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

Technology appraisal committee B [12 January 2023]

Slides for public - redacted

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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 and 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

Patient perspectives

Patients value treatments that put myeloma into remission for as long as possible

Submissions from Myeloma UK:

- Myeloma is a highly individual and complex cancer
- Myeloma complications can be significant, debilitating and painful
- There is currently no cure, but treatment can halt its progress and improve quality of life
- However, myeloma is a relapsing and remitting cancer which evolves over time and becomes resistant to treatment
- The most common current therapy (LEN+DEX) is administered orally, which has helped keep patients out of hospital settings
- Treatment side effects and frequent hospital visits have a social and practical impact on people's lives, including financial implications
- The disease also heavily impacts carers

> Myeloma creeps up on you, engulfs you and, if you win the battle, leaves you wondering when it will come back.
>
> - A person with myeloma

> I had to think of my husband. You are in this as a team, it is not an individual battle.
>
> - A carer and family member

Abbreviations: DEX, dexamethasone; LEN, lenalidomide

Clinical perspectives

Therapy options for transplant ineligible people are limited

Submissions from clinical experts and the UK Myeloma Forum:

- Patients are clinically better if in complete response rather than partial response
- So, the goal is gaining a good response with maximal disease control; but even partial remission is clinically significant
- Additionally, this would also allow patients to be well enough to receive further treatment at relapse
- Since daratumumab is already used in the NHS, clinicians have experience of delivering it and dealing with any associated toxicities
- Daratumumab therapy would require additional hospital visits, but administering it subcutaneously would reduce the amount of time spent in hospital

> Multiple unlinked NICE HTAs [have] led to a rigid artificial pathway which limits individualised patient treatment decision.
>
> - UK Myeloma Forum

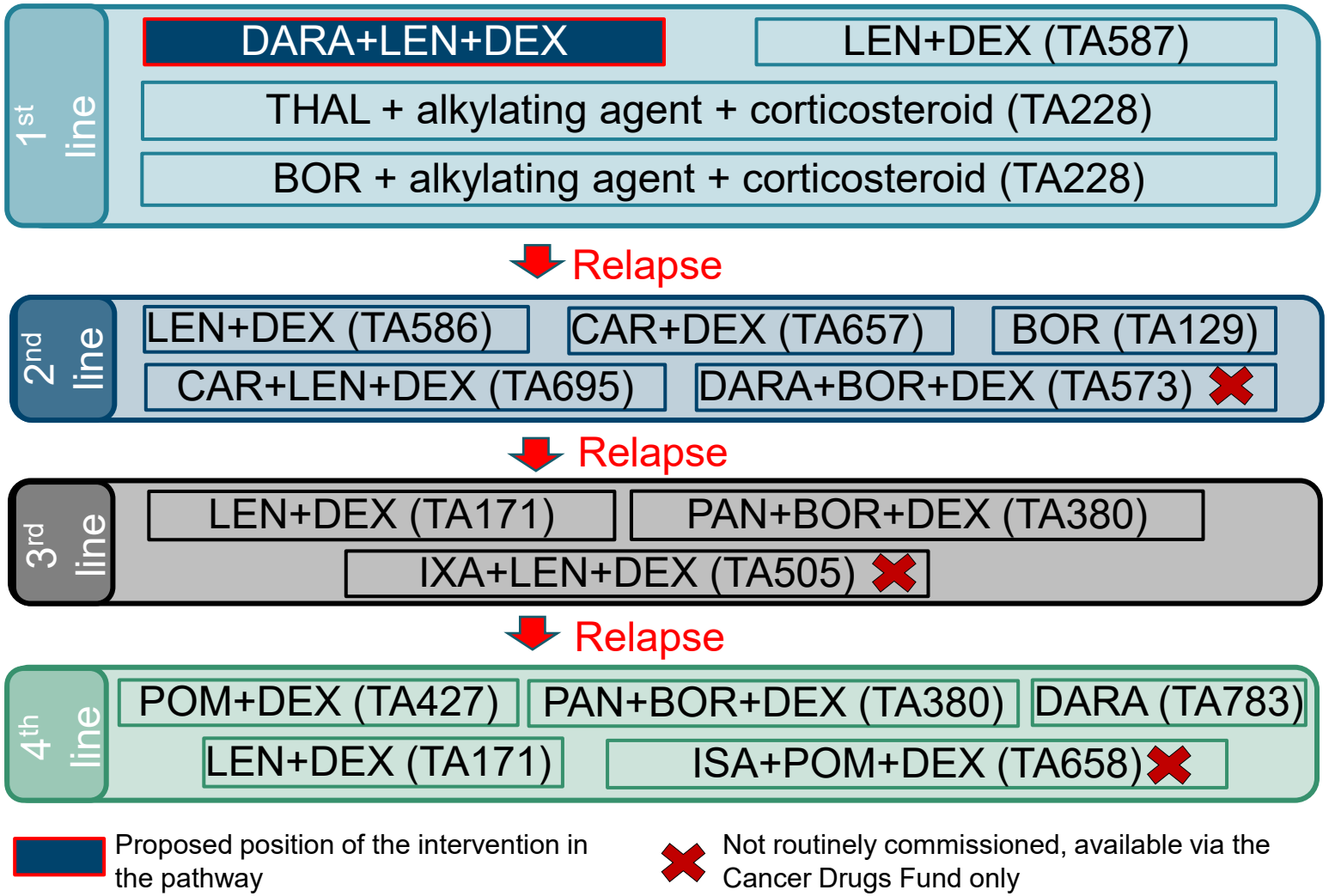
> Daratumumab would easily fit into the current treatment algorithm.
>
> - UK Myeloma Forum

