Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more prior therapies [ID2701]

Slides for public – contains no confidential information

PART 1

Technology appraisal committee D [13 April 2023, 1st evaluation meeting]

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Key abbreviations

Belantamab mafodotin has been shortened to ‘Belantamab’ in the slides

1L / 2L / 3L / 4L / 5L	1st / 2nd / 3rd / 4th / 5th line	MM	Multiple myeloma
BCMA	B cell maturation antigen	NCRAS	National Cancer Registration and Analysis Service
CDF	Cancer Drugs Fund	NPP	Named Patient Program
CI	Confidence interval	OS	Overall survival
EQ-5D	European Quality of Life-5 Dimensions	PFS	Progression-free survival
HR	Hazard ratio	PSA	Probabilistic sensitivity analysis
HRQoL	Health-related quality of life	QALY	Quality-adjusted life year
ICER	Incremental cost-effectiveness ratio	RRMM	Relapsed refractory multiple myeloma
ITC	Indirect treatment comparison	TCR	Triple class refractory
ITT	Intention-to-treat	TTD	Time to treatment discontinuation
MAIC	Matched adjusted indirect comparison	TTNT	Time to next treatment
MHRA	Medicines and Healthcare products Regulatory Agency		

Background on multiple myeloma

- Multiple myeloma (MM) is an incurable blood cancer that arises from plasma cells in the bone marrow
- Myeloma cells supress the development of normal blood cells that are responsible for fighting infection, carrying oxygen around the body and blood clotting
- People with MM can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems
- **Relapsed refractory multiple myeloma (RRMM) is defined as disease that becomes non-responsive while on therapy or that is progressive within 60 days of the last treatment that previously achieved minimal response or better on prior therapy**

Incidence and survival for people with MM in England

Sources: Company submission, NICE final scope for ID2701 and NHSE budget impact analysis submission

Patient perspectives

Submission from Myeloma UK

- Myeloma is a relapsing and remitting cancer which evolves over time and becomes resistant to treatment
- People with multiply relapsed myeloma face a worse prognosis and a greater symptomatic burden which can result in reduced quality of life
- Limited treatment options at 5L+ can cause worry for people with myeloma, their carers and family members
- Experience with belantamab suggests that it may offer important benefits for people with multiple myeloma:
  - good progression-free survival and quality of life
  - avoidance of toxic side effects from combination steroids
  - less burdensome frequency of administration compared to other treatments
- Eye-related side effects* are frequently reported with belantamab but these are manageable and do not negate the overall treatment benefit

*includes keratopathy (a condition involving changes to the cornea) and loss of visual acuity

"…for people in my situation who have gone through a long list of treatments, there is a serious concern that you're running out of options…"

"I started taking belantamab …and so far it has been totally effective in controlling my myeloma. I'm in remission thanks to this treatment."

"The side effects that I've had with belantamab are minimal in comparison to those of other treatments. The eyesight problem is the only thing, but it's not a big issue and it does correct itself."

Clinical perspectives

Joint submission from 2 clinical experts

- Current treatment options for people who have had 4 or more prior therapies are limited with little evidence to support use
- Treatments with new targets and mechanisms of action are urgently required for people whose disease is triple class refractory
- Belantamab is the first antibody drug conjugate to be licensed for MM which targets the B cell maturation antigen (BCMA) protein
- People whose disease responds to belantamab have a long duration of response, demonstrating clinical efficacy of the technology
- Eye-related adverse events (including keratopathy):
    - requires regular ophthalmology/ optician review and frequent administration of preservative free eye drops. This will pose an additional burden for patients
    - blurring of vision will impact HRQoL but is reversible and intermittent
- Belantamab is suitable for all people, including those older and frailer

"As many patients at 5th line and beyond are remaining fit and physically well, this meets an unmet need for such patients who would otherwise predominantly receive limited treatment."

"This technology represents a step change for treatment of patients at 4th line and beyond."

Other considerations

Equality considerations

- Multiple myeloma (MM) is more common in:
  - men than in women
  - older people
    - 43% of new cases of MM in England are in people aged ≥75 years
  - people of African and Caribbean family background
- **No potential equality issues have been raised by stakeholders**

