues: No clinical evidence for full treatment sequence of comparator (4/4)

ICER impact: Unknown

Company and EAG base case use IPTW-ATT analysis with base case variables from PERSEUS to estimate the effect of DAR+LEN versus LEN

Company

- PH assumption holds and all variables were balanced after reweighting in base case - HR as a summary for the treatment effect for OS and PFS appropriate
- Results from IPTW broadly consistent with other adjustment methods (see slide) with minimal impact on ICERs

EAG comments:

- Most covariates are balanced before reweighting due to randomised design of PERSEUS
- IPTW reweighing reduces differences in MRD status and improves overlap
- HRs for PFS and OS generally increase with reweighing (see slide) – least biased HRs likely fall between [redacted] for PFS and [redacted] for OS
- Scenario using IPTW reweighted HRs with additional variables does not have a major impact on the ICER

Is it appropriate to use the IPTW-ATT base case HRs to estimate outcomes for LEN maintenance?

Abbreviations: ATT, average treatment effect on the treated; CI, confidence interval; DAR, daratumumab; HR, hazard ratio; ICERs, incremental cost-effectiveness ratios; IPTW, inverse probability of treatment weighting; LEN, lenalidomide; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival.

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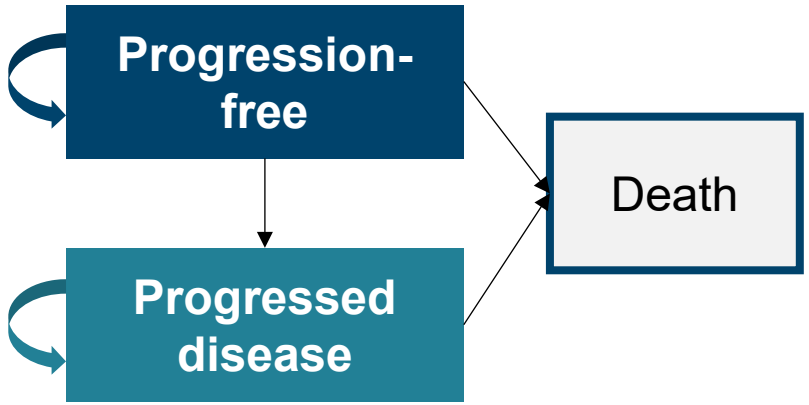
Model structure

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 – DAR+LEN efficacy from PERSEUS trial
- Relative efficacy for DAR+BOR+THA+DEX - LEN applies HRs to intervention arm extrapolations:
  - ACM1: HRs from AURIGA trial
  - **ACM2: HRs from reweighted PERSEUS**



Changes at ACM2:

- **Same base case for Company and EAG**
- Reweighted HRs from PERSEUS for DAR+LEN vs LEN
- Subsequent treatment proportions from RWE and expert clinical opinion
- TTD for LEN in DAR+BOR+THA+DEX - LEN from extrapolations fitted to PERSEUS comparator arm.

Abbreviations: ACM2, Appraisal Committee Meeting 2; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; RWE, real-world evidence; TTD, time to discontinuation; THA, thalidomide.

Key issue: Survival extrapolations (1/2)

ICER impact: Small

Company and EAG use generalised gamma to extrapolate PFS

Background:

- PFS and OS extrapolations for DAR+BOR+LEN+DEX – DAR+LEN fitted to PERSEUS. Proxy extrapolation for DAR+BOR+THA+DEX - LEN applies reweighted PFS HR ([redacted]) and OS HR ([redacted]) from PERSEUS.

PFS – Generalised Gamma

Company:

- Gen. gamma has closest fit to clinician estimates and observed hazards for DAR+BOR+LEN+DEX – DAR+LEN
- DAR+BOR+THA+DEX – LEN proxy extrapolation aligned with clinician estimates at 10 and 25 years (see figure)
- Scenario applying Gompertz had little impact on ICER.

EAG:

- All other curves except Gompertz predict higher PFS (see figure)
- Gompertz scores better in AIC/BIC but overestimates company clinician estimates at 10 years (see figure)
- ICER very sensitive to PFS HR; lower HRs lead to more people progressing on to expensive subsequent treatments.

Is the generalised gamma or Gompertz extrapolation of PFS more plausible?

Survival Model	PFS (%)		
	10 Years	15 Years	25 Years
DAR+BOR+LEN+DEX – DAR+LEN			
Gen. Gamma (base case)	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
DAR+BOR+THA+DEX – LEN*			
Gen. Gamma (base case)	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]

*Applies PFS HR to intervention extrapolation

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: Survival extrapolations (2/2)

ICER impact: Small

Company and EAG use exponential to extrapolate OS

OS - Exponential

Company:

- Exponential aligns with observed hazards and clinician estimates; and has best statistical fit.
- Proxy extrapolation for DAR+BOR+THA+DEX – LEN in line with clinician estimates at 15 and 25 years.

EAG:

- Exponential assumes constant hazards: inconsistent with observed hazards for DAR+BOR+LEN+DEX – DAR+LEN (see figure) and could overestimate OS
- Alternative extrapolations do not provide a better fit
- All scenarios changing OS distribution has little impact on the ICER

Survival Model	OS (%)		
	10 Years	15 Years	25 Years
DAR+BOR+LEN+DEX – DAR+LEN			
Exponential (base case)	[redacted]	[redacted]	[redacted]
DAR+BOR+THA+DEX – LEN*			
Exponential (base case)	[redacted]	[redacted]	[redacted]

*Applies OS HR to intervention extrapolation

Is the exponential distribution to extrapolate OS plausible?

See appendix for figures.

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

Key Issue: Modelled subsequent treatments (1/2)

ICER impact: Large

Company and EAG subsequent treatment proportions based on estimated future use

ACM1 considerations

- Committee requested additional evidence on subsequent treatment use in the NHS
- Updated company base case includes proportions that combine real-world NHS prescribing from the VSTx dataset (October 2024 to September 2025) and clinical opinion to derive **future subsequent treatments**

Company

- **Prescribing rapidly changes due to new NICE recommendations** - RWE showed that established treatment use was stable but recently approved treatments such as BEL+BOR+DEX had increasing use month on month
- Progression to 2nd line due to PFS curves and subsequent treatment proportions assumed the same regardless of prior treatment (see next slide)
- ICERs most sensitive to cost of BEL at 2nd line; updated base case reduces market share from 80% to 50%

EAG comments

- Subsequent treatment proportions should reflect current NHS prescribing; proportions based on expert opinion of projected market shares could introduce structural uncertainty.
- ICERs very sensitive to subsequent treatments; modelling current RWE proportions for all subsequent treatments has a major impact

Is it appropriate to model subsequent treatments based on their estimated future use?