Treatment pathway- when stem cell transplant is unsuitable

DARA+LEN+DEX is proposed as a first-line therapy

- Myeloma is characterised by cycles of remission and relapse
- Treatment aims to achieve depth of response, prolong remission, maximise QoL and prolong survival by offering the optimal front-line therapy
- As the number of lines of therapy increases, time in remission decreases
- Multidrug regimens are thought to result in a deeper response and better long-term outcomes

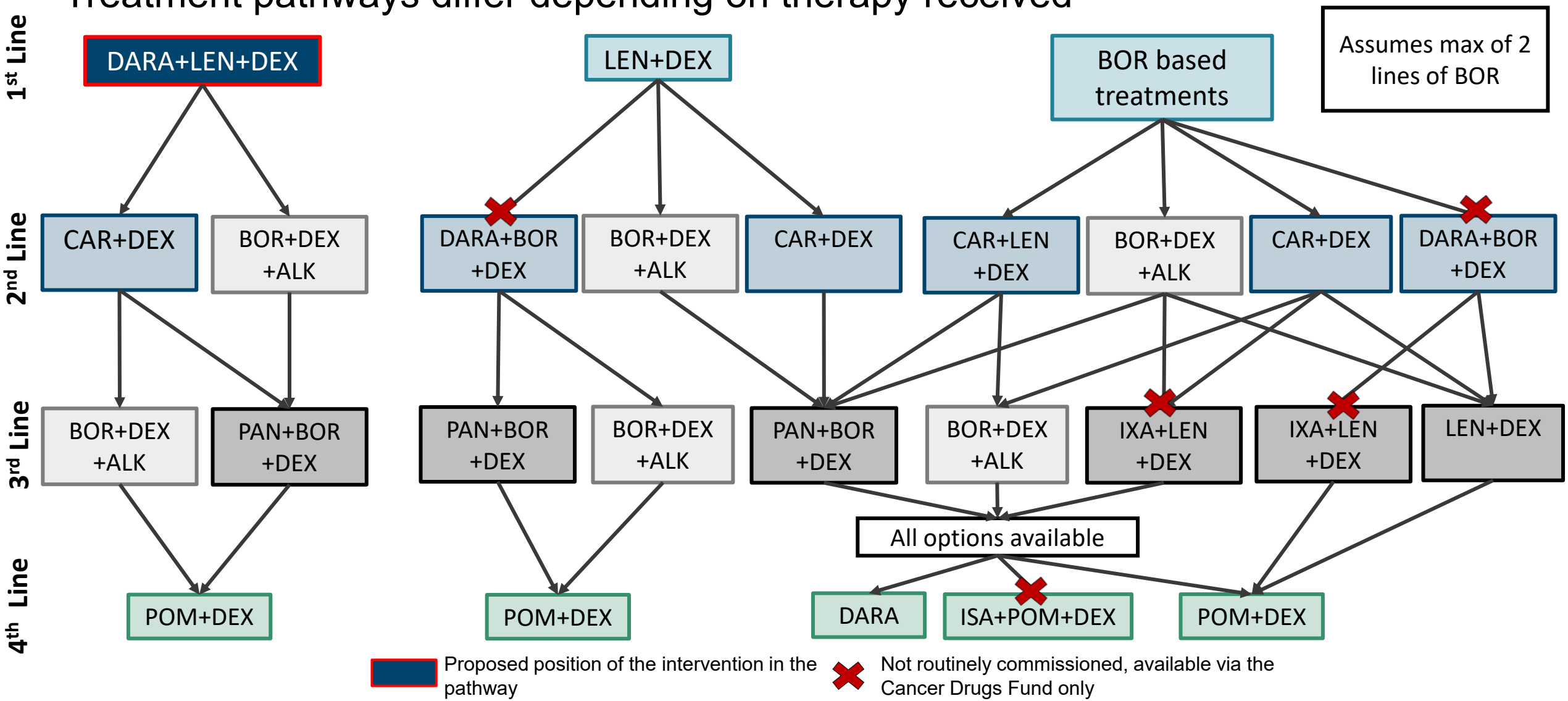
Overview of available therapies



Abbreviations: BOR, bortezomib; CAR, carfilzomib; CYC, cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; MEL, melphalan; PAN, panobinostat; POM, pomalidomide; PRE, prednisone; THAL, thalidomide; QoL, quality of life

Treatment pathway- based on first-line therapy received

Treatment pathways differ depending on therapy received



Abbreviations: ALK, alkylator; BOR, bortezomib; CAR, carfilzomib; CYC, cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide

Key issues

Several key issues remain after technical engagement

Table Key issues

Issue	Resolved?	ICER impact
Clinical effectiveness evidence issues:		
What is the most appropriate comparator?	Partially – for discussion	Large
Is the follow up from the MAIA clinical trial sufficient for robust estimation of OS?	No – for discussion	Unknown
Are BOR+MEL+PRE and BOR+CYC+DEX equivalent?	No – for discussion	Small
Cost effectiveness evidence issues:		
Which are the most appropriate parametric models for TTD?	No – for discussion	Large
Should treatment waning scenarios be considered in decision-making?	No – for discussion	Large

Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; ICER, incremental cost effectiveness ratio; MEL, melphalan; OS, overall survival; PRE, prednisone; TTD, time to treatment discontinuation

Additional areas of uncertainty for committee considerations

Table Additional areas of uncertainty

Additional areas of uncertainty that cannot be currently resolved - Committee should be aware of these when making its recommendations	ICER impact
Generalisability of MAIA results to the NHS in England, given proportion of participants that received 2nd and 3rd line treatments not routinely commissioned by NHS England.	Unknown 
Most appropriate market share of treatments used at 2nd and 3rd line in England	Large 
Inclusion of drugs only available through the Cancer Drugs Fund	Large 