Source: NICE final scope for ID2701

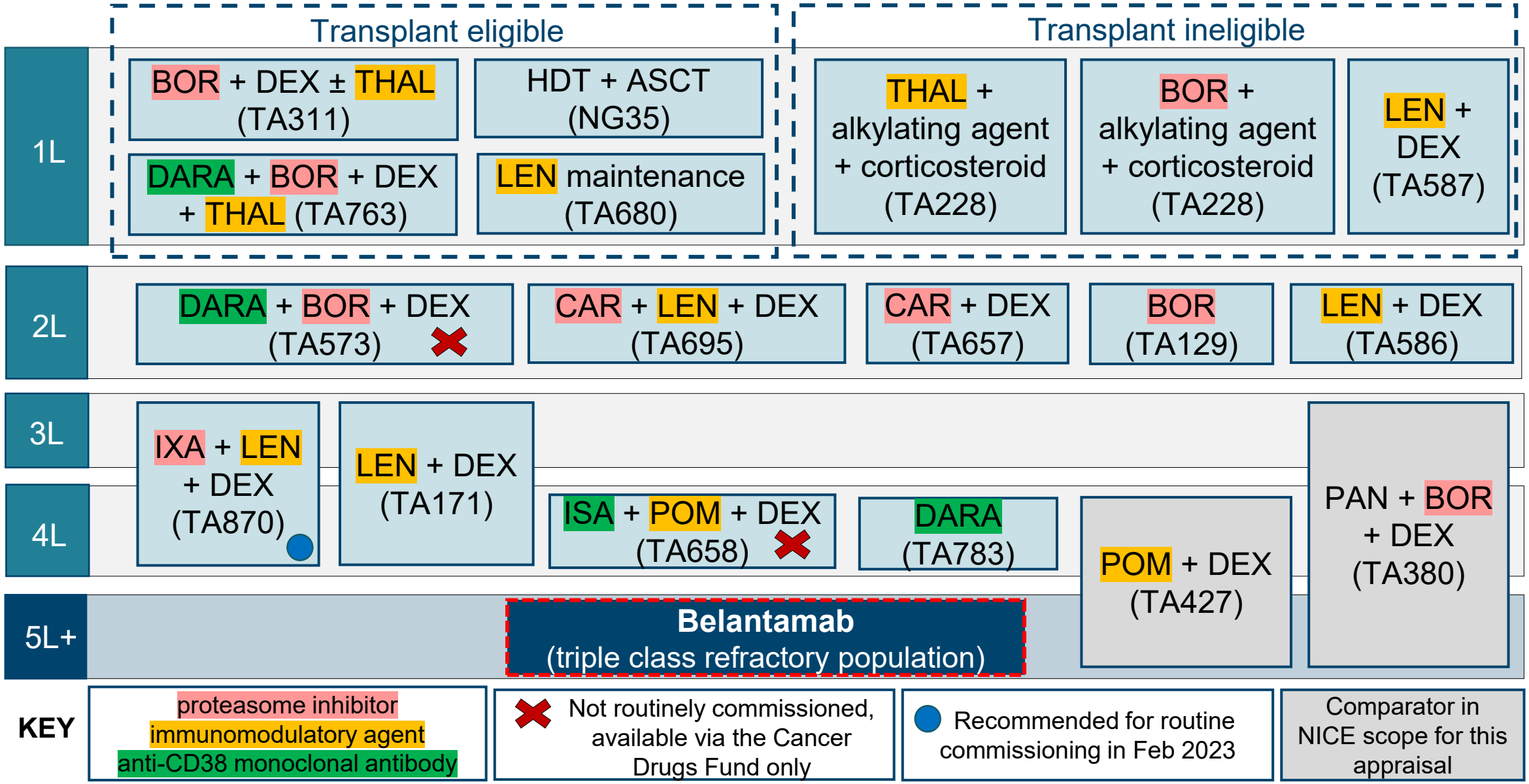
Key issues

Issue	Resolved?	ICER impact
Appropriateness of pomalidomide plus dexamethasone (PomDex) as a comparator to belantamab	No – for discussion	NA
Inappropriate source data presented as evidence for efficacy of belantamab and PomDex	No – for discussion	Large
Choice of severity modifier	No – for discussion	Large
Inappropriate selection of proxy progression-free survival (PFS) measure	No – for discussion	Unknown
Utility values	Yes – EAG consider company's updated utility values to be reasonable	Small

Belantamab mafodotin (Blenrep, GSK)

Conditional marketing authorisation (MHRA, January 2021)	Belantamab is indicated as a monotherapy for the treatment of multiple myeloma in adult patients, who have received **at least 4 prior therapies** and whose disease is refractory to at least: • **1 proteasome inhibitor** • **1 immunomodulatory agent** • **1 anti-CD38 monoclonal antibody** and who have demonstrated disease progression on the last therapy **5L+ and triple class refractory MM**
Mechanism of action	Monoclonal antibody conjugated with a cytotoxic agent that targets BCMA protein on the surface of myeloma cells
Administration	• Intravenous (IV) infusion, recommended dose is 2.5 mg/kg once every 3 weeks • Treatment continued until disease progression or unacceptable toxicity • Dose modifications recommended in response to certain adverse events (including corneal adverse events)
Price	• The list price is £5,707.83 for a 100mg vial • The company has a confidential commercial arrangement (simple discount patient access scheme – **updated post technical engagement**)

