Daratumumab with lenalidomide and dexamethasone for treating untreated multiple myeloma when stem cell transplant is unsuitable

Technology appraisal committee B [7 June 2023]

Slides for the public - contains no ACIC or CPAS information

Chair: Charles Crawley

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Company: Janssen-Cilag

Background on myeloma

Myeloma is a type of bone marrow cancer

Causes:

- Myeloma is a cancer of the plasma cells; cells accumulate in the bone marrow and supress the development of normal blood cells

Symptoms:

- Infections
- Bone pain and fractures
- Tiredness (as a result of anaemia)
- Hypercalcaemia (elevated calcium levels)
- Kidney problems

Diagnosis:

- Myeloma is diagnosed based on the results of blood tests, bone marrow biopsies, MRI and CT scans

Epidemiology:

- 6,377 newly diagnosed cases of myeloma in the UK in 2020
- 75% are over the age of 65
- Myeloma is more common in men and people of African family background

Prognosis:

- Myeloma is an incurable disease
- Treatment outcomes are worse in the stem cell transplant ineligible population

High-dose therapy (HDT) followed by a stem cell transplant (SCT):

- Involves giving high doses of chemotherapy to kill myeloma cells followed by an infusion of stem cells to allow the bone marrow to recover
- People can be ineligible to receive a SCT due to frailty, performance status and presence of comorbidities

Abbreviations: CT, computed tomography; HDT, high-dose therapy; MRI, magnetic resonance imaging; SCT, stem cell transplant

Daratumumab (Darzalex, Janssen-Cilag)

Marketing authorisation	• "In combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant" • Only *"in combination with lenalidomide and dexamethasone"* is within the scope of this appraisal • Granted November 2019, EMA
Mechanism of action	• Human immunoglobulin G1 kappa monoclonal antibody that binds to CD38, a glycoprotein overexpressed on surface of myeloma cells, inducing tumour cell death
Administration	• Fixed dose subcutaneous (SC) injection or intravenous (IV) infusion • Weeks 1 to 8: once weekly • Weeks 9 to 24: every two weeks • Week 25 onwards: every four weeks until disease progression.
Price	• List price 1,800 mg (fixed-dose vial; SC injection) = £4,320.00 • Patient access scheme (PAS) discount available • PAS was updated ahead of ACM2

Abbreviations: ACM, appraisal committee meeting; EMA, European Medicines Agency; SC, subcutaneous

Clinical effectiveness recap

NICE National Institute for Health and Care Excellence

Key clinical trials

The main clinical data is from the Phase 3 MAIA study

	MAIA (Phase 3) (n=737)
Design	Randomised, open-label, active controlled, parallel-group, multicentre,
Population	Adults with previously untreated myeloma ineligible for ASCT
Intervention	DARA+LEN+DEX
Comparator(s)	LEN+DEX
Follow up	73.6 months *(Based on the October 2022 data cut provided post consultation)*
Primary outcome	Progression-free survival (PFS)
Key secondary outcomes	Overall survival (OS), Health related quality of life (HRQoL), Adverse events (AEs), Progression-free survival on next line of therapy, Time to next treatment, Time to response, Duration of response, Time to disease progression, Overall response rate, Complete response rate, Stringent complete response rate, Better than very good partial response, Minimal residual disease negativity rate
Locations	176 hospitals in 14 countries
Used in model?	Yes

Abbreviations: ASCT, autologous stem cell transplant; DARA, daratumumab; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PFS, progression free survival

MAIA results - PFS

Hazard ratio shows progression benefit of DARA+LEN+DEX

Figure Kaplan-Meier plot of PFS (ITT population) (64.5 months median follow up)

