Daratumumab in combination for treating newly diagnosed systemic amyloid light-chain amyloidosis

Technology appraisal committee B

PART 1: For PUBLIC – contains no ACIC information

Chair: Charles Crawley

Lead team: Sanjeev Patel, Tony Wootton

Evidence assessment group: York CRD and CHE Technology Assessment Group

Technical team: Sharlene Ting, Yelan Guo, Carl Prescott, Henry Edwards

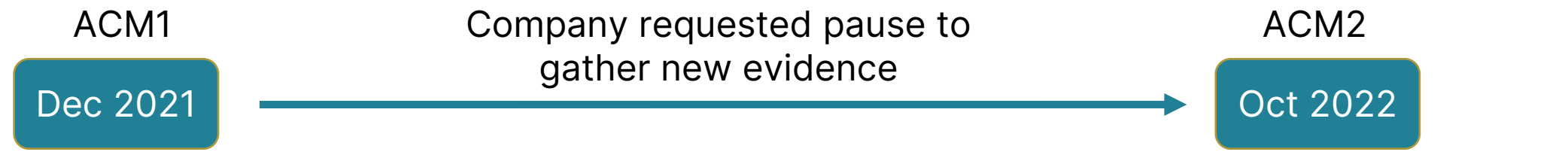
Company: Janssen-Cilag

13th October 2022: 2nd meeting

Appraisal history

Preliminary recommendation

Daratumumab plus bortezomib, cyclophosphamide and dexamethasone (daratumumab in combination) is **not recommended**, within its marketing authorisation, for treating newly diagnosed systemic amyloid light-chain (AL) amyloidosis in adults



ACD released

ACD consultation comments

- Company: new evidence and analyses
- Myeloma UK
- Clinical expert

NICE

Abbreviations: ACD, appraisal consultation document; ACM, appraisal committee meeting

ACD noted high level of uncertainty

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Clinical

- No evidence on people with more severe complications from ongoing clinical trial, ANDROMEDA
- Overall survival (OS) data from ANDROMEDA immature
  - No difference between daratumumab in combination and standard care seen

Economic

- Used observational studies to model full licensed population and extrapolate long-term OS by haematological response. Company preferred EMN23 post-2010. ERG preferred ALchemy. Neither explored fit compared to ANDROMEDA OS curves
- Haematological response used as surrogate endpoint for OS; confounding not fully addressed
- Effects of treatment switching on consistency of modelled distribution of haematological response between observational studies and ANDROMEDA uncertain
- Company used haematological response at 6 months, but NHS practice usually assess response at 3 months
- Some utility values lack face validity
- Company base case did not include stopping rule as from trial or market authorisation
- Administration costs for bortezomib and daratumumab underestimated

Other considerations: daratumumab in combination

- is innovative and there may be benefits not captured in model e.g. benefits for people with concomitant multiple myeloma
- does not meet end-of-life criteria
- is not eligible for Cancer Drugs Fund

Abbreviations: ERG, Evidence Review Group

Key issues

- **Haematological response criteria**
  - Which criteria were used in ALchemy?
  - Are the haematological response criteria applied in ANDROMEDA used in NHS clinical practice?
- **EMN23-UK vs ALchemy:** Which data provides credible overall survival extrapolations? Re-categorised EMN23-UK or unadjusted ALchemy?
- **Additional sustained response of daratumumab monotherapy and associated long-term survival benefit**
  - Is it appropriate to model a sustained response for daratumumab monotherapy compared with standard care and extrapolate its effect on overall survival in the longer term?
  - Is it appropriate to apply an expected survival benefit to all haematological response states?
- **Confounding:** Has the issue of confounding in the relationship between haematological response and overall survival been adequately addressed?
- **Utility values:** Are the utility values plausible?
- **Administration cost for daratumumab and bortezomib:** Which estimate best reflects the likely NHS administration cost of daratumumab and bortezomib? £99, £123, 332?
- **End-of-life criteria:** Has any new evidence been presented to change the committee's views on whether daratumumab meets end-of-life criteria for full population?
- **Innovation:** Are there any additional benefits not captured in the model?
- **Cancer Drugs Fund:** Could further data collection reduce uncertainty in the model?

Clinical evidence recap

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Background

Amyloid light-chain (AL) amyloidosis

- Light chain proteins clump together and deposit in organs
- Non-specific symptoms → delayed diagnosis
- UK annual incidence 1 in 100,000; increases with age; 4-year survival 54%
- Death commonly from heart failure; stage 3b most severe cardiac involvement
    - ~20% UK patients, median survival 4.5 months vs 31.1 months for cardiac stage 3a

Treatment pathway, company positioning and marketing authorisation of daratumumab (Darzalex, Janssen-Cilag) in combination with bortezomib, cyclophosphamide and dexamethasone

- Current treatment follows multiple myeloma pathway: no licensed options; chemotherapy
    - Aim: rapid and durable haematological response

1st

Newly diagnosed AL amyloidosis

Bortezomib with cyclophosphamide and dexamethasone (BORT/CYC/DEX)

If BORT contraindicated or not tolerated, LEN/DEX or MEL/DEX (rarely used)

Daratumumab in combination?