Treatment pathway for multiple myeloma



ASCT: autologous stem cell transplantation; BOR: bortezomib; CAR: carfilzomib; DARA: daratumumab; DEX: dexamethasone: HDT: high dose therapy: ISA: isatuximab; IXA: ixazomib; LEN: lenalidomide; PAN: panobinostat; POM: pomalidomide; THAL: thalidomide

Key issue: Appropriateness of PomDex as a comparator (1)

Comparators in NICE scope	Company considerations
Pomalidomide + dexamethasone (PomDex)	**Most relevant comparator for appraisal**
Panobinostat + bortezomib + dexamethasone (PanoBorDex)	Usage is limited and likely driven by desperation
Chemotherapy +/- a steroid and +/- thalidomide	Not relevant as use likely reflects palliative usage

Background

- Company state that there is no established standard of care for 5L+ RRMM which is also triple class refractory (TCR), but consider PomDex to be the most relevant comparator for this appraisal
- EAG consider that PomDex is rarely used in this population because it will have already been used earlier in the pathway (with isatuximab at 4L) → disease will be refractory to pomalidomide on relapse
- EAG did not identify an alternative comparator for consideration

Company response to technical engagement (1)

- NICE methods guide states that technologies recommended by NICE with managed access are not considered established practice in the NHS [and are not considered suitable comparators]
- When technologies recommended within the Cancer Drugs Fund (CDF) are not considered (isatuximab + PomDex – TA658), people would typically have daratumumab (TA783) or PomDex (TA427) at 4L

Key issue: Appropriateness of PomDex as a comparator (2)

Company response to technical engagement (2)

- People who receive PomDex at 4L and progress are typically not refractory to an anti-CD38 therapy and therefore are not considered to be at 5L+ and TCR
- So, most people in the 5L+ and TCR population would have daratumumab monotherapy at 4L, followed by PomDex in the 5L+ setting
  - supported by PomDex usage ([redacted]%) in National Cancer Registration and Analysis Service (NCRAS) dataset for 5L+ TCR MM population (reflects treatment pathway without CDF funded options)

EAG comments

- Uncertainty remains around appropriateness of PomDex as a valid comparator

Clinical expert comments

- PomDex is the most appropriate comparator within the NHS (excluding CDF approvals)
- PanoBorDex is rarely used and not appropriate for disease refractory to a proteasome inhibitor. Use of this regimen is likely out of desperation when all other options have been exhausted

Is PomDex the most relevant comparator for the population under consideration?

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial – DREAMM-2

Design	Phase 2, open-label, randomised, 2-arm (without a comparator) multi-centre study
Population	People with multiple myeloma who had disease progression on or after receiving ≥3 previous lines of anti-myeloma treatments, and are refractory to a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody
Intervention	• Belantamab 2.5 mg/kg (n=97 ITT population, n=[redacted] 5L+ only population) • Belantamab 3.4 mg/kg
Comparator(s)	None
Duration	Final analysis - [redacted] months follow-up
Primary outcome	Overall response rate (ORR) - assessed by an Independent Review Committee
Secondary outcomes	ORR (investigator assessment), clinical benefit rate, duration of response, time to response, progression-free survival, time to progression, overall survival, and HRQoL
Locations	58 centres in 8 countries, including 7 centres in the UK (n=[redacted])

- Results have only been considered for licensed dose (2.5 mg/kg) in this appraisal
- Trial permitted a single dose reduction for toxicities after first cycle (to 1.92 mg/kg)
- DREAMM-2 trial underpins the current GB licence for belantamab in the population under evaluation

DREAMM-2 key trial results

- In the intention-to-treat (ITT) population, n=[redacted] people received 3 prior lines of therapy which is outside of the population considered in this appraisal
- Company considered that the baseline characteristics (beside the number of prior lines received) and treatment effect of belantamab to be broadly comparable between the 5L+ only cohort and ITT population
- Therefore, it used the results from the ITT population to inform the appraisal and economic model

Outcome	Final analysis ([redacted] months follow-up)
	2.5 mg/kg (n=97) ITT population
Overall response rate*, n	[redacted] ([redacted]%) 97.5% CI: [redacted]
Median overall survival (OS), months	[redacted], 95% CI: [redacted]
Median progression-free survival (PFS), months	[redacted], 95% CI: [redacted]

Adverse events with belantamab (final analysis)

- Most frequent grade ≥3 adverse events reported were keratopathy ([redacted]%), anaemia ([redacted]%), thrombocytopenia ([redacted]%), and decreased lymphocyte count ([redacted]%)
- Recovery and resolution of keratopathy and best corrected visual acuity occurred for most people in DREAMM-2 with [redacted] reports of permanent loss of vision