Abbreviations: ACM1, Appraisal Committee Meeting 1; BEL, belantamab mafodotin; BOR, bortezomib; DEX, dexamethasone; ICERs, incremental cost-effectiveness ratios; LEN, lenalidomide; NHS, National Health Service; PFS, progression-free survival; RWE, real-world evidence;

Key Issue: Modelled subsequent treatments (2/2)

ICER impact: Large

Treatment	Current (RWE)	Future (RWE + expert opinion)	NHSE Blueteq data 2025
2nd Line			
DAR+BOR+DEX	[redacted]	[redacted]	903 (52.1%)
CAR+LEN+DEX	[redacted]	[redacted]	291 (16.8%)
CAR+DEX	[redacted]	[redacted]	79 (4.6%)
SEL+BOR+DEX	[redacted]	[redacted]	221 (12.8%)
LEN+DEX	[redacted]	[redacted]	<1%
BEL+BOR+DEX	[redacted]	[redacted]	239 (13.8%)
3rd Line			
IXA+LEN+DEX	[redacted]	[redacted]	-
PAN+BOR+DEX	[redacted]	[redacted]	-
4th Line			
DAR	[redacted]	[redacted]	-
POM + DEX	[redacted]	[redacted]	-
TEC	[redacted]	[redacted]	-
TAL	[redacted]	[redacted]	-

Company:

- Current treatments from snapshot of VSTx dataset on NHS prescribing in September 2025 after removing treatments not recommended or only available through managed access.
- Future proportions based on current treatments and clinical expert opinion

Company/EAG base case

NHSE Blueteq data: See appendix for 2nd line treatment trends (Jan 2023 to Dec 2025)

Are the modelled subsequent treatments (future projections) aligned with expected NHS clinical practice?

Abbreviations: BEL, belantamab; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; DAR, daratumumab; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; RWE, real-world evidence; TAC, talquetamab; TEC, teclistamab.

Key issue: MRD-negativity stopping rule (1/4)

ICER impact: Large

ACM1 considerations

- **MRD stopping rule:** DAR maintenance can be discontinued if MRD-negativity sustained for 1 year after receiving maintenance for 2 years – Committee were unclear if this would be feasible in the NHS.
- Company present supporting evidence on feasibility of MRD-guided treatment and scenario analysis.

Company

*Leeds and The Royal Marsden

New supporting evidence from UK Clinical Advisory Board:

- Stopping rule is feasible within the existing NHS infrastructure and not limited to specialist sites; two NHS Trusts* currently conduct NGF MRD testing and eight NHS labs have the capability to deliver testing
- Bone marrow transfer to specialist labs for testing is routine in CLL: Two NHS trusts* regularly receive samples from other NHS sites with established sampling, packaging and transport pathways; risk of testing delays is low.
- Two Trusts* confirmed expected MRD testing volume for stopping rule is within their combined capacity
- Company committed to support education and training across Trusts to support MRD testing in line with PERSEUS stopping rule.
- First NGF test would be around 21-months after the start of therapy; giving sufficient time for training.

Patient Organisation (Myeloma UK):

- Bone marrow biopsies are routine in NDMM and people willing to have them to inform their treatment decisions; every tertiary hospital has a flow cytometry lab that could deliver MRD testing with sufficient training.

Abbreviations: ACM1, Appraisal Committee Meeting 1; CLL, chronic lymphocytic leukaemia; DAR, daratumumab; MRD, minimal residual disease; NGF, next-generation flow; NDMM, newly diagnosed multiple myeloma

Key issue: MRD-negativity stopping rule (2/4)

ICER impact: Large

MRD methods and availability in the NHS

Method	Sample	Presentation testing	Used in PERSEUS?	Sensitivity	Availability	Cost
Flow cytometry	Marrow. 99% informative	Desirable	Yes	~1 in 100,000 cells	Limited number of NHS labs. Used in trials. Not routine across NHS.	££
Next generation sequencing (NGS) e.g. clonoSeq	Marrow. (plasma cell enrichment) 95% informative	Essential	No	~1 in 1,000,000 cells	Oxford (research) London (private). Used in US. Very early days in NHS.	£££
Mass spectrometry	Blood	?	No	Measures M protein	Not used in NHS currently. Needs further evaluation.	£

MRD testing used in UK trials e.g. RADAR

Mass spec ref. https://pubmed.ncbi.nlm.nih.gov/39293025/

Key issue: MRD-negativity stopping rule (3/4)

ICER impact: Large

Companion testing for NICE recommended technologies

- MRD testing in myeloma is **not** widely or routinely available in the NHS
- If NICE recommend, NHSE required to commission MRD testing
  - Funding mandate for 'package' – drug plus test
- Precedent – mostly a single diagnostic test
  - e.g Trastuzumab HER-2; olaparib BRCA; alectinib ALK & others
  - Blinatumomab (TA589 – MRD based but already standard)
- Flow cytometry is probably the most logical to use initially (as in trial)
- NGS promising
  - More sensitive. Patients might test negative by flow but positive by NGS
- Mass spec would require further evaluation

Is MRD testing feasible in 100% of the eligible population across the NHS?