Abbreviations: ICER, incremental cost effectiveness ratio

Daratumumab (Darzalex, Janssen-Cilag)

Table Technology details

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

Abbreviations: EMA, European Medicines Agency; SC, subcutaneous

Decision problem

Table Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with untreated MM when stem cell transplant is unsuitable	Adults with newly diagnosed MM who are ineligible for autologous stem cell transplant	Population matches the scope
Intervention	DARA+LEN+DEX		Intervention matches the scope
Comparators	• THAL+alkylating agent+ corticosteroid People who are unable to tolerate, or have contraindications to THAL: • BOR+alkylating agent+ corticosteroid • LEN+DEX	Main comparators: • LEN+DEX • BOR+alkylating agent+corticosteroid (BOR+CYC+DEX or BOR+MEL+PRE) Comparisons also provided for: • THAL+alkylating agent+corticosteroid	Key issue - discussed on the next slide
Outcomes	OS, PFS, RR, MRD, adverse events and HRQoL	Additional outcomes included: TTP, PFS2, DOR, time to subsequent anticancer therapy and time to response	Outcomes are consistent with the scope

Abbreviations: BOR, bortezomib; DARA, daratumumab; DEX, dexamethasone; DOR, Duration of response; HRQoL, health-related quality-of-life; LEN, lenalidomide; MM, multiple myeloma; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on next line of therapy; RR, response rates; THAL, thalidomide; TTP, Time to disease progression;

Key issue: Most appropriate comparators

Company and EAG both agree THAL containing regimens rarely used

Background

- 5 treatment regimens were included as comparators in the scope: LEN with DEX, BOR with CYC+DEX or with MEL+PRE, and THAL with CYC+DEX or with MEL+PRE

Regimen	Company and EAG positions	Clinical experts
LEN+DEX	Most relevant first line comparator, is the current standard of care	Most frequently used
BOR+CYC+DEX	The company considered low usage, but the EAG was advised that they are commonly used	Used to a lesser extent
BOR+MEL+PRE		
THAL+CYC+DEX	The company considered THAL-based therapies to have negligible use and the EAG agreed they are rarely used	Now used in the smallest minority as first line therapy
THAL+MEL+PRE		

What are the most relevant comparators for this appraisal?

Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; EAG, evidence assessment group; LEN, lenalidomide; MEL, melphalan; PRE, prednisone; THAL, thalidomide

Clinical effectiveness compared with lenalidomide

NICE National Institute for Health and Care Excellence

Key clinical trials

The main clinical data is from the Phase 3 MAIA study

Table Clinical trial designs and outcomes – MAIA

	MAIA (Phase 3)
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	64.5 months
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)

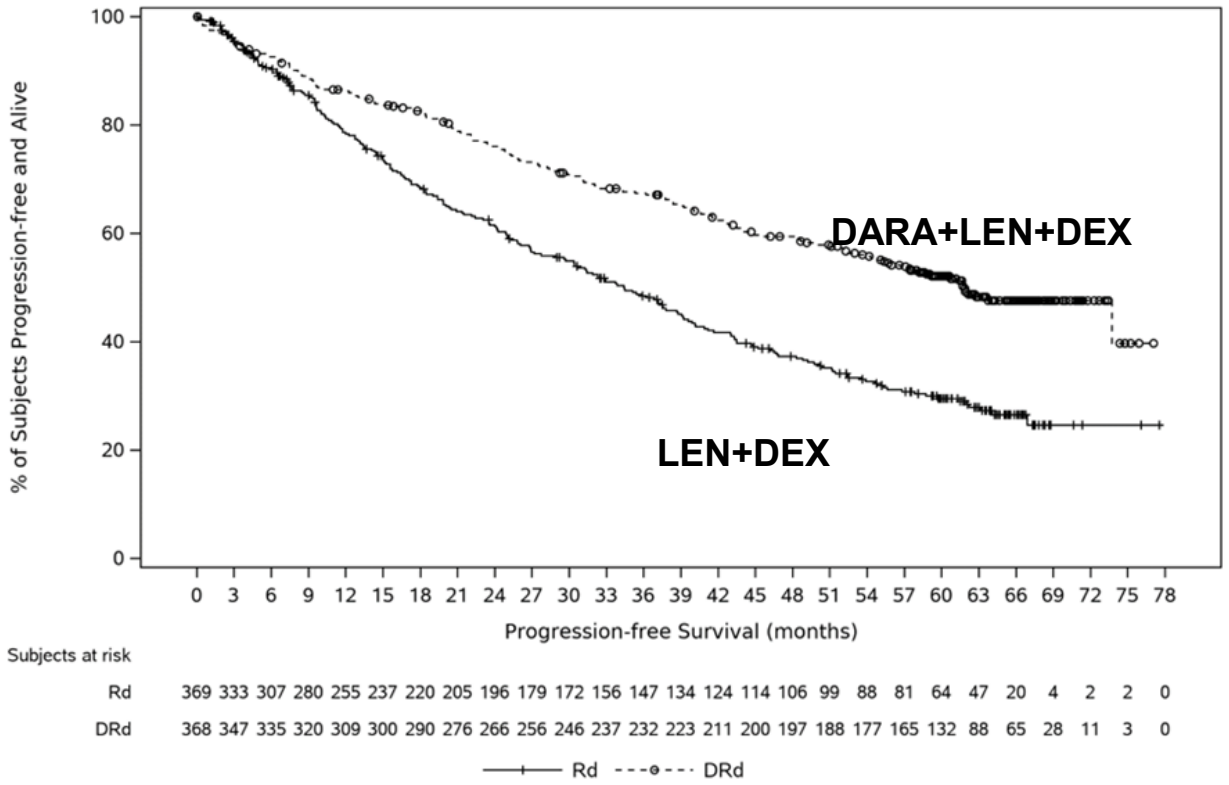


Table Summary of PFS in the MAIA trial (ITT Population) (64.5 months median follow up)