*Overall response rate (based on Independent Review Committee assessment of response) was defined as the percentage of patients with a confirmed partial response or better according to the International Myeloma Working Group (IMWG) response criteria

Company's indirect treatment comparison (1)

National Cancer Registration and Analysis Service (NCRAS) dataset

- In the 5L+ and TCR MM population, company systematic literature review did not identify evidence:
  - directly comparing belantamab to PomDex or
  - PomDex alone for inclusion in an indirect treatment comparison (ITC) versus belantamab
- So, company used its real-world NCRAS study to inform efficacy data for PomDex (and PanoBorDex):
  - NCRAS study was a descriptive, retrospective, non-interventional study which uses routine patient-level health data from England available through the NCRAS dataset*
  - study identified a population† (n=[redacted]) which the company considered to be closely aligned with the licensed population for belantamab who did not have treatments funded through the CDF
  - n=[redacted] received PomDex at a dose [redacted]
  - outcomes included OS, time to next treatment (TTNT) and time to treatment discontinuation (TTD)

Proxy PFS

- PFS is not collected in the NCRAS dataset, so the company used TTNT from NCRAS and DREAMM-2 as a proxy to inform PFS in the model:
  - TTNT was not reported in DREAMM-2 and was derived by combining TTD and time to the start of next therapy from discontinuation (post-hoc analysis)

*combines linked data from the Hospital Episode Statistics, the Systemic Anti-Cancer Therapy dataset, National Radiotherapy Dataset and Office for National Statistics mortality data † Data were collected for patients diagnosed between January 2013 and December 2019

Company's indirect treatment comparison (2)

Unanchored matched adjusted indirect comparison (MAIC)

- Company initially conducted an unanchored MAIC using individual patient data from DREAMM-2 (ITT population, n=97) and aggregate data from NCRAS dataset (n=[redacted])
- Outcomes used in the MAIC included OS, PFS (comparison of TTNT used as a proxy) and TTD
- After matching baseline characteristics, the effective sample size of DREAMM-2 reduced to n=[redacted]
- Company considered that it was not possible to adjust for all imbalances in the important prognostic factors and treatment effect modifiers* because of limitations in the data reported in the NCRAS dataset
- Because of this and the small effective sample size, the company considered the MAIC results to be too uncertain. **Instead, it used a naïve ITC to inform its base-case for belantamab versus PomDex**

	Naïve comparison (median, months)		MAIC results (effective sample size [redacted])
	Belantamab (DREAMM-2, n=97)	PomDex (NCRAS, n=[redacted])	Belantamab vs PomDex (HR)
OS	[redacted] (95% CI [redacted])	[redacted] (95% CI [redacted])	[redacted] (95% CI [redacted])
TTNT (proxy PFS)	[redacted] (95% CI [redacted])	[redacted] (95% CI [redacted])	[redacted] (95% CI [redacted])
TTD	[redacted] (95% CI [redacted])	[redacted] (95% CI [redacted])	[redacted] (95% CI [redacted])

Company also presented results versus PanoBorDex but do not consider it a main comparator in this appraisal

*__Age, number of prior lines of therapy, extramedullary disease__, ECOG PS, (R-)ISS, cytogenetic risk, renal impairment, median time to diagnosis, prior ASCT, lytic bone lesions at baseline and sex (validated by UK clinical experts). **Bold = covariates included in MAIC**

Large impact on ICER

Key issue: Source data for comparative efficacy (1)

Background

- EAG considered that the company submission fails to present evidence that belantamab is a clinically effective intervention:
  - outcomes from DREAMM-2 and NCRAS lack a control, so it is not possible to determine the true impact/direction of belantamab, and their populations are likely to differ regarding prognostic factors
  - this is associated with substantial uncertainties that are impossible to calibrate in a meaningful way
  - DREAMM-2 and NCRAS dataset also differ in terms of study design/aims (single arm versus retrospective, non-interventional real world evidence study, which are both inherently subject to bias)
  - EAG agree with the company that the estimates produced via the unanchored MAIC are implausible and contribute to further uncertainty in the economic analysis due to low patient numbers
  - unadjusted efficacy results (naïve ITC) are subject to bias and lack validity for an economic analysis
  - **EAG considered that the cost effectiveness results should be viewed with extreme caution**

Large impact on ICER

Key issue: Source data for comparative efficacy (2)

Company response to technical engagement (1) – new efficacy evidence for belantamab

- Company presented new efficacy evidence for belantamab from a UK real-world evidence study in people who have received belantamab as part of its Named Patient Program (NPP)
- NPP study (n=[redacted]) is a non-interventional retrospective evaluation of people who have had [redacted] belantamab in line with its licensed indication (5L+ and TCR MM)
- Company deemed an unanchored MAIC versus PomDex (using data from NCRAS) unfeasible
- **Company selected a naïve comparison of belantamab (NPP) versus PomDex (NCRAS) to inform its revised base case because it considered the populations to be broadly comparable across the 2 datasets and both represent a UK population with 5L+ and TCR MM**