Key issue: MRD-negativity stopping rule (4/4)

ICER impact: Large

Company and EAG base case apply MRD stopping rule

Company:

- No evidence on efficacy or safety of DAR maintenance until progression in an unselected population – if MRD-testing is not feasible; a fixed 2-year discontinuation of DAR is preferable to no access.
- NHS 10-year plan to expand genomic profiling could allow NGS-based MRD testing in 1-2 years; at least 3 tests required to stop DAR maintenance.
- DAR+BOR+LEN+DEX – DAR+LEN remains dominant in all cost-effective all scenarios explored:

Scenario 1	NGS instead of NGF testing (company base case) through NHS Genomic Medicines Service
Scenario 2	2-year fixed DAR maintenance for all, DAR TTD from phase 2 GRIFFIN study
Scenario 3	2-year fixed DAR maintenance for all; DAR TTD from pooled PERSEUS and GRIFFIN study
Scenario 4	2-year fixed DAR maintenance excl. high-risk MM (21.7%), who get DAR+LEN until progression

EAG comments:

- ICER is very sensitive to DAR TTD assumptions - DAR maintenance until progression has a major impact

- If NGS testing is used, is the same sensitivity threshold used to define MRD-negativity (i.e. 10^{-6} or 10^{-5})?
- Is modelling an MRD stopping rule appropriate?
- If MRD-guided discontinuation is not feasible, is assuming a 2-year fixed discontinuation of daratumumab appropriate? If so, is company scenario 2,3 or 4 more plausible?

Abbreviations: DAR, daratumumab; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MM, multiple myeloma; MRD, minimal residual disease; NGS, next-generation sequencing; NGF, next-generation flow; PFS, progression-free survival

Key issue: Treatment discontinuation of DAR and LEN maintenance in the intervention arm (1/2)

ICER impact: Large

Background

- TTD modelled separately for DAR and LEN maintenance due to stopping rule in intervention arm:

Maintenance component	Assumption	Data source (Extrapolation)
DAR (with sustained MRD-)	Stop DAR after 2 years MRD-	PERSEUS TTD (Mature KM)
DAR (without sustained MRD-)	Continue DAR	PERSEUS TTD (Exponential)
LEN	LEN until progression	PERSEUS TTD (Exponential)

Company:

- Exponential showed best AIC/BIC, aligned with observed hazards and clinician estimates at 5, 8, and 10 years for DAR (people without sustained MRD-) and LEN TTD (see next slide and appendix).
- EAG scenario of DAR until progression is not clinically validated and there is no data to inform this assumption

EAG comments:

- ICER is very sensitive to other extrapolations fitted to DAR TTD (without sustained MRD-)
- Exploratory scenarios assuming DAR (all), DAR (people without sustained MRD-), and DAR (people with sustained MRD-) until progression has a major impact on the ICER. LEN until progression has minimal impact.

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DAR, daratumumab; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MRD, minimal residual disease; TTD, time to discontinuation.

ICER impact: Large

Key issue: Treatment discontinuation of DAR and LEN maintenance in the intervention arm (2/2)

DAR (without sustained MRD-) TTD:

Extrapolation	Statistical fit		People receiving DAR (%)			
	AIC	BIC	Median (years)	5 Years	8 Years	10 Years
DAR+BOR+LEN+DEX – DAR+LEN						
Exponential (base case)	278.1	280.8	3.4	36.2	19.8	13.3
Weibull	279.8	285.3	3.5	37.8	22.2	15.7
Gompertz	279.3	284.8	3.4	29.7	8.5	2.7
Log-logistic	283.6	289.1	3.9	43.0	31.6	26.8
Log-normal	298.5	304	4.8	49.0	40.6	36.7
Gamma	279.3	284.8	3.6	38.1	22.6	16.1
Gen. Gamma	279.1	287.4	3.3	31.4	9.2	2.6

See appendix for figures and details on extrapolations for LEN maintenance

Is the exponential plausible to extrapolate TTD for DAR (without sustained MRD-) and TTD LEN maintenance?

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; MRD, minimal residual disease; TTD, time to discontinuation.

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

- ❑ ACM1 recap and DG consultation responses
- ❑ 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
- A stakeholder raised that BOR + LEN is less likely to cause peripheral neuropathy compared to BOR + THA

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: BOR, bortezomib; MM, multiple myeloma; LEN, lenalidomide; THA, thalidomide.

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

- ❑ ACM1 recap and DG consultation responses
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Key issue	ICER impact	Slide
No clinical evidence for full treatment sequence of comparator	Unknown	13
Survival extrapolations	Small	19
Modelled subsequent treatments	Large	21
MRD-negativity stopping rule	Large	23
Treatment discontinuation of DAR and LEN maintenance	Large	27

NICE Abbreviations: DAR, daratumumab; LEN. Lenalidomide; MRD, minimal residual disease

Summary of company and EAG base case assumptions:

Assumptions in company and EAG base case at ACM2:

Assumption	Company and EAG base case
Phases of intervention	• Model full treatment sequence
Induction and consolidation	• Equal efficacy between arms
Maintenance	• Intervention: Extrapolations for OS and PFS fitted to PERSEUS trial • Comparator: Proxy extrapolations by applying IPTW reweighted HR from PERSEUS
Utilities	• Single utility in progressed state
Subsequent treatment	• Proportions for future projections based on RWE and clinical opinion
Stopping rule	• MRD-stopping rule for DAR maintenance
Maintenance discontinuation	• Intervention: DAR (with MRD-) from mature TTD KM, DAR (without MRD-) and LEN from extrapolations of TTD from PERSEUS • Comparator: LEN from extrapolations fitted to comparator arm TTD in PERSEUS

Abbreviations: ACM2, Appraisal Committee Meeting 2; DAR, daratumumab; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LEN, lenalidomide; MRD, minimal residual disease; RWE, real-world evidence; TTD, time to discontinuation.

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.