	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]

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; 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)

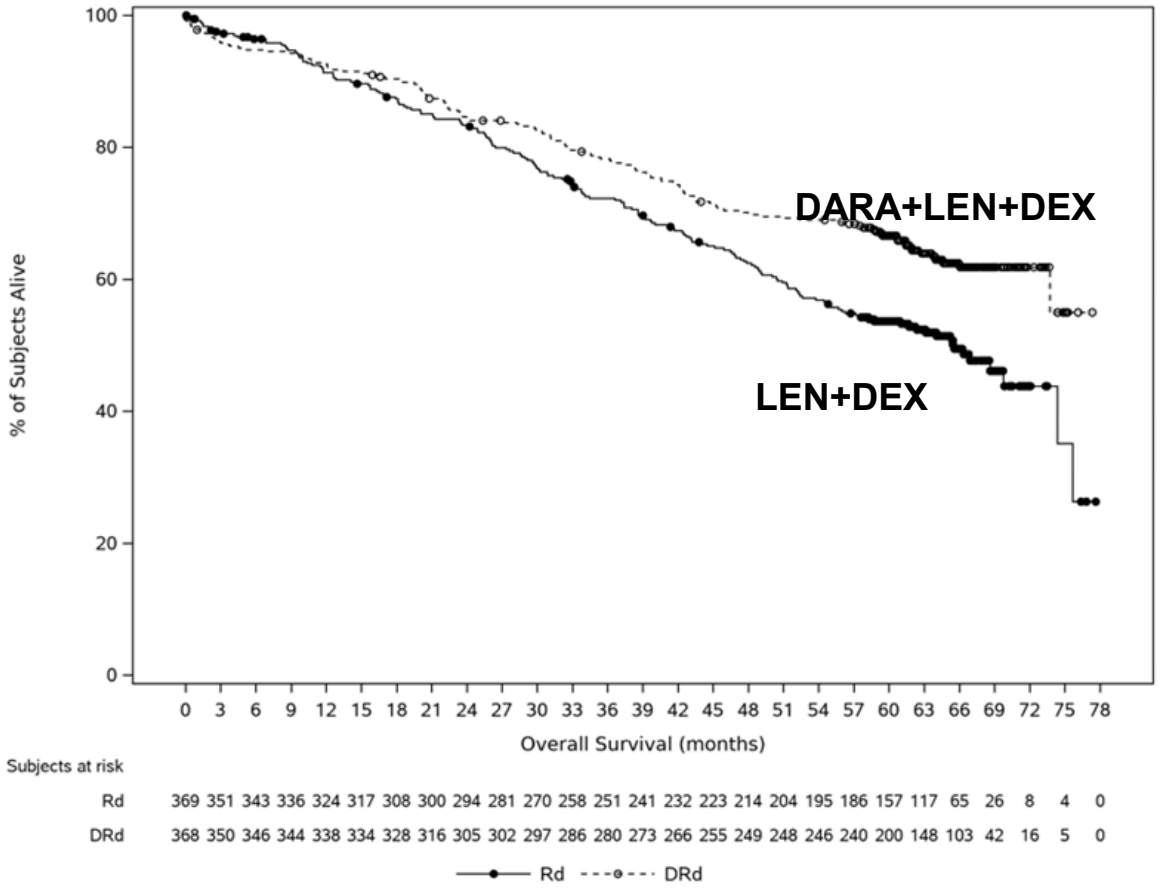


Table Summary of OS in the MAIA trial (ITT Population)

	DARA+LEN+DEX (n=368)	LEN+DEX (n=369)
Number of Events (%)	[redacted]	[redacted]
Median Months (95% CI)	NE [redacted]	65.5 [redacted]
HR (95% CI)	0.66 (0.53, 0.83)	
p-value	[redacted]	
60-Month OS Rate, %, (95% CI)	[redacted]	[redacted]

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;

Key issue: follow-up in the MAIA trial estimation of OS

MAIA OS data is relatively immature

Background

- Median follow up from most recent data cut 64.5 months
- Median OS was only just reached for LEN+DEX

Company

- Length of follow up is enough for a robust estimation of OS
- Follow-up from MAIA is now similar to the follow-up from the trial that informed TA587 (LEN+DEX)
- Additional follow up will not materially reduce long term modelling uncertainty

EAG comments

- Long-term benefit of DARA+LEN+DEX for OS is uncertain (OS data is still immature)
- DARA+LEN+DEX has longer survival than LEN+DEX therefore longer follow-up is needed
- A further [redacted] months [redacted] additional follow-up would inform the long term relative OS benefit
- OS of DARA+LEN+DEX has the largest impact on the ICER in the company's sensitivity analyses

Clinical expert comments

- Expect further data would secure OS benefit

Is the available data sufficient for decision making?