EAG comments (1) - new efficacy evidence for belantamab

- Company have not provided a valid reason for changing the intervention source from DREAMM-2 to NPP
- Feasibility of a MAIC has not been improved by using NPP and introduces additional uncertainty
- **Company's updated naïve ITC lacks validity and should not be used for an economic analysis**

Large impact on ICER

Key issue: Source data for comparative efficacy (3)

Company response to technical engagement (2) – 5L+ and TCR subgroup from DREAMM-3

- DREAMM-3 (n=325, ITT population) is an ongoing phase 3, open-label, randomised study comparing belantamab (2.5 mg/kg) with PomDex in people with RRMM who received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor. Study includes 10 UK sites.
- **DREAMM-3 did not meet its primary endpoint of PFS in the ITT population (primary analysis results)**
- Company presented results for a subgroup with 5L+ TCR MM (subgroup not pre-specified)
- Company consider that because the subgroup includes a [redacted] number of people on PomDex → [redacted] can be made regarding the comparative efficacy of belantamab versus PomDex
- Company state that because of the very high degree of uncertainty associated with this data (evidenced by the [redacted]), the inclusion in a scenario analysis was deemed inappropriate

DREAMM-3 subgroup: 5L + TCR MM	Belantamab (n=[redacted]) Median, months	PomDex (n=[redacted]) Median, months	Hazard ratio
PFS	[redacted], 95% CI: [redacted]	[redacted], 95% CI: [redacted]	[redacted] 95% CI: [redacted]
OS	[redacted], 95% CI: [redacted]	[redacted], 95% CI: [redacted]	[redacted] 95% CI: [redacted]

NA = not available
Maximum follow-up for belantamab subgroup = around [redacted] months

Company has requested for DREAMM-3 subgroup results to not be discussed in public

Large impact on ICER

Key issue: Source data for comparative efficacy (4)

EAG comments (2) - 5L+ and TCR subgroup from DREAMM-3

- Subgroup evidence from the only head-to-head comparative study [redacted]
- EAG acknowledge that [redacted] subgroup data with [redacted] generate great uncertainty
- However, EAG consider the randomised subgroup data from DREAMM-3 may be less biased because:
  - data comes from a single study rather than 2 independent studies (and so are more comparable)
  - DREAMM-3 data is [redacted] than NPP data ([redacted])
  - DREAMM-3 provides PFS results for both arms, so there is no necessity to use proxy-PFS measure
  - [redacted]
  - uncertainty associated with subgroup outcomes from DREAMM-3 [redacted] than that in the NPP study
- EAG analysis explored 5L+ TCR subgroup data from DREAMM-3 to estimate the cost-effectiveness of belantamab compared with PomDex → [redacted]
- **EAG considers randomised subgroup data from DREAMM-3 study preferable for assessment**

Company has requested for DREAMM-3 subgroup results to not be discussed in public

Large impact on ICER

Key issue: Source data for comparative efficacy (5)

Company response to technical engagement (3) – use of single arm trial data

- In previous NICE appraisals for RRMM, evidence from single arm trials has been sufficient to inform efficacy inputs used in the cost effectiveness analyses
- Use of single arm trials in oncology is common as they allow people quicker access to novel therapies
- DREAMM-2 lacks a comparator arm because there is not a clearly defined standard of care for people with triple-class refractory disease
- Small numbers of people with late stage disease means it can be challenging to obtain data sources with sufficient numbers and similar baseline characteristics for both belantamab and PomDex