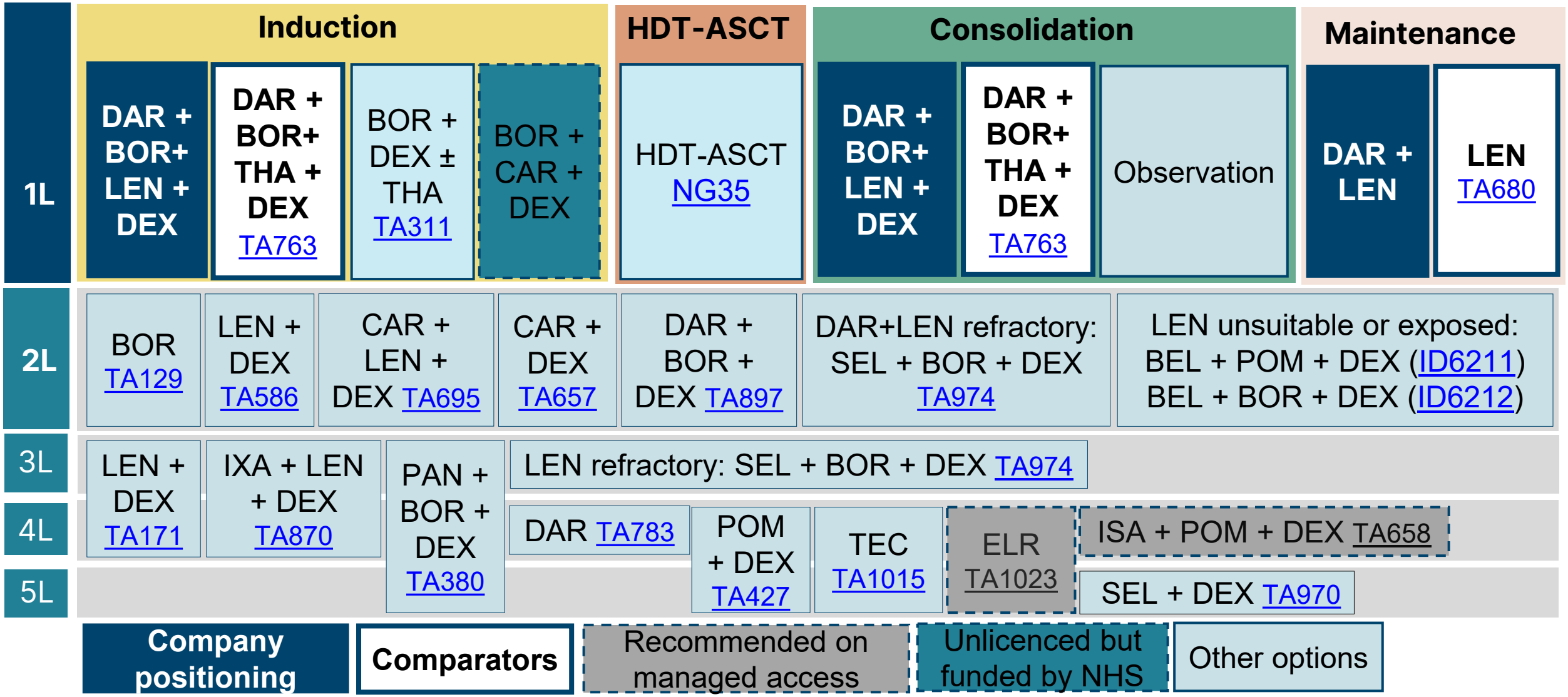
- This appraisal ID6249 focuses on the ASCT-eligible population, ID3843 focuses on ASCT-ineligible population;.

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

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

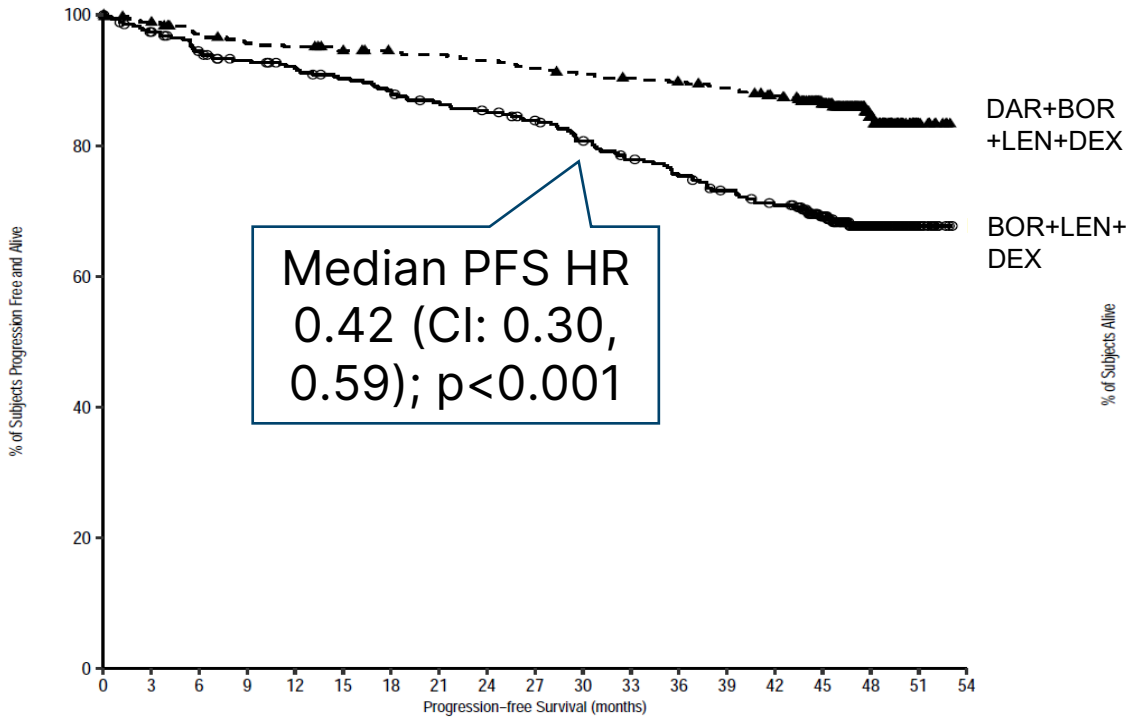


Abbreviations: 1/2/3/4/5L, 1st /2nd/3rd/4th/5th line; ASCT, autologous stem cell transplant; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; ELR, elranatamab; HDT, high dose therapy; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; NDMM, newly diagnosed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