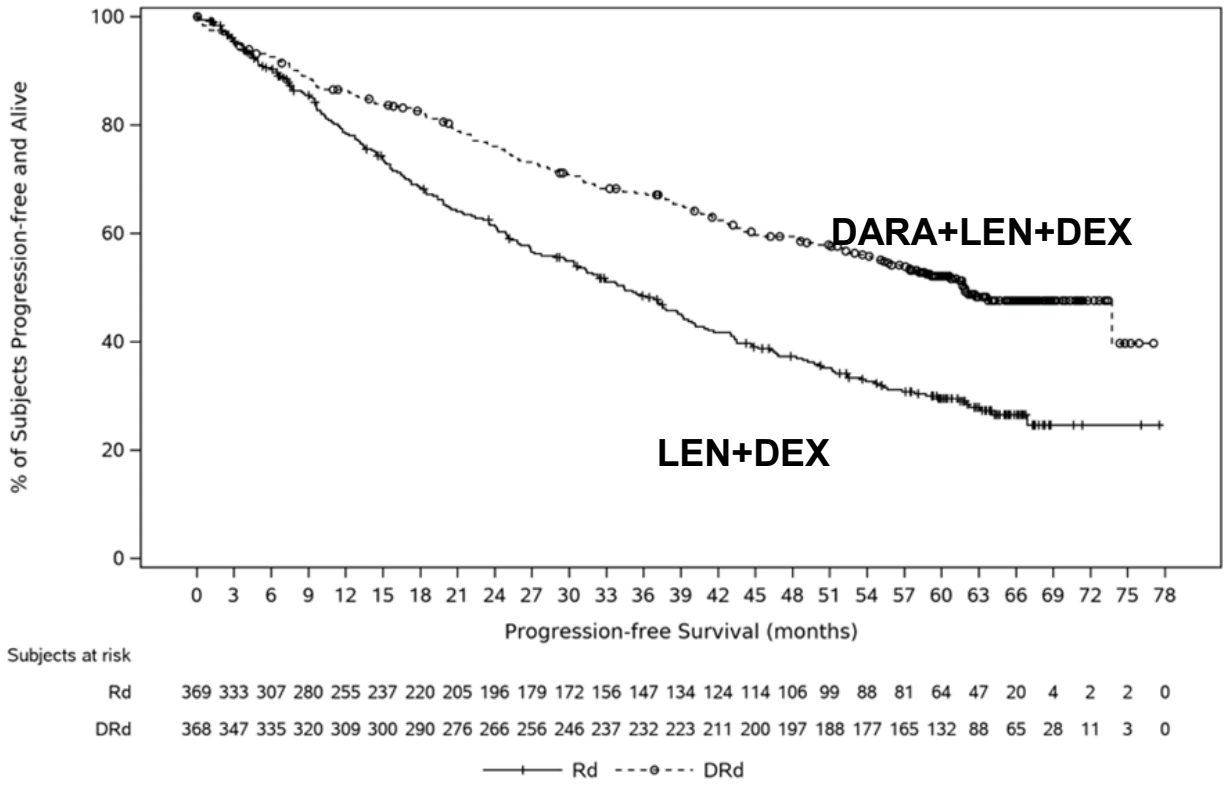


Table Summary of PFS in the MAIA trial (ITT population) (64.5 months median follow up)

	DARA+LEN+DEX (n=368)	LEN+DEX (n=369)
Number of Events (%)	[redacted]	[redacted]
Median Months (95% CI)	61.9 [redacted]	34.4 [redacted]
HR (95% CI)	0.55 (0.45, 0.67)	
p-value	<0.0001	
60-Month PFS Rate, %, (95% CI)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DARA, daratumumab; DEX, dexamethasone; DRd, daratumumab, lenalidomide and dexamethasone; HR, hazard ratio; ITT, intent-to-treat; LEN, lenalidomide; NE, not estimable; PFS, progression-free survival; Rd, lenalidomide and dexamethasone;

MAIA results - OS

Hazard ratio shows survival benefit of DARA+LEN+DEX

Figure Kaplan-Meier plot of OS (ITT population) (73.6 months follow-up)