EAG comments (3) - use of single arm trial data

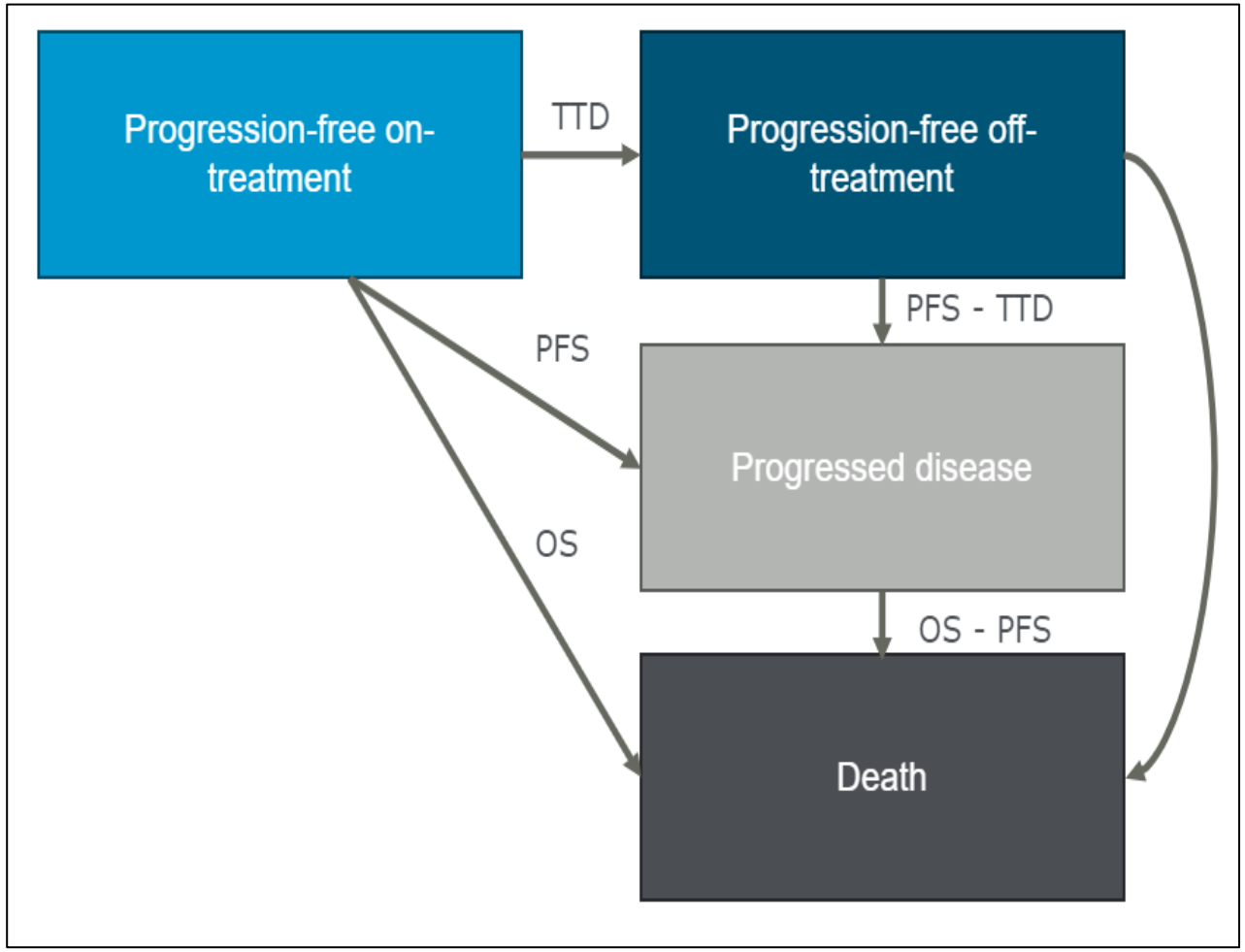
- EAG acknowledge that single arm trial data has been used in previous NICE appraisals
- For this appraisal, the EAG consider the use of single arm trial data inappropriate and insufficient to demonstrate the comparative clinical efficacy of belantamab

Is the company's updated naïve comparison appropriate for decision making? Should subgroup data from DREAMM-3 be used to inform the model?

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview



Model structure: partitioned survival model with 4 mutually exclusive health states:

- progression-free: on treatment
- progression-free: off treatment*
- progressed disease
- death

Population: adults with RRMM who have had at least 4 prior therapies and whose disease is triple class refractory and progressed on last therapy (5L+ and TCR MM)

Intervention: belantamab

Comparator: PomDex (for base case)

Cycle length: 1 week (no half cycle correction)

Time horizon: 25 years (lifetime)

EAG consider model structure is appropriate for modelling the decision problem

*progression-free off-treatment health state applied to people who have withdrawn from treatment before the disease has progressed

How company incorporated evidence into model

Key inputs reflect company revised base-case analysis after technical engagement

Input	Assumption and evidence source
Baseline characteristics	2.5 mg/kg belantamab arm of DREAMM-2 (ITT population)
Belantamab efficacy	OS, PFS and TTD from individual patient data in NPP
PomDex efficacy	OS, TTNT (proxy PFS) and TTD reconstructed Kaplan–Meier data from NCRAS
Survival curves	PFS → Exponential, OS and TTD → Weibull (independently fitted to both arms)
Utilities	• DREAMM-2 final analysis (both arms) • DREAMM-2 did not report EQ-5D data, so patient reported outcomes from EORTC-QLQ-C30 and EORTC-QLQ-MY20 were mapped to the EQ-5D-3L to generate health state utility values. No IV disutility applied for belantamab.
Costs and resource use	BNF, NHS reference costs, previous NICE multiple myeloma appraisals, PSSRU 2021, published literature, expert opinion
Subsequent treatments	Informed by NCRAS dataset for both belantamab and PomDex
Treatment waning	PFS capped at 2-years with a 50% waning applied after 1-year (both arms)
Drug wastage	None
Adverse events (AEs)	Grade ≥3 AEs costs and disutilities applied as a one-off cost and during the first 4 weeks on treatment (includes keratopathy)