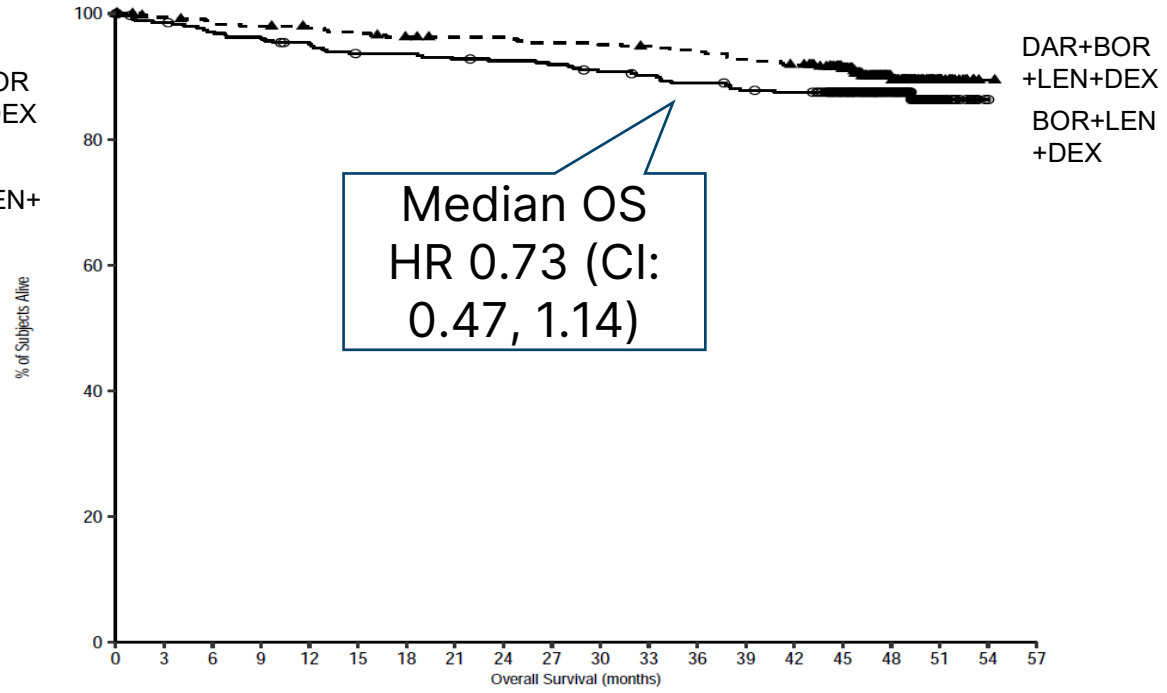
Key clinical trial results – PERSEUS

- 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 for intervention arm.
- **BOR + LEN + DEX is not the comparator in this appraisal**

PFS



OS



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

PERSEUS - PFS and OS outcomes

Outcome	BOR + LEN + DEX	DAR + BOR + LEN + DEX
Full Treatment Sequence* PFS (% people (95% CI))		
12-Month	[redacted] ([redacted])	[redacted] ([redacted])
24-Month	[redacted] ([redacted])	[redacted] ([redacted])
36-Month	[redacted] ([redacted])	[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])	[redacted] ([redacted])
24-Month	[redacted] ([redacted])	[redacted] ([redacted])
36-Month	[redacted] ([redacted])	[redacted] ([redacted])
48-Month	[redacted] ([redacted])	[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.

Results of ITC from PERSEUS for OS and PFS

	PFS	OS
DAR+LEN vs LEN from PERSEUS	**HR (95% CI)**	
Unweighted	[redacted] ([redacted])	[redacted] ([redacted])
IPTW-ATT (base case covariates)	[redacted] ([redacted])	[redacted] ([redacted])
IPTW-ATT (additional covariates)	[redacted] ([redacted])	[redacted] ([redacted])
Doubly robust (base case covariates)	[redacted] ([redacted])	[redacted] ([redacted])
Doubly robust (additional covariates)	[redacted] ([redacted])	[redacted] ([redacted])
Multivariate regression (base case covariates)	[redacted] ([redacted])	[redacted] ([redacted])
Multivariate regression (additional covariates)	[redacted] ([redacted])	[redacted] ([redacted])

NICE

Abbreviations: ATT, average treatment effect on the treated; CI, confidence interval; DAR, daratumumab; LEN, lenalidomide; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; PFS, progression-free survival

SACT estimated long-term survival

Parametric model	10-year survival	AIC	BIC
Exponential	79.3%	480.62	**485.25**
Weibull	76.1%	482.29	491.56
Log-normal	82.4%	479.93	489.2
Log-logistic	77.6%	482.09	491.36
Gamma	75.2%	482.23	491.49
Generalised Gamma	87.5%	**479.28**	493.17
Gompertz	87.8%	482.23	491.5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Base case PFS extrapolation

Base case (generalised gamma) and proxy extrapolation with clinician estimates

PFS extrapolations

PFS extrapolations fitted to DAR+BOR+LEN+DEX – DAR+LEN from PERSEUS

PFS extrapolations

Survival Model	PFS (%)		
	10 Years	15 Years	25 Years
DAR+BOR+LEN+DEX – DAR+LEN			
Clinician Estimates (Company)	64 [60, 65]	48 [45, 55]	21 [15, 35]
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Gen. Gamma (base case)	[redacted]	[redacted]	[redacted]

Survival Model	PFS (%)		
	10 Years	15 Years	25 Years
DAR+BOR+THA+DEX – LEN*			
Clinician Estimates (Company)	34 [25, 40]	10 [0, 15]	3 [0, 5]
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Gen. Gamma (base case)	[redacted]	[redacted]	[redacted]