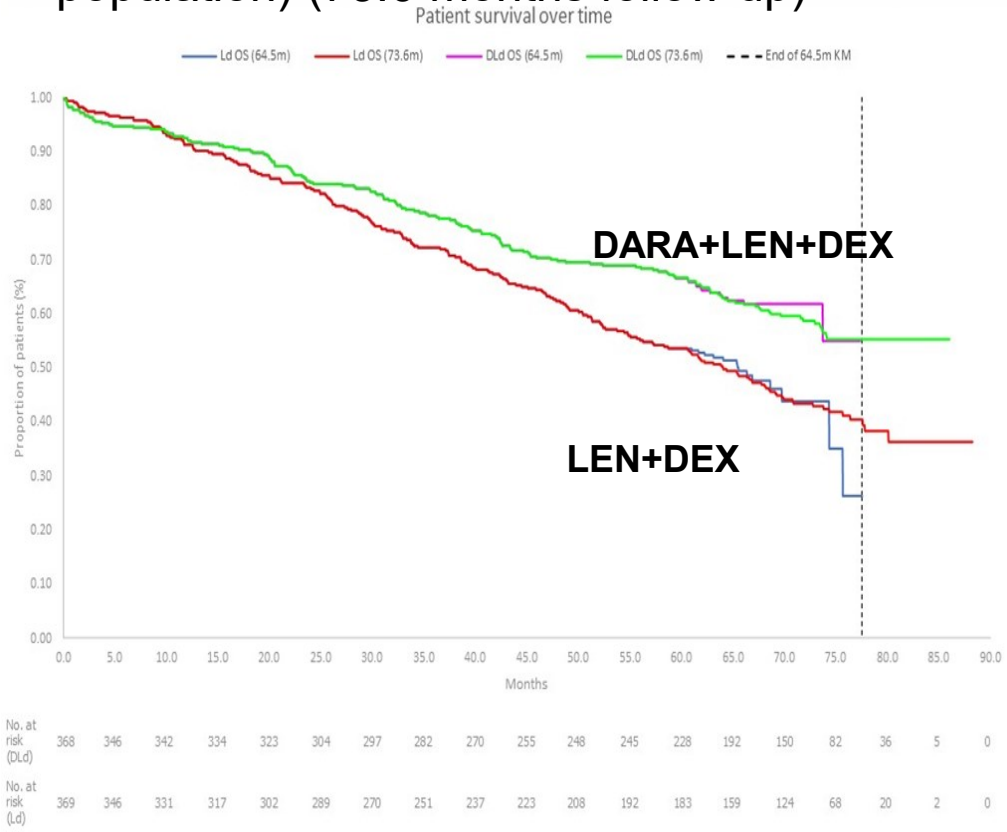


Table Summary of OS in the MAIA trial (ITT Population)

	73.6 months follow up		64.5 months follow up	
	DARA+LEN +DEX (n=368)	LEN+DEX (n=369)	DARA+LEN +DEX (n=368)	LEN+DEX (n=369)
Number of Events (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median Months (95% CI)	NE [redacted]	64.07 [redacted]	NE [redacted]	65.5 [redacted]
HR (95% CI)	0.65 (0.52, 0.80)		0.66 (0.53, 0.83)	
p-value	0.0001		0.0003	
60-Month OS Rate, %,	66.7	53.7	66.6	53.6

NICE

Abbreviations: CI, confidence interval; DARA, daratumumab; DEX, dexamethasone; DRd, daratumumab, lenalidomide and dexamethasone; HR, hazard ratio; ITT, intent-to-treat; LEN, lenalidomide; NE, not estimable; OS, overall survival; Rd, lenalidomide and dexamethasone;

MAIA results – Piecewise Cox analysis of MAIA OS over time

MAIA Follow up duration		OS HR	95% CI	P value
Months	Years			
≤6	≤0.5	[redacted]	[redacted]	[redacted]
≤12	≤1.0	[redacted]	[redacted]	[redacted]
≤18	≤1.5	[redacted]	[redacted]	[redacted]
≤24	≤2.0	[redacted]	[redacted]	[redacted]
≤30	≤2.5	[redacted]	[redacted]	[redacted]
≤36	≤3.0	[redacted]	[redacted]	[redacted]
≤42	≤3.5	[redacted]	[redacted]	[redacted]
≤48	≤4.0	[redacted]	[redacted]	[redacted]
≤54	≤4.5	[redacted]	[redacted]	[redacted]
≤60	≤5.0	[redacted]	[redacted]	[redacted]
≤66	≤5.5	[redacted]	[redacted]	[redacted]
≤72	≤6.0	[redacted]	[redacted]	[redacted]
≤78	≤6.5	[redacted]	[redacted]	[redacted]
≤84	≤7.0	[redacted]	[redacted]	[redacted]

What trend can be observed in the OS HR over time?

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival;