BNF: British National Formulary; EORTC-QLQ: European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire; PSSRU: Personal Social Services Research Unit

QALY weighting for severity

NICE methods now include a QALY weighting system based on disease severity

Severity reflects future health lost by people living with a condition having current standard care

Health: length and quality of life (QALYs)

QALYs people without the condition (A)

QALYs people with the condition (B)

Health lost by people with the condition: QALY shortfall

Absolute shortfall: total = A – B

Proportional shortfall: fraction = (A – B) / A

NICE QALY weighting for severity used to decide whether to apply additional weight, and how much

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

- QALY weightings for severity can be applied based on whichever of absolute or proportional shortfall implies the greatest severity
- If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply
- Additional weight applied to QALYs within cost effectiveness calculation

Company QALY shortfall analysis

- Company consider that PomDex represents the most relevant comparator in this population
- Company used a **weighted average of PomDex and PanoBorDex** for calculating remaining QALYs for people with the condition on standard of care ([redacted]% on PomDex → weighted from usage in NCRAS dataset)
- After technical engagement, company updated data inputs for QALY shortfall calculations:
  - mean age ([redacted] years) and sex distribution ([redacted]% male) from NPP dataset (originally from DREAMM-2)
  - utilities from the [redacted]-month follow-up analysis of DREAMM-2 (originally 13-month follow-up analysis)
  - impact of updated data inputs on QALY shortfall calculations is minimal

Deterministic calculations	Mean QALYs	Absolute shortfall (has to be ≥12)	Proportional shortfall: • 0.85 to 0.95 for x1.2 • at least 0.95 for x1.7
General population	[redacted]	[redacted]	[redacted]
1) People with 5L+ TCR MM on PomDex	[redacted]	[redacted] ✖	[redacted]%
2) People with 5L+ TCR MM on PanoBorDex	[redacted]	[redacted] ✖	[redacted]%
3) Weighted average of 1) + 2)	[redacted]	[redacted] ✖	[redacted]% (95 CI: [redacted]% to [redacted]%)

- **Company consider QALY weight of x1.7 should apply**
- **EAG consider QALY weight of x1.2 to be more appropriate**

Large impact on ICER

Key issue: Choice of severity modifier (1)

Background – based on company's original proportional shortfall calculation

- Company consider that a QALY weighting of x1.7 should apply because:
  - 95% CI around the point estimate includes both the x1.2 and x1.7 multiplier
  - company probabilistic analysis explored the proportion of people for whom x1.7 weighting would apply by varying age at treatment start (using the same values in the PSA base case)
    - ➢ x1.7 weighting would apply to ~[redacted]%
- EAG consider that a QALY weighting of x1.2 should be applied:
  - weighting applied by company seems inconsistent with the NICE QALY weightings for severity
  - for company's deterministic base case, the correct weighting should be based on the point estimate

Company response to technical engagement (1)

- NICE methods guide does not specify that deterministic base cases are required for calculating severity weighting and that probabilistic approaches should be preferred when presenting the base case results
- The company consider that 'the new methods assume a probabilistic approach to severity'
- Using updated data inputs (NPP and final cut-off DREAMM-2 utility values):
  - 95% CI ([redacted]% to [redacted]%) around the point estimate ([redacted]%) includes both the x1.2 and x1.7 multiplier
  - company's updated probabilistic analysis suggests x1.7 weighting would apply to ~[redacted]% (population in NPP are slightly younger than the population of DREAMM-2 → mean age = [redacted] years)

Large impact on ICER

Key issue: Choice of severity modifier (2)

Company response to technical engagement (2)

- Company consider that the estimate of the proportional QALY shortfall falls on the cut-off between thresholds and that NICE methods state that in this situation the higher modifier should be applied
- **Company maintains its initial position that the most applicable severity weight is x1.7**

EAG comments (1)

- Mean QALYs in company model for PomDex ([redacted]) differs to value used in shortfall calculations ([redacted])
- NPP introduces more uncertainty around the data and inputs for the cost-effectiveness analysis
- EAG prefers NCRAS as a data source for deriving patient characteristics for the comparators as this was used by the company to derive evidence on real world use of PomDex and PanoBorDex
- NCRAS study → mean age for people on PomDex is [redacted] years, and [redacted]% of people are male
- EAG re-calculated the proportional shortfalls using NCRAS data above for PomDex only → company's model did not allow a naïve comparison of belantamab (using NPP data) versus PanoBorDex