Abbreviations: DARA, daratumumab; DEX, dexamethasone; ICER, Incremental cost effectiveness ratio; LEN, lenalidomide; OS, overall survival

*73.6 month follow up data was published in December 2022. Due to timings, this could not be included within this appraisal

Clinical effectiveness compared with bortezomib regimens

NICE National Institute for Health and Care Excellence

Key clinical data for comparisons with bortezomib regimens

Company used IPD from ALCYONE to inform BOR+MEL+PRE comparison

Table Clinical trial designs and outcomes

	ALCYONE (Phase 3)
Design	Randomised, open-label, active-controlled, multicentre
Population	People newly diagnosed with symptomatic myeloma and ineligible for ASCT
Intervention	DARA+BOR+MEL+PRE
Comparator(s)	BOR+MEL+PRE
Follow up	40.1 months
Primary outcome	Progression-free survival (PFS)
Key secondary outcomes	Overall Survival (OS), Adverse events (AEs), Time to disease progression, Duration of response, Overall response rate, Complete response rate, Stringent complete response rate, Description of MRD status and depth, Proportion of subjects who achieve Very Good Partial Response (VGPR) or better.
Locations	162 sites in 25 countries
Used in model?	Yes

NICE

Abbreviations: ASCT, autologous stem cell transplant; BOR, bortezomib; DARA, daratumumab; IPD, individual patient data; MEL, melphalan; PFS, progression free survival; PRE, prednisone;

DARA+LEN+DEX versus BOR+MEL+PRE results

- A PS based IPW approach was used to account for differences in the populations between trials.
- The BOR+MEL+PRE arm of ALCYONE was weighted towards the DARA+LEN+DEX arm of MAIA
- The EAG and Company agree that the IPW approach produced more conservative estimates compared with other approaches considered
- 8 covariates used: Age, Gender, ECOG performance status, ISS stage at diagnosis, Creatinine clearance, Cytogenetic risk factors, Hepatic function, MM type (IgG/not IgG)

Table Estimates of effect of DARA+LEN+DEX relative to BOR+MEL+PRE – post-adjustment

OS HR (95% CI)	PFS HR (95% CI)
[redacted]	[redacted]

Figure OS KM Curves - IPW (ATT)

Figure PFS KM Curves - IPW (ATT)

Abbreviations: ATT, average treatment effect on the treated; BOR, bortezomib; DARA, daratumumab; DEX, dexamethasone; ECOG, eastern cooperative oncology group; HR, hazard ratio; IPW, inverse probability weighting; KM, kaplan-meier; LEN, lenalidomide; MEL, melphalan; OS, overall survival; PFS, progression free survival; PRE, prednisone; PS, propensity score

Evidence for the BOR+MEL+PRE comparison

Both Company and EAG Post-TE base-cases use parametric NMAs for the comparison with BOR+MEL+PRE

Background

- There is no RCT directly comparing DARA+LEN+DEX and BOR+MEL+PRE

Method	How is it used	Considerations
Parametric NMA	EAG and company base-case post-TE	• Relaxes the PH assumption and fits curves to all treatments simultaneously assuming the same parametric distributional form for each treatment • Is based on randomised comparisons
Piecewise NMA	Scenario analyses	• Company only adjusts for non-PH for the FIRST study and the PFS outcome
uITC	Scenario analyses	• Assumes all prognostic factors and effect modifiers have been adjusted for – can not be tested • Is not limited by a long chain linking the studies • Adjusts for clinically relevant prognostic factors and uses data from similar studies • Company consider this approach to be the most robust but updated base-case to match EAG preference at TE due to small impact

Abbreviations: BOR, bortezomib; DARA, daratumumab; DEX, dexamethasone; EAG, evidence assessment group; LEN, lenalidomide; MEL, melphalan; NMA, network meta-analysis; PH, proportional hazards; PRE, prednisone; RCT, randomised controlled trial; TE, technical engagement; uITC, unanchored indirect treatment comparison

Key issue: Assuming equivalence between BOR+MEL+PRE and BOR+CYC+DEX

Company and EAG disagree on the relative effectiveness of BOR regimens

Background: BOR+CYC+DEX is used in the NHS. No RCT was identified that would allow BOR+CYC+DEX to be included in the NMA

Company

- Assume BOR+CYC+DEX is clinically equivalent to BOR+MEL+PRE
- The MAIC *(CS Appendix D.6),* using data from ALYCONE and an observational study, not robust enough to include in the model and results were inconclusive with PFS and OS HRs close to 1 and CIs crossing 1
- Clinical equivalence assumption supported by naive comparisons, RWE and clinical expert opinion

EAG comments

- Prefer to use the MAIC, but accept it is not robust
- PFS, CI just spans 1 suggesting BORT+CYC+DEX may have an advantage

Clinical expert comments

- In essence BOR+MEL+PRE and BOR+CYC+DEX are equivalent
- BORT+CYC+DEX is generally more tolerable

Table MAIC Results: HR BOR+MEL+PRE vs BOR+CYC+DEX

	Adjusted MAIC
OS	[redacted]
PFS	[redacted]

Is it acceptable to assume equivalence between BOR+MEL+PRE and BOR+CYC+DEX?

Abbreviations: BOR, bortezomib; CI, confidence interval; CS, company submission; CYC, cyclophosphamide; DEX, dexamethasone; MAIC, matching adjusted indirect comparison; MEL, melphalan; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PRE, prednisone; RCT, randomised controlled trial;