*Applies OS HR to intervention extrapolation

Base case OS extrapolation

Base case (exponential) and proxy extrapolation with clinician estimates

OS extrapolations

OS extrapolations fitted to DAR+BOR+LEN+DEX – DAR+LEN from PERSEUS

OS extrapolations

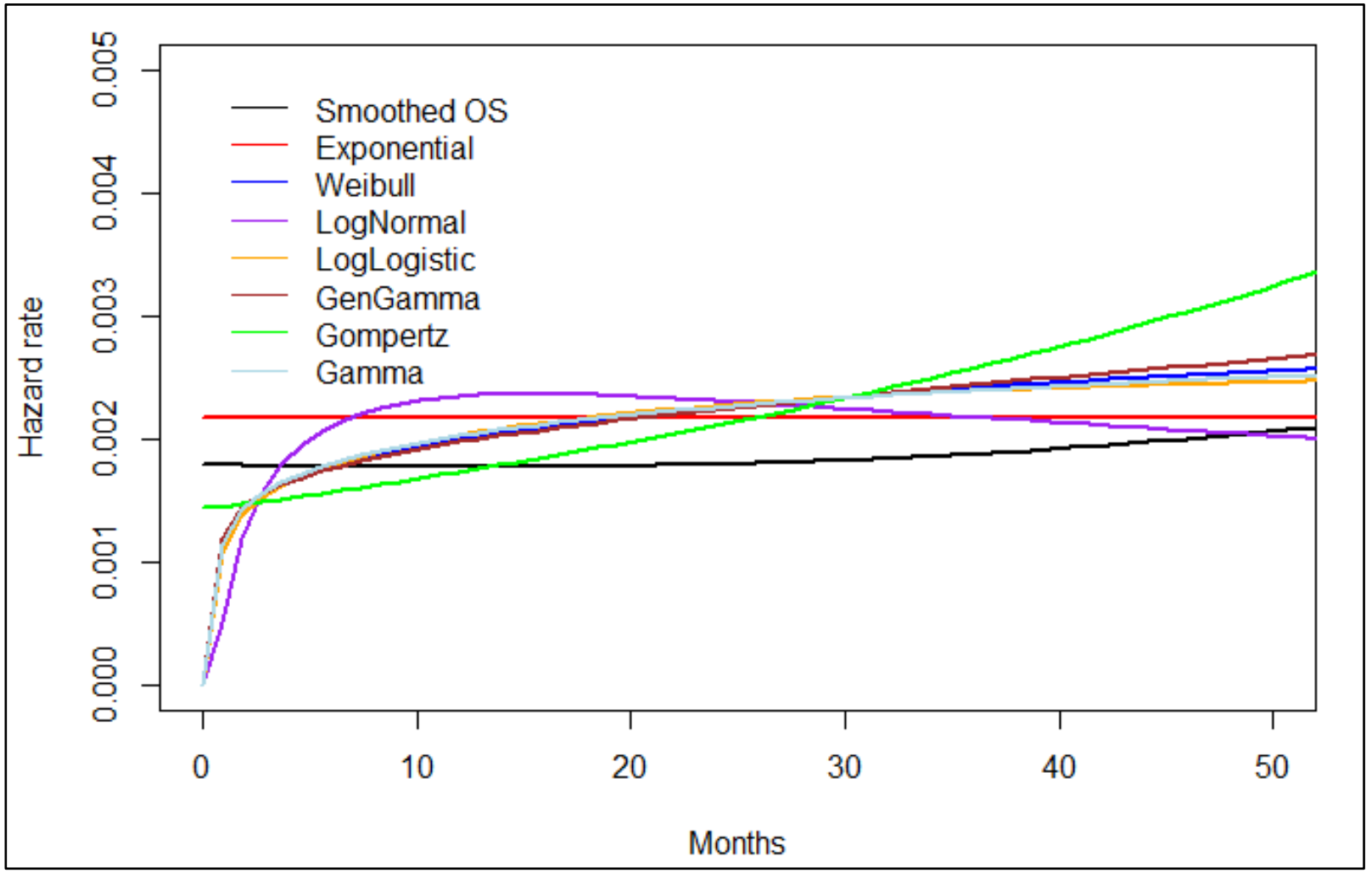
Survival Model	OS (%)		
	10 Years	15 Years	25 Years
DAR+BOR+LEN+DEX – DAR+LEN			
Clinician Estimates (Company)	77 [75, 80]	67 [65,70]	38 [25, 53]
Exponential (base case)	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]

Survival Model	OS (%)		
	10 Years	15 Years	25 Years
DAR+BOR+THA+DEX – LEN*			
Clinician Estimates (Company)	68 [60, 70]	55 [45, 65]	30 [15, 45]
Exponential (base case)	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]

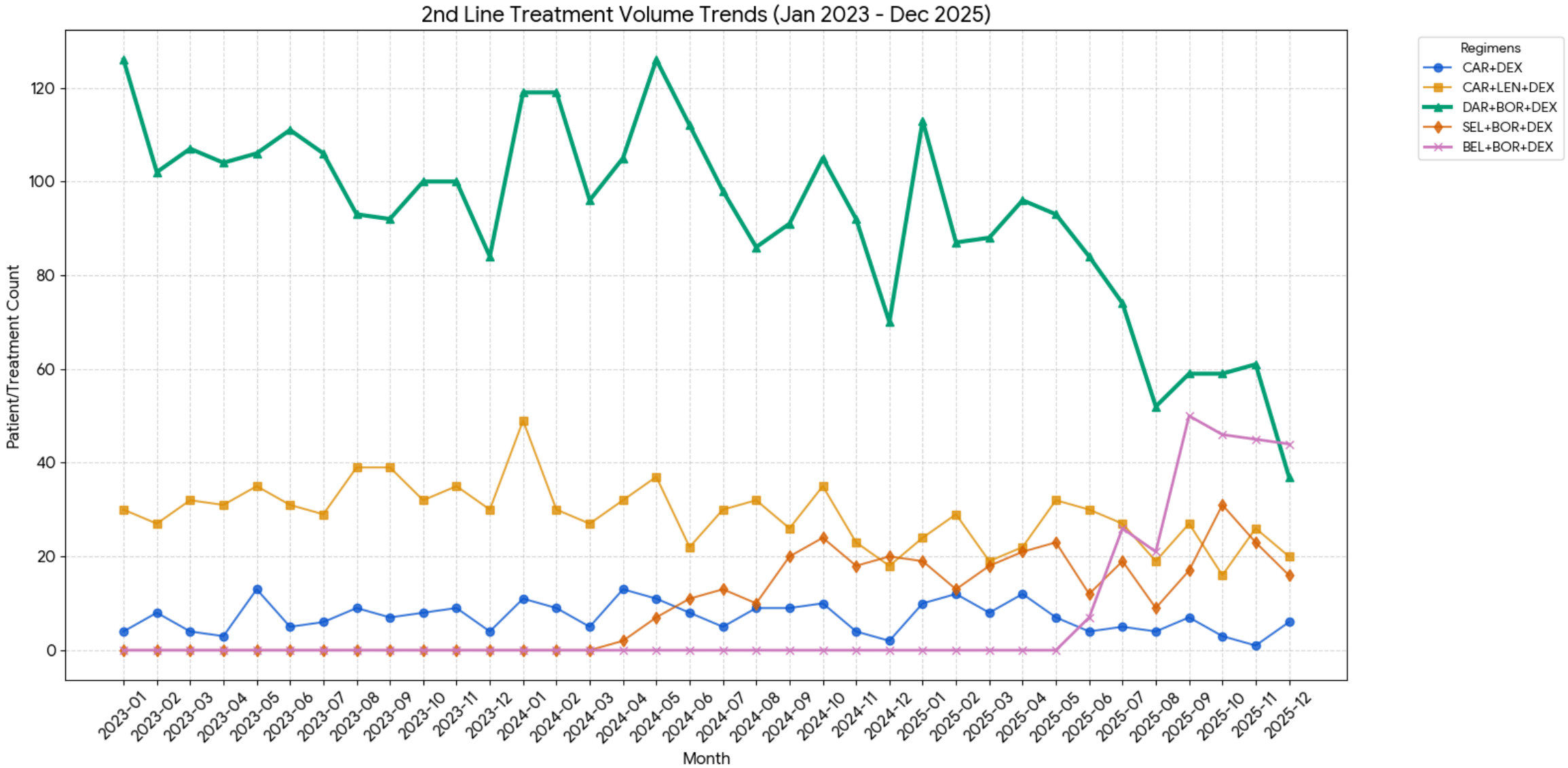
*Applies OS HR to intervention extrapolation