Deterministic calculations		Mean QALYs	Absolute shortfall	Proportional shortfall
NCRAS	General population	[redacted]	[redacted]	[redacted]
	People with 5L+ TCR MM on PomDex	[redacted]	[redacted]	[redacted]%

Large impact on ICER

Key issue: Choice of severity modifier (3)

EAG comments (2)

- EAG note that the company consider PomDex to be the most relevant comparator → based on this, EAG considers the most applicable proportional shortfall calculations would be for PomDex
- If a probabilistic analysis was to be chosen, the EAG argue that the mean QALYs for current treatment should have been based on the company's main PSA analysis. This mean QALY value would incorporate uncertainty around all key parameters including age at which treatment is started
- EAG has recalculated the QALY shortfall for PomDex based on company's PSA main analysis and using NCRAS for age and sex distribution

Probabilistic calculations		Mean QALYs	Absolute shortfall	Proportional shortfall
NCRAS	General population	[redacted]	[redacted]	[redacted]
	People with 5L+ TCR MM on PomDex	[redacted]	[redacted]	[redacted]%

- **EAG maintains its initial position that the most applicable severity weight is x1.2**

Technical team comments

- NICE methods guide does not specify whether deterministic or probabilistic QALYs should be used for shortfall calculations

Are the company's QALY shortfall calculations appropriate?
Which severity weighting should be applied?

Unknown impact on ICER

Key issue: TTNT selected as a proxy for PFS

Background – based on company's initial naïve ITC using belantamab efficacy data from DREAMM-2

- PFS was not reported in NCRAS dataset → TTNT was used as a proxy for PFS in the model
- EAG considered that the use of proxy-PFS introduces uncertainty into the cost-effectiveness estimates:
  - TTNT is unlikely to be comparable across treatment arms because healthcare systems are likely to differ between DREAMM-2 trial centres and NCRAS (treatment pathways, availability of technologies)
  - proxy-PFS will tend to accumulate more QALY than using PFS

Company response to technical engagement

- Differences in healthcare systems may exist between DREAMM-2 trial centres and NCRAS NHS setting but is unlikely to impact comparability of outcomes such as TTNT
- Use of proxy-PFS has been accepted in previous NICE appraisals for multiple myeloma
- Company consider this issue is largely resolved because NPP and NCRAS are both UK studies so access to next treatment would be equitable

EAG comments

- TTNT and PFS from NPP are almost identical but uncertainty remains as to whether this also applies to NCRAS → cannot be addressed without access to PFS from a real-world dataset
- EAG consider TTNT is not an appropriate proxy measure for PFS, but no alternative is available

Is TTNT an appropriate proxy measure for PFS in the model?

Cost-effectiveness results

As confidential discounts are available for comparators and subsequent treatments in the pathway, ICERs will be presented in Part 2b slides

ICER ranges have been presented below for transparency

Summary – belantamab versus PomDex

- Company base case probabilistic ICER:
  - with no severity weighting: above £30,000/QALY gained
  - with 1.2 severity weighting: above £30,000/QALY gained
  - with 1.7 severity weighting: below £30,000/QALY gained **(company preferred ICER)**
- **EAG considers the cost-effectiveness results to be implausible because of limitations in the clinical evidence → no preferred ICER presented**
- EAG exploratory analysis for DREAMM-3 subgroup (5L+ and TCR MM) also presented in Part 2b slides

Managed access

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (**maximum of 5 years**) without **undue burden**.

Managed access proposal in company submission (prior to NPP data being presented)

- Company considered that access to belantamab via the CDF would allow real-world evidence collection in an NHS setting improving the feasibility of a comparison with PomDex efficacy outcomes (from NCRAS)
  - outcome data: OS, TTD and TTNT, 3 years expected duration of managed access
  - data source: Systemic Anti-Cancer Therapy (SACT) dataset and Blueteq

Ongoing studies → DREAMM-3 (estimated study completion date: March 2025)

- DREAMM-3 forms part of the specific European Medicines Agency (EMA) regulatory obligation for DREAMM-2
- Further data collection from DREAMM-3 not included in company proposal

NICE feasibility assessment of company's managed access proposal → further data collection would be unlikely to resolve uncertainty around comparative efficacy

Key issues

Issue	Resolved?	ICER impact
Appropriateness of pomalidomide plus dexamethasone (PomDex) as a comparator to belantamab	No – for discussion	NA
Inappropriate source data presented as evidence for efficacy of belantamab and PomDex	No – for discussion	Large
Choice of severity modifier	No – for discussion	Large
Inappropriate selection of proxy progression-free survival (PFS) measure	No – for discussion	Unknown
Utility values	Yes – EAG consider company's updated utility values to be reasonable	Small

Thank you.

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