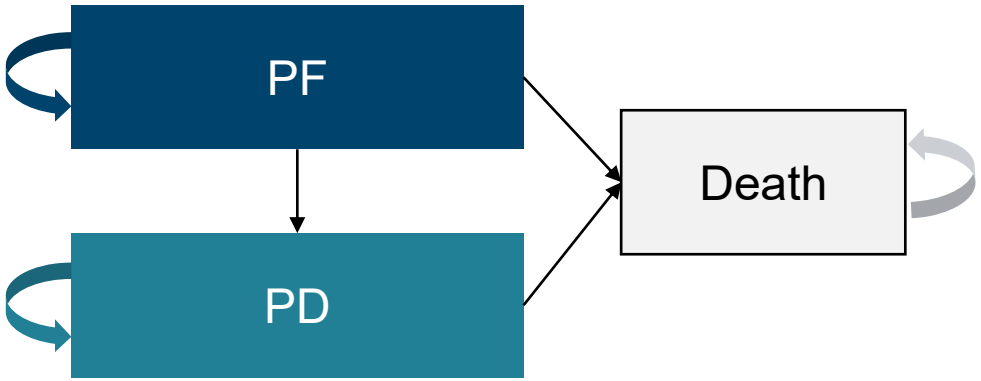
Cost effectiveness recap

NICE National Institute for Health and Care Excellence

Company's model overview

Company implemented a partitioned survival model to inform cost-effectiveness

Figure Model structure



Time to treatment discontinuation (TTD) was used to determine the time on treatment (ToT), to account for when people discontinued treatment before progression. Treatment could be received, in both the PF and PD states

Technology affects costs by:

- Increased 1st line treatment acquisition costs
- Higher PF heath state costs (higher resource use / AEs)
- Lower PD health state costs (lower acquisition costs for 2nd line)

Technology affects QALYs by:

- Increasing the time spent in the PF health state

Source of inputs into the model:

- Baseline characteristics, intervention and comparator efficacy, utilities, resources use and AEs → MAIA trial
- Costs → British National Formulary, pharmaceutical electronic market information tool (eMIT) , NHS reference costs 2019-20, previous NICE appraisals

Abbreviations: AE, adverse events; OS, overall survival; PD, progressed disease; PF, progression-free; QALYs, quality-adjusted life year; ToT, time on treatment; TTD, time to treatment discontinuation;

ACD: committee main conclusions/considerations

NICE National Institute for Health and Care Excellence

Key clinical issues from ACM1

Recommendation: DARA+LEN+DEX is not recommended, within its marketing authorisation, for untreated multiple myeloma in adults, when an autologous stem cell transplant is unsuitable

Issue	Committee's conclusion
The most appropriate comparator (3.2)	• LEN+DEX is the main comparator
BOR+MEL+PRE and BOR+CYC+DEX equivalence (3.7)	• Equivalence not demonstrated → was satisfied that the decision did not materially impact the fully incremental analysis cost-effectiveness results
Generalisability of the MAIA results (given proportion of participants that received 2nd and 3rd line treatments not routinely commissioned by NHS England). (3.4)	• Population in MAIA is generalisable to the NHS and represents the best available evidence • Subsequent treatments in MAIA likely to differ from those in the NHS → impacts generalisability and leads to uncertainty in the long-term treatment effect of DARA+LEN+DEX
Is follow up from MAIA sufficient for robust estimation of OS (3.5)	• MAIA showed a survival benefit, but OS modelling was uncertain

Abbreviations: ACM, appraisal committee meeting; BOR, bortezomib; CYC, cyclophosphamide; DARA, daratumumab DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; OS, overall survival; PRE, prednisone

Key cost-effectiveness issues from ACM1

Issue	Committee's conclusion
Market share of treatments used at 2nd and 3rd line in England (3.11)	• Acknowledged the uncertainty → Concluded that the company's estimates were acceptable for decision making
Inclusion of subsequent treatments only available through the CDF (3.12)	• CDF treatments should not be considered at ACM1 • Acknowledged ongoing reviews → If CDF treatments are recommended for routine practice modelling could be updated
Most appropriate parametric models for TTD (3.9)	• The exponential curve was most appropriate • Would reconsider its decision if additional data suggested another extrapolation is more appropriate
Long-term extrapolation of the treatment effect (3.10)	• Considered each of the scenarios presented • Company's base case could potentially be plausible → It is highly optimistic and associated with high uncertainty. • Possible there could be an attenuation of the treatment effect where the relative treatment effect reduced overtime but where the HR did not reach 1

Abbreviations: ACM, appraisal committee meeting; CDF, cancer drugs fund; DARA, daratumumab; DEX, dexamethasone; LEN, lenalidomide; TTD, time to treatment discontinuation;

Other key issues from ACM1

Issue	Committee's conclusion
Uncaptured benefits (3.17)	• DARA+LEN+DEX likely improves outcomes and addresses unmet need → Uncertain if there were additional benefits not captured in the QALY
ICER threshold (3.13)	• The ICER would have to be substantially below £30,000 per QALY gained for routine commissioning