OS smoothed hazards

DAR+BOR+LEN+DEX – DAR+LEN observed OS smoothed hazards

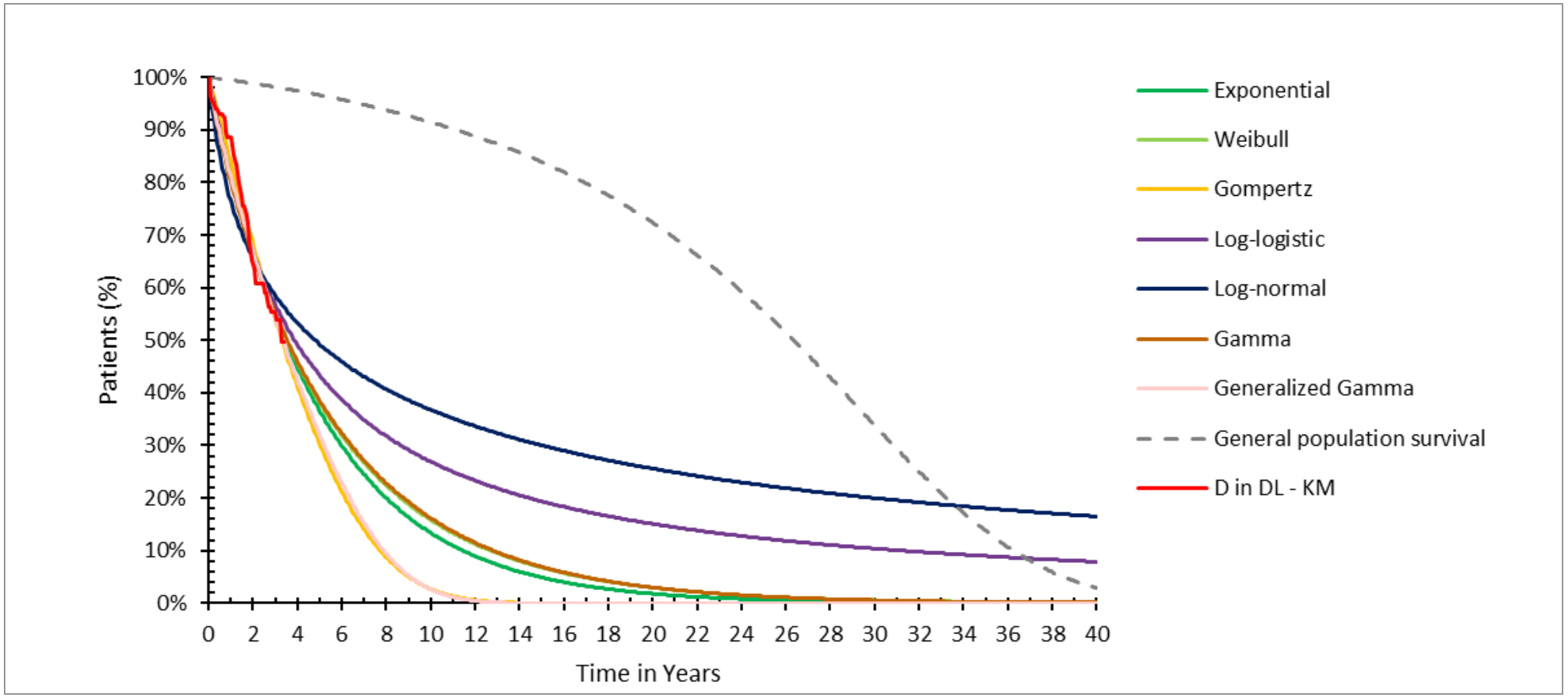


2nd line treatment trends over 3 years – NHSE Blueteq data



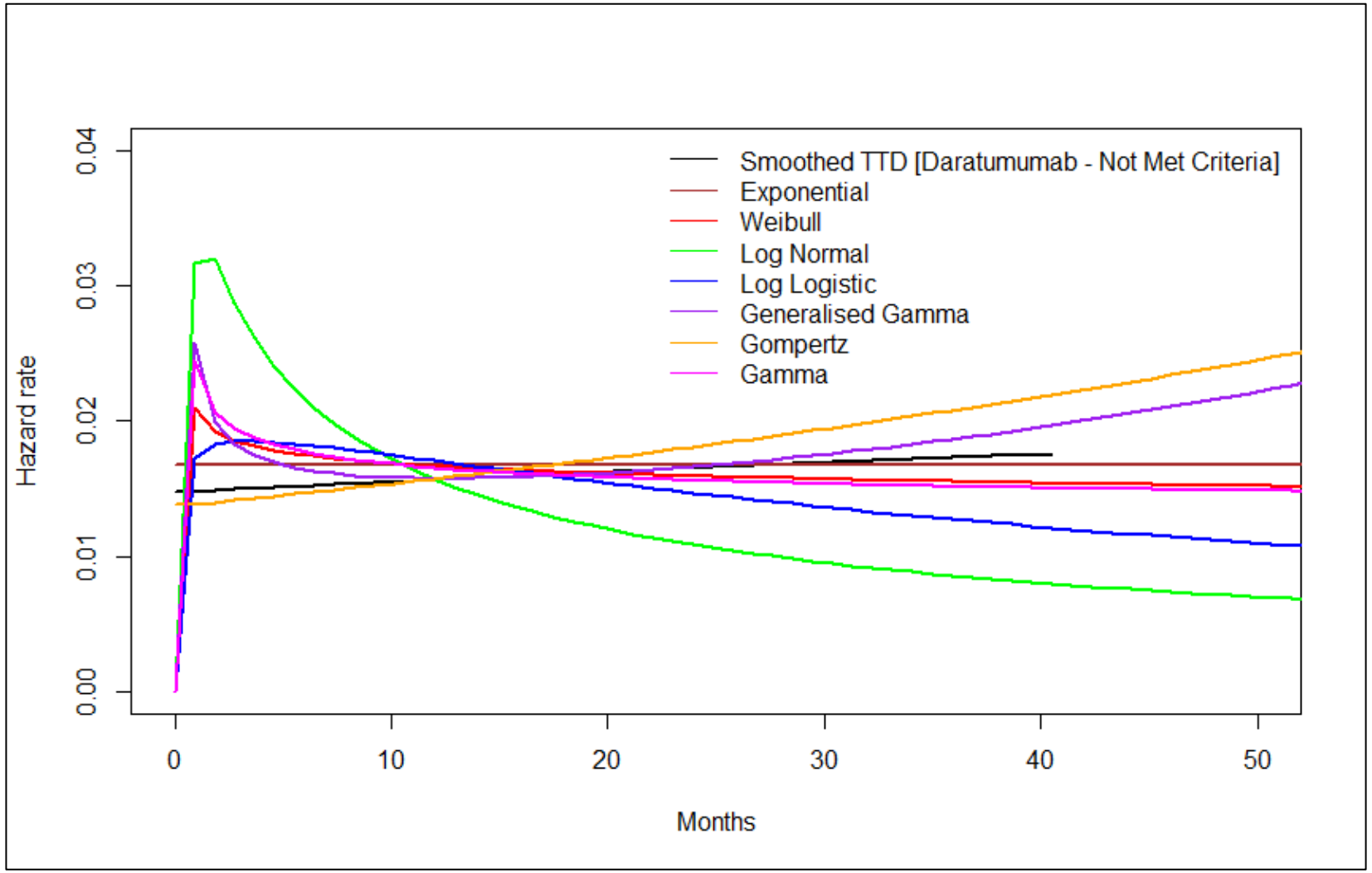
DAR (without sustained MRD-) TTD extrapolations

Exponential fitted in base case



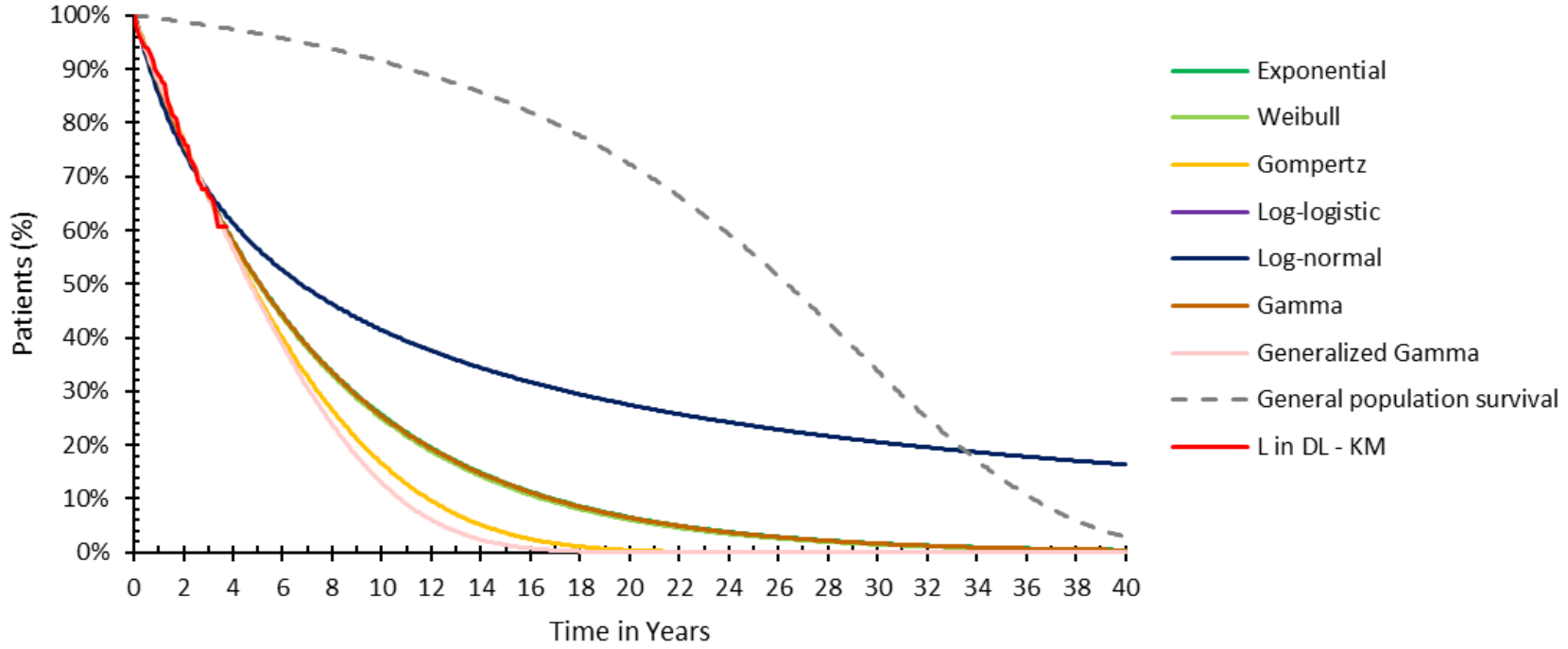
DAR (without sustained MRD-) TTD hazards

Exponential fitted in base case



Intervention LEN TTD extrapolations

Exponential fitted in base case.



Extrapolation	People receiving LEN in intervention arm (%)		
	5 Years	8 Years	10 Years
Exponential (base case)	50.2	33.4	25.5
Weibull	49.9	32.9	24.8
Gompertz	47.3	26.3	16.4
Log-logistic	52.8	40.0	34.3
Log-normal	56.3	46.1	41.3
Gamma	50.1	33.3	25.3
Gen. Gamma	46.7	23.5	12.8