NICE **Marketing authorisation:** adults with newly diagnosed systemic light chain amyloidosis

Source: Company submission B.1.3.1. **Abbreviations**: AL, amyloid light-chain; BORT, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan

ANDROMEDA: ongoing randomised open-label trial

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Trial population broadly generalisable to NHS but excluded people with severe complications. People can switch treatment after 3 or 6 cycles. Daratumumab monotherapy after 6 cycles up to 24 cycles

Adults newly diagnosed AL amyloidosis, ≥1 organ, haematological disease, ECOG 0-2

Exclude: Mayo cardiac stage 3b, NYHA IIIB or IV heart failure

Daratumumab in combination (cycle 1-6)
n=195

BORT/CYC/DEX (cycle 1-6)
n=193

People can **switch** to another treatment after ③ or ⑥ cycles:

Haem. response	Organ function		
	Improve	Stable	Worsen
CR			③ ⑥
VGPR			③ ⑥
PR			③ ⑥
NR	⑥	⑥	③ ⑥

1º outcome
- Overall complete haematological response*

2º outcome
- MOD-PFS*
- **Overall survival – not in model; data from ALchemy or EMN23**
- Adverse events
- HRQoL (EQ5D-5L*; SF36v2 – not in model)

*in model

Daratumumab monotherapy
- if after 6 cycles, ≥PR + stable or improved major organ failure
- every 4 weeks until MOD-PFS or **max. 24 cycles**
N.B. NOT in licence

Post-treatment observation until 200 MOD-PFS events

Long-term follow up 5 years after last randomised person

Source: Company submission B.2.3.1. **Abbreviations:** AL, amyloid light-chain; BORT, bortezomib; CR, complete response; CYC, cyclophosphamide; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; EQ5D5L, EuroQol 5 dimension; Haem., haematological; HRQoL, health-related quality of life; MOD-PFS, major organ deterioration progression-free survival; NR, no response; NYHA, New York Heart Association; PR, partial response; SF36, 36-Item Short Form Health Survey; VGPR, very good partial response

ANDROMEDA results: 12-month landmark analysis

Haematological response, usually assessed at 3 months, is a surrogate endpoint for overall survival. Daratumumab improves haematological response better than standard care

	Haematological response, % (95% CI) at 12-month landmark analysis 13 Nov 2020 (median 20.3 months)	
	Daratumumab in combination (n=195)	BORT/CYC/DEX (n=195)
CR	59% XXXX	19% XXXX
Odds ratio (95% CI)		5.0 (3.7, 9.4)
VGPR	XXXX	XXXX
PR	XXXX	XXXX
NR	XXXX	XXXX

Source: Company submission Tables 17 and 22, Figure 7. **Abbreviations:** BORT, bortezomib; CI, confidence interval; CR, complete response; CYC, cyclophosphamide; DEX, dexamethasone; NR, no response; PR, partial response; VGPR, very good partial response

ANDROMEDA 2º endpoint: overall survival interim analysis

Data immature; another analysis planned XXXX. Daratumumab's effect on overall survival is uncertain; no difference seen between arms at planned interim analysis

	Overall survival at interim analysis 14 Feb 2020 (median 11.4 months)	
	Daratumumab in combination (n=195)	BORT/CYC/ DEX (n=193)
N events (%)	XXXX	XXXX
N censored (%)	XXXX	XXXX
Hazard ratio (95% CI)	XXXX	
6-month survival % (95% CI)	XXXX	XXXX
12-month survival % (95% CI)	XXXX	XXXX
18-month survival % (95% CI)	XXXX	XXXX

Source: Company submission Table 22, Figure 7. **Abbreviations:** BORT, bortezomib; CI, confidence interval; CYC, cyclophosphamide; DEX, dexamethasone; N, number; OS, overall survival

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Observational studies used to inform model: ALchemy and EMN23

Source of overall survival data has large impact on cost-effectiveness results. Large overlap in UK-based population in EMN23 and ALchemy

- OS by haematological response modelled using data from observational studies (include cardiac stage 3b) for standard care (BORT/CYC/DEX), then applying ANDROMEDA relative treatment effect for daratumumab in combination
- **Company**: preferred EMN23 post-2010 subset. ALchemy: survival curves for CR and VGPR cross
- **ERG**: preferred ALchemy. EMN23: different standard care and assessment time points in other countries, 'looser' interpretation of internationally recommended response criteria

	EMN23 post 2010 – Company	ALchemy – ERG
N	XXXX **1156 UK based**	**1194** (ITT cohort); 1133 (1-month landmark cohort)
Design	Retrospective	Prospective
Recruitment	2