Abbreviations: ACM, appraisal committee meeting; DARA, daratumumab; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; QALY, quality-adjusted life year;

Response to consultation

NICE National Institute for Health and Care Excellence

Consultation responses (1/2)

Consultation comments

Comments received from:

- Janssen-Cilag (company – manufacturer of DARA)
- UK myeloma society (professional group)
- Myeloma UK (patient/carer group)

Janssen-Cilag

- Provided updated data from MAIA → Suggested this reduces the uncertainty surrounding the long-term treatment effect for OS and the choice of TTD curve
- Acknowledged uncertainty remains when modelling the long-term treatment effect → Provided scenarios
- Responded to committees concerns about generalisability of subsequent treatments in MAIA → Questioned the direction of potential bias
- Suggested treatments only available through the CDF at ACM1 should be incorporated into the model following recent positive NICE guidance
- Responded to the committee's consideration that the ICER would have to be substantially below £30,000 per QALY → Discussed benefits not captured in the QALY and the reduction of uncertainties

Abbreviations: ACM, appraisal committee meeting; CDF, cancer drugs fund; DARA, daratumumab; ICER, incremental cost-effectiveness ratio; OS, overall survival; TTD, time to treatment discontinuation; QALY, quality-adjusted life year;

Consultation responses (2/2)

UK myeloma society (professional group)

- Stated that there is no case for treatment waning
- Stated their view that subsequent therapies in MAIA are generalisable to UK practice

Myeloma UK (patient/carer group)

- Was concerned that the committee did not fully consider benefits not captured in the QALY
- Disagreed with the committee's conclusion that the OS data is immature → Stated that the threshold for maturity in unclear

Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; OS, overall survival; QALY, quality-adjusted life year;

Committee discussion at ACM2

	Outstanding Issues	Committee DGD conclusions	ICER Impact
1.	**Generalisability of subsequent treatments in MAIA**	**Section 3.4**. • Subsequent treatments used in MAIA likely to differ from those offered by the NHS This would impact generalisability and lead to uncertainty in the long-term treatment effect of DARA+LEN+DEX • Despite the uncertainty, the MAIA trial represented the best available evidence	Unknown 
2.	**Time to treatment discontinuation (TTD) extrapolation**	**Section 3.9.** • At ACM 1, the exponential curve was most appropriate for decision making • Committee said that it would reconsider its decision if evaluation of the most recent data cut suggested another extrapolation is more appropriate	Large 
3.	**Improving effectiveness:** The assumption of a constantly improving treatment effect	**Section 3.10** • Company's base case potentially plausible, but is highly optimistic and uncertain	Large 
4.	**Long term effectiveness:** OS benefit of DARA+LEN+DEX	**Section 3.5.** • Current follow up from MAIA showed a survival benefit • With the 64.5 month data cut, median OS was only just being reached for LEN+DEX • OS modelling was uncertain and would benefit from longer follow-up data from MAIA	Large 
5	**Additional benefits not captured in the QALY**	**Section 3.17.** • It was uncertain if there were any additional benefits that had not been captured in the QALY calculations because evidence had not been provided	N/A

Abbreviations: ACM, appraisal committee meeting; DARA, daratumumab; DEX, dexamethasone; DGD, draft guidance document; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; OS, overall survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation;

Key issue: Generalisability of the MAIA trial results (1/2)

Committee comments at ACM1

- Subsequent treatments in MAIA likely differ from those used in the NHS → impacts generalisability and leads to uncertainty in the long-term treatment effect of DARA+LEN+DEX

NICE

- Following the positive recommendation of DARA+BOR+DEX at 2nd line for routine commissioning the model assumes that after 1st line LEN+DEX 90% of patients receive DARA+BOR+DEX at 2nd line
- In MAIA [redacted] of patients in the LEN+DEX arm that received 2nd line therapy received DARA

Company response to DGD

Direction of potential bias is uncertain, and the results used are potentially conservative

- Updated IPCW to include treatments available through the CDF at ACM1 → Results continue to show a greater OS benefit for DARA+LEN+DEX vs LEN+DEX than the unadjusted results used in the base-case
- Subsequent treatments in the DARA+LEN+DEX arm were generalisable → The majority (75%) of 2nd and 3rd line treatments were BOR based
- Subsequent treatment combinations in the LEN+DEX arm included DARA
- In the LEN+DEX arm subsequent treatments included investigational treatments → Could uplift the LEN+DEX outcomes relative to NHS clinical practice
- UKMF commented that the outcomes for LEN+DEX in MAIA reflect NHS clinical practice
- MAIA recruited people from the UK
- Outcomes for LEN+DEX in MAIA in the UK are better than in the FIRST trial