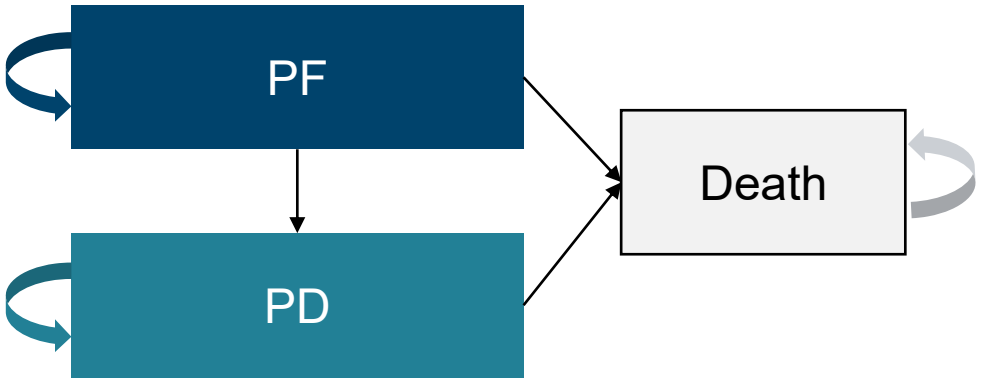
Cost effectiveness

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
  - Assuming that the OS benefits are maintained for the whole duration of the time horizon (i.e. no waning of treatment benefits)
- Assumptions with greatest ICER effect:
  - Treatment effect waning
  - Parametric curve used to extrapolate TTD
  - Market share of 2nd and 3rd line treatments

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;

How company incorporated evidence into model

MAIA trial is the main source of inputs into the model

Table Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	MAIA trial
Intervention efficacy	MAIA trial
Comparator efficacy	DARA+LEN: MAIA trial BOR+CYC+DEX/BOR+MEL+PRE: Parametric NMA
Utilities	MAIA trial
Costs	British National Formulary, pharmaceutical electronic market information tool (eMIT) , NHS Reference Costs 2019-20, previous NICE appraisals
Resource use	MAIA trial and ALCYONE trial
AEs	DARA+LEN+DEX / LEN+DEX: MAIA trial BOR+CYC+DEX/BOR+MEL+PRE: ALCYONE trial

Pooled utility data was used [redacted]
Company believe this approach is conservative against DARA+LEN+DEX given it was observed to produce an improvement in the EORTC-QLQ-C30 pain subscale

Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire; LEN, lenalidomide; MEL, melphalan; PRE, prednisone;

Extrapolation PFS/OS

Approach to extrapolating PFS and OS agreed at technical engagement

Background

- **DARA+LEN+DEX and LEN+DEX:** company and EAG use the same parametric models for OS and PFS
- **BOR+MEL+PRE:** company and EAG use the results of the parametric NMA for estimations
- **BOR+CYC+DEX:** approach depends on whether BOR+MEL+PRE equivalence is accepted (see slide 21)
  - Company: assume equivalence and use same extrapolation as BOR+MEL+PRE
  - EAG: use MAIC results

Figure OS extrapolation by regimen

Figure PFS extrapolation by regimen

Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; EAG, evidence assessment group; LEN, lenalidomide; MAIC, matching adjusted indirect comparison; MEL, melphalan; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PRE, prednisone;

Key issue: Extrapolation TTD (1/2)

The company base case uses a Gompertz extrapolation for DARA+LEN+DEX

Background

- TTD used to determine ToT to account for people that may discontinue treatment before progression

Company submission: Gompertz for DARA+LEN+DEX in base-case

- DARA+LEN+DEX and LEN+DEX TTD extrapolated using data from MAIA trial
- Choice of curve informed by best statistical fit and relationship between TTD and PFS
- Statistical fit for generalised gamma, gompertz and exponential is broadly comparable, with exponential and generalised gamma providing an upper- and lower-bound respectively
- Gompertz sits within clinically plausible range and aligns with relationship between PFS and TTD in MAIA (difference widening over time)
- Insufficient evidence to consider exponential as base case as it sits at an extreme end of plausible scenarios

EAG: exponential for DARA+LEN+DEX in base-case (lowest BIC)

- Generalised gamma and exponential have similar AIC. Exponential has lowest BIC, followed by gompertz
- The three curves give different extrapolations – results may be sensitive
- All curves demonstrate a reducing HR over time for TTD vs PFS
- The relationship between PFS and TTD after six years is unclear

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Abbreviations: AIC, akaike information criterion; BIC, bayesian information criteria; DARA, daratumumab; DEX, dexamethasone; EAG, evidence assessment group; HR, hazard ratio; LEN, lenalidomide; PFS, progression free survival; ToT, time on treatment; TTD, time to treatment discontinuation;

Key issue: Extrapolation TTD (2/2)

EAG and Company disagree on the most appropriate parametric model for TTD

Table Parametric distribution company and EAG base case - TTD

	Company	EAG
DARA+LEN+DEX base-case	Gompertz	Exponential
Rationale	Is within the plausible range / Aligns with relationship observed in MAIA	Has the lowest BIC

Figure DARA+LEN+DEX TTD extrapolations compared to base case PFS extrapolation

What is the most appropriate parametric model for DARA+LEN+DEX TTD?

Abbreviations: BIC, bayesian information criteria; DARA, daratumumab; DEX, dexamethasone; EAG, evidence assessment group; LEN, lenalidomide; PFS, progression free survival; TTD, time to treatment discontinuation;

Key issue: Treatment waning (1/3)

The company do not believe treatment waning should be included

Background: Company assume OS benefit of DARA+LEN+DEX is maintained for duration of time horizon. EAG prefer scenario where treatment waning starts at 12 years for a duration of 7 years

Company

- DARA mechanism of action does not support waning and waning is not in related guidance
- MAIA data shows:
  - OS HR decreasing over time (indicating an improved treatment effect in favour of DARA+LEN+DEX)
  - DARA+LEN+DEX is associated with a deeper and more sustained response which is inconsistent with treatment waning
- Studies of DARA in the relapsed setting show no indication of OS waning (POLLUX and CASTOR)
- EAG:
  - Applies waning only to DARA arm which is inappropriate (would expect it to be similar across arms)
  - Prefer a curve resulting in longer TTD for DARA arm. Intuitively, this would correlate to a longer OS (which is inconsistent with an OS waning assumption)
- OS waning leads to a relatively sharp decrease to the OS curve at the time waning is included

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

Key issue: Treatment waning (2/3)

EAG technical engagement comments response:

- Acknowledges that the there is no data on which to base treatment waning assumptions
- Period after the observed data is uncertain – POLLUX shows small attenuation of effect ~6.5 years
- Company's analysis of MAIA data shows HR is stable over 4-6 years, but the end of the curves are uncertain
- Preferred scenario assumes waning of the hazard for DARA+LEN+DEX relative to the hazard for LEN+DEX

Clinical expert comments:

- Clinical experts felt strongly that treatment waning is not appropriate in the myeloma space and agreed that if present would not be observed in the experimental arm only

NICE:

- 10 previous myeloma appraisals were reviewed, including three of DARA (TA763, TA783 and TA573), and none concluded that treatment waning should be included

Abbreviations: DARA, daratumumab; DEX, dexamethasone; LEN, lenalidomide; HR, hazard ratio;

Key issue: Treatment waning (3/3)

OS extrapolations and HR plots

Figure: OS extrapolations - EAG/Company base case + constant HR post MAIA scenario

Figure: HR Plots - EAG/Company base case + constant HR post MAIA scenario

Should treatment waning be included for decision making?

Abbreviations: DARA, daratumumab; DEX, dexamethasone; EAG, evidence assessment group; HR, hazard ratio; LEN, lenalidomide; OS, overall survival;

Other issues for committee's attention

Additional areas of uncertainty that cannot be resolved in current submission. Committee should be aware of these when making its recommendations

NICE National Institute for Health and Care Excellence

Generalisability of the MAIA trial results

Company and EAG prefer unadjusted results but note these may be conservative

Background

- People in both arms of MAIA trial received subsequent treatments not routinely commissioned in England (treatments either available via the CDF or that are not recommended in existing NICE guidance)

Company

- Proportion receiving treatments not routinely commissioned balanced across treatment arms at second-line (DARA+LEN+DEX: [redacted], LEN+DEX: [redacted])
- Performed IPCW adjustment for treatments not routinely commissioned in England
- IPCW generated OS HR lower than unadjusted ITT HR (IPCW: [redacted], ITT: 0.66 (0.53, 0.83))
- Used unadjusted HR in base case stating it may underestimate the relative difference and be conservative

EAG comments

- Proportion receiving treatments not routinely commissioned differed across treatment arms at third-line (DARA+LEN+DEX: [redacted], LEN+DEX: [redacted]) this might be expected to favour LEN+DEX.
- Prefer unadjusted values as IPCW relies on assumptions that can not be validated

Clinical expert comments

- Baseline characteristics are very close to the population seen in NHS clinical practice
- Post relapse treatments were not protocol specified and could differ from NHS clinical practice

NICE

Abbreviations: DARA, daratumumab; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; EAG, evidence assessment group; HR, hazard ratio; ITT, intention-to-treat; IPCW, inverse probability of censoring weights; CDF, cancer drugs fund;

Subsequent treatment considerations (1/2)

Market share assumptions are based on clinical input, which has a high variation in estimates

Company:

- Costs included in the model were based on the average of the market share estimates provided by seven clinical experts at an advisory board meeting

EAG comments

- The market share estimates differed between the company's clinical advisors
- EAGs clinical advisors noted that there is considerable variation in practice across centres and regions
- Treatment benefits at 2nd and 3rd line are based on the distributions of treatments received in RCTs but the costs are based on clinical opinion
- Acknowledge the company's approach is as good as any and do not identify an alternative
- Scenario analysis using individual clinical experts estimates shows ICERs are very sensitive to subsequent treatment assumptions

Abbreviations: EAG, evidence assessment group; RCT, randomised controlled trial; ICER, incremental cost effectiveness ratio;

Subsequent treatment considerations (2/2)

Background

- Drugs available only through the CDF are used at 2nd and 3rd line
- NICE position statement: products recommended in the CDF should not be considered as comparators, or included in a treatment sequence

Table Estimates of the use of drugs available only through the CDF

Treatment	Review	Company experts estimates of the proportion of patients that receive each treatment
DARA+BOR+DEX (TA573) – 2nd Line	In progress (ID4057)	Post DARA+LEN+DEX: 0%, Post LEN+DEX: 90%, Post BOR regimens: 30%
IXA+LEN+DEX (TA505) – 3rd Line	In progress (ID1635)	Post DARA+LEN+DEX: 15%, Post LEN+DEX:10% Post BOR regimens:40%

Company: Present results both including and excluding CDF treatments from cost inputs

EAG comments

- These treatments may not be made available for routine commissioning after the CDF period ends, and even if they do move to routine commissioning their cost is unknown

Abbreviations: BOR, bortezomib; DARA, daratumumab; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; CDF, cancer drugs fund

Other considerations

Severity Modifier:

- Company and EAG agree a severity modifier of 1 is appropriate based on absolute and proportional QALY shortfall

Equality considerations

- Myeloma is most frequently diagnosed in older people and is more common in men; its incidence is reported to be higher in people of African family background
- People with myeloma who are transplant-ineligible tend to be of older age (but age itself is not the criterion for eligibility for transplant) and have fewer treatment options
- Company also note that further lines of treatment following relapse after DARA treatment are being developed; people may be ineligible for trial participation or potential future treatment if having not received DARA

Innovation

- The company described DARA as a first-in-class, fully human monoclonal antibody that binds to the CD38 glycoprotein
- Clinical experts shared the same opinion and described the technology as a “game changer”

Are there any relevant equality or health inequality issues that should be considered in decision making, and if so how?