Abbreviations: ACM, appraisal committee meeting; BOR, bortezomib; CDF, cancer drugs fund; DARA, daratumumab; DEX, dexamethasone; DGD, draft guidance document; IPCW, inverse probability of censoring weights; LEN, lenalidomide; OS, overall survival; UKMF, UK myeloma forum

Key issue: Generalisability of the MAIA trial results (2/2)

EAG comments

- Updated IPCW results show that the unadjusted results from MAIA remain a conservative estimate
- In MAIA after DARA+LEN+DEX the majority of 2nd and 3rd line treatments were BOR-based

Professional group comments

- Variation in subsequent treatments is to be expected in large multinational trials
- Subsequent treatments are generalisable to UK practice and MAIA represents best available evidence

Has the committee seen any evidence to provide clarity around the generalisability of the MAIA trial results and the uncertainty in the long-term treatment effect?

Abbreviations: BOR, bortezomib; DARA, daratumumab; DEX, dexamethasone; EAG, external assessment group; IPCW, inverse probability of censoring weights; LEN, lenalidomide;

Key issue: Extrapolation TTD (1/2)

Committee comments at ACM1

- The exponential curve was the most appropriate for extrapolating DARA+LEN+DEX TTD

Company response to DGD

Updated base case DARA+LEN+DEX and LEN+DEX TTD: generalised gamma

- Based on the MAIA 73.6-month data cut generalised gamma had the lowest AIC/BIC for DARA+LEN+DEX and the lowest AIC for LEN+DEX
- Visual inspection of the TTD extrapolation for DARA+LEN+DEX supports generalised gamma and Gompertz but not exponential → Scenario analysis provided using Gompertz

EAG comments

Updated base case DARA+LEN+DEX and LEN+DEX TTD: generalised gamma

- Generalised gamma has the overall best fit across treatments and model fit measures
- Gompertz may also be plausible based on statistical and visual fit
- Generalised gamma has a steep trajectory and after 10 years nobody remains on DARA+LEN+DEX → may impact plausibility of OS extrapolations

Abbreviations: ACM, appraisal committee meeting; DARA, daratumumab; DEX, dexamethasone; EAG, external assessment group; LEN, lenalidomide; OS, overall survival; TTD, time to treatment discontinuation; DGD, draft guidance document; AIC, Akaike information criterion; BIC, Bayesian information criterion;

Key issue: Extrapolation TTD (2/2)

Table: Goodness-of-fit statistics for DARA+LEN+DEX and LEN+DEX TTD survival models (73.6m data cut)

Survival model	DARA+LEN+DEX		LEN+DEX	
	AIC	BIC	AIC	BIC
Exponential	2623.9	2627.8	2963.3	**2967.2**
Weibull	2625.4	2633.2	2963.6	2971.4
Loglogistic	2649.5	2657.3	3001.5	3009.3
Lognormal	2679.8	2687.6	3030.5	3038.3
Generalised Gamma	**2614.0**	**2625.7**	**2961.2**	2972.9
Gompertz	2619.2	2627.0	2965.2	2973.0

Figure: Extrapolation of TTD for DARA+LEN+DEX using IPD (73.6m data cut)

Is the committee satisfied with the TTD extrapolation approach (generalised gamma) used by both the EAG and company based on the MAIA 73.6-month data cut?

Abbreviations: AIC, akaike information criterion; BIC, bayesian information criterion; DARA, daratumumab; DEX, dexamethasone; EAG, external assessment group; IPD, individual person data; KM, Kaplan-Meier; LEN, lenalidomide; TTD, time to treatment discontinuation;

Key issue: Long term effectiveness: The assumption of a constantly improving treatment effect (1/3)

Committee comments at ACM1

- Scenarios were considered but none were likely to reflect the expected long-term treatment effect:
  - Company base-case (constantly improving treatment effect) → Not implausible but highly optimistic and uncertain
  - EAG base-case (treatment effect declined linearly at 12 years for 7 years) → Allowed results from a more conservative extrapolation to be considered
  - Constant treatment effect after the 64.5-month MAIA data cut → Supported by company's analysis which showed a stable OS HR over the 4–6-year period
- Possible that there could be a reduction of treatment effect over time but where the HR did not reach 1

Company response to DGD

No change to ACM1 base-case→ continues to assume constantly improving treatment effect

- Updated piecewise Cox model (MAIA 73.6m) → OS HR improved at a reduced rate over the last 2 years but analysis indicates a 'stepped downward trend" with step-downs observed at 2 and 4 years
- Reiterated that in MAIA DARA+LEN+DEX is associated with a deeper and more sustained response that they suggests results in a fundamental shift in disease trajectory and patient outcomes
- Provided a range of scenarios where the HR is either fixed after a certain timepoint or begins to attenuate but does not reach 1

Abbreviations: ACM, appraisal committee meeting; DARA, daratumumab; DEX, dexamethasone; DGD, draft guidance document; EAG, external assessment group; HR, hazard ratio; LEN, lenalidomide; OS, overall survival;

Key issue: Long term effectiveness: The assumption of a constantly improving treatment effect (2/3)

EAG comments

Updated base-case: Fixed OS HR from end of the observed KM (Scenario 1)

- DARA+LEN+DEX is clinically effective, and the survival benefit is maintained into the long-term
- Survival benefit could be mediated by depth and durability of response
- Updated piecewise Cox model (MAIA 73.6m) → HRs are stable beyond 60 months → supports stabilisation (Scenario 1) or a small decrease (Scenario 4) in the survival benefit after the 73.6m data cut
- Scenario 4 is optimistic → based on generalised gamma TTD curve after 10 years nobody remains on DARA+LEN+DEX

Professional group comments

- Waning is not appropriate in the myeloma space and should not be included in this appraisal
- Reiterated that there is no evidence or biological justification to support waning of the treatment effect

Abbreviations: DARA, daratumumab; DEX, dexamethasone; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; TTD, time to treatment discontinuation;

Key issue: Long term effectiveness: The assumption of a constantly improving treatment effect (3/4)

EAG BC

EAG most optimistic plausible scenario

Table: Additional scenarios exploring OS HR uncertainty

Scenario	Approach	Description
1	Fix OS HR from end of observed KM	Treatment effect improves until end of observed MAIA period (7.16 years) and then remains constant
4	Reduced OS HR improvement until fix at 12-years *(constant at midpoint between generated OS HR at 12-years and OS HR at 7.16 years)*	Treatment effect improves until 7.16 years (Scenario 1) but then improves at a reduced rate from 7.16 year until 12-years and then remains constant.
5	Exploratory attenuation scenario: from 12-years	Treatment effect improves until 12-years and then attenuates from 12-19 years by 25%
2	Fix OS HR at 12-years	Treatment effect improves until 12-years and then remains constant
6	Exploratory attenuation scenario: from 15-years	Treatment effect improves until 15-years and then attenuates from 15-25 years by 25%
3	Fix OS HR at 15-years	Treatment effect improves until 15-years and then remains constant
CBC	OS HR continuously improves	Treatment effect improves with time

Abbreviations: BC, Base-case; CBC, company base-case; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival;

Key issue: Long term effectiveness: The assumption of a constantly improving treatment effect (4/4)

Figure: Visual representation of scenarios exploring modelled OS HRs over time

- Has the assumption of a constantly improving treatment effect been justified sufficiently?
- Which extrapolation of OS treatment effect should be used for decision making?

Abbreviations: BC, base-case; EAG, external assessment group; HR, hazard ratio; OS, overall survival;

Key issue: Long term effectiveness: OS benefit of DARA+LEN+DEX (1/2)

Committee comments at ACM1

- Current follow up from MAIA showed a survival benefit
- OS modelling was uncertain and would benefit from longer follow-up data from MAIA

Company response to DGD

Provided updated OS data from a new MAIA data cut (73.6 months median follow up)

- Across the new data cut the Exponential has the best statistical fit for the extrapolation of DARA+LEN+DEX OS
- Base case retains the Gompertz but this is considered conservative

EAG comments

- The most appropriate distributions for extrapolation of OS is uncertain
- The Exponential is preferred based on BIC, but there is very little to choose between the Exponential, Gompertz, Weibull, and Generalised Gamma, based on AIC
- A common distribution for both treatments is preferred
- Base case retains the Gompertz as it has the overall best fit across treatments and model fit measures
- Agrees with the company that a scenario using the Exponential for DARA+LEN+DEX is clinically plausible.