Abbreviations: DARA, daratumumab; EAG, evidence assessment group; QALY, quality adjusted life year;

Cost-effectiveness results

- All ICERs are reported in PART 2 slides because they include confidential comparator discounts
- All decision making ICERs are above the threshold normally considered as an effective use of NHS resources

Summary of key base case assumptions

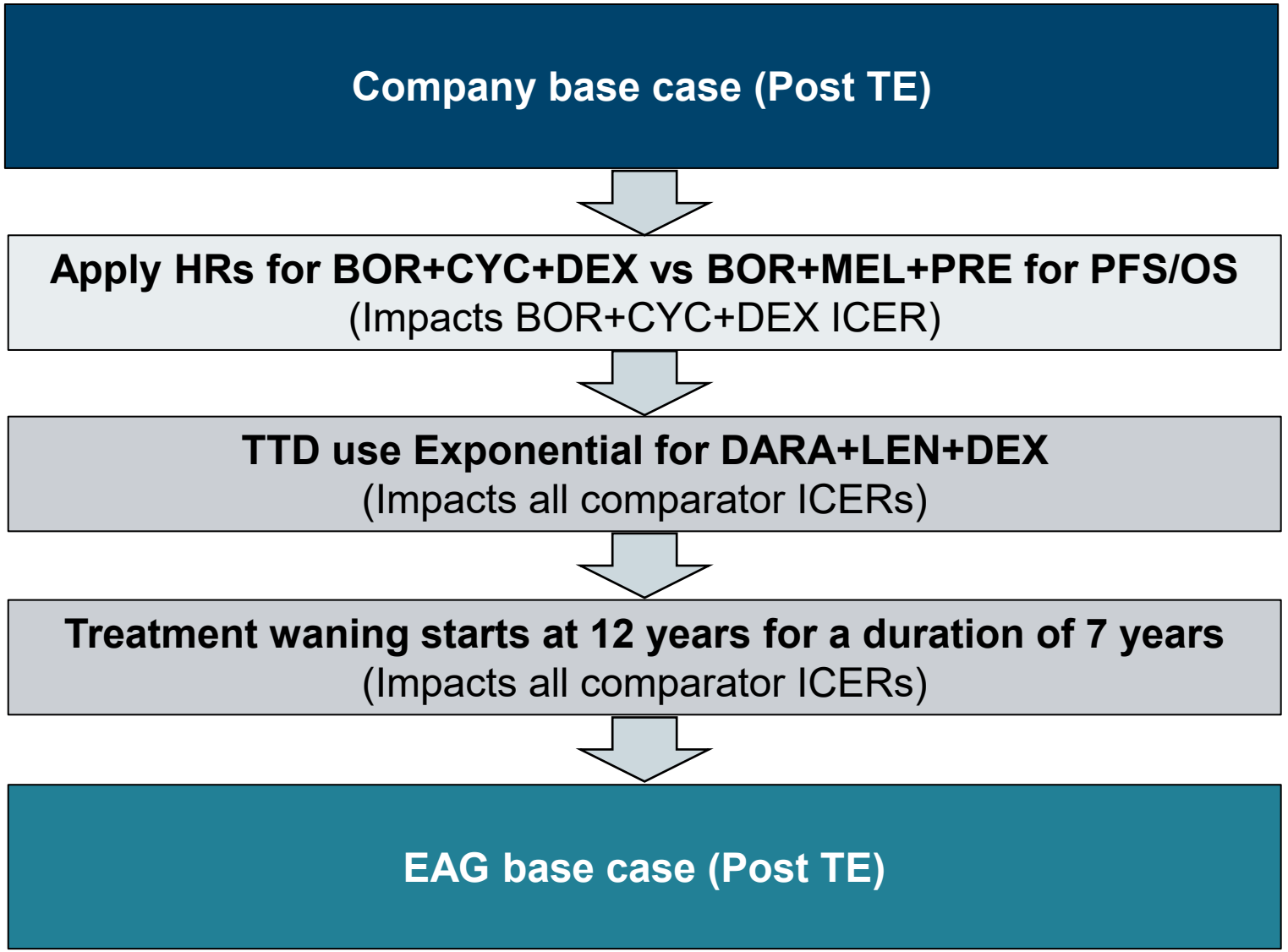
Three key differences in company and EAG base case

Table Assumptions in company and EAG base case

Assumption	Company base case	EAG base case	ICER impact
Comparators	LEN+DEX, BOR+MEL+PRE, BOR+CYC+DEX		N/A
Comparison of BOR+MEL+PRE vs DARA+LEN+DEX	Parametric NMA model		N/A
Equivalence between BOR regimens	Assumed equivalent	Used HRs estimated from the MAIC	Moderate
TTD DARA+LEN+DEX extrapolation	Gompertz	Exponential	Moderate
Treatment waning	Not included	Waning starts at 12 years for a duration of 7 years	High
Utility values	MAIA health-state utilities		N/A
Dose-reductions using RDIs	Included		N/A

Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; N/A, not applicable; PRE, prednisone; EAG, evidence assessment group; NMA, network meta-analysis; TTD, time to treatment discontinuation; HR, hazard ratio; MAIC, matching adjusted indirect comparison; RDI, relative dose intensity;

Cost-effectiveness results and scenario



Abbreviations: BOR, bortezomib; CYC, cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; MEL, melphalan; OS, overall survival; PFS, progression free survival; PRE, prednisone; EAG, evidence assessment group; HR, hazard ratio; ICER, incremental cost effectiveness ratio; TE, technical engagement;