Abbreviations: ACM, appraisal committee meeting; AIC, akaike information criterion; BIC, bayesian information criterion; DARA, daratumumab; DEX, dexamethasone; DGD, draft guidance document; LEN, lenalidomide; OS, overall survival;

Key issue: Long term effectiveness: OS benefit of DARA+LEN+DEX (2/2)

Table: Goodness-of-fit statistics for DARA+LEN+DEX and LEN+DEX OS survival models (73.6m data cut)

Survival model	DARA+LEN+DEX		LEN+DEX	
	AIC	BIC	AIC	BIC
Exponential	1804.1	1808.0	2,264.7	2,268.6
Weibull	1805.9	1813.7	2,254.3	2,262.1
Loglogistic	1811.6	1819.4	2,262.9	2,270.7
Lognormal	1831.6	1839.5	2,287.5	2,295.3
Generalised gamma	1804.3	1816.0	2,253.9	2,265.6
Gompertz	1805.3	1813.1	2,251.9	2,259.7

Figure: Extrapolation of OS for DARA+LEN+DEX (73.6m data cut, with General population mortality cap)

- Are any of the extrapolations of OS for DARA+LEN+DEX clinically plausible?
- Is the company approach (Gompertz curve) of extrapolating OS acceptable for decision making?
- Has the additional evidence provided reduced the uncertainty around the long-term effectiveness of DARA+LEN+DEX?

Abbreviations: AIC, akaike information criterion; BIC, bayesian information criterion; DARA, daratumumab; DEX, dexamethasone; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival;

Key issue: Additional benefits not captured in the QALY

Committee comments at ACM1

- It is uncertain if there are any additional benefits that have not been captured in the QALY calculations because evidence was not provided

Company response to DGD

- Reiterated there are wider benefits associated with DARA+LEN+DEX not captured in the QALY calculation:
  - Extended periods of remission reduce anxiety associated with relapse
  - Reduction in the burden on carers
  - Removal of the inequity in access to effective treatments based on ASCT eligibility status
  - Allowing access to future trials and treatments that potentially specify anti-CD38 exposure

EAG comments

- Agree that the benefits described by the company are not captured in its existing model
  - The company could have modelled the benefits of a reduction in anxiety and carer burden
  - Allowing access to future trials and treatments is speculative

Patient group comments:

- Was concerned the committee did not fully consider:
  - The difference in outcomes depending on if a person is eligible for an ASCT or not
  - The significant patient benefit of increased PFS and importance of quality first remission

Has the committee seen any evidence that there are additional benefits that have not been captured in the QALY calculations?

Abbreviations: ASCT, autologous stem cell transplant; DARA, daratumumab; DEX, dexamethasone; DGD, draft guidance document; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year;

Differences in company and EAG base case assumptions

Assumption	Company base case	EAG base case	ICER impact
Long term effectiveness: The assumption of a constantly improving treatment effect	• Constantly improving treatment effect • (HR continues to fall)	• Treatment effect improves until end of observed MAIA period (7.16 years) and then remains constant • (Fix OS HR from end of observed KM)	High

Abbreviations: EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival;

Decision Framework

	Outstanding Issues	DGD Sections	Committee Questions
1.	**Generalisability of subsequent treatments in MAIA**	3.4.	• Has the committee seen any evidence to provide clarity around the generalisability of subsequent treatments in MAIA and the uncertainty in the long-term treatment effect?
2.	**Time to treatment discontinuation (TTD)**	3.9.	• Is the committee satisfied with the TTD extrapolation approach (generalised gamma) used by both the EAG and company based on the MAIA 73.6-month data cut?
3.	**Improving effectiveness:** The assumption of a constantly improving treatment effect	3.10	• Has the assumption of a constantly improving treatment effect been justified sufficiently? • Which extrapolation of OS treatment effect should be used for decision making?
4.	**Long term effectiveness:** OS benefit of DARA+LEN+DEX	3.5.	• Is the company approach (Gompertz curve) of extrapolating OS acceptable for decision making? • Has the additional evidence provided reduced the uncertainty around the long-term effectiveness of DARA+LEN+DEX?
5.	**Additional benefits not captured in the QALY**	3.17.	• Has the committee seen any evidence that there are additional benefits that have not been captured in the QALY calculations?

NICE

Abbreviations: DARA, daratumumab; DEX, dexamethasone; DGD, draft guidance document; EAG, external assessment group; LEN, lenalidomide; OS, overall survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation;

Cost-effectiveness results

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

- Company and EAG ICERs are above the threshold normally considered as an effective use of NHS resources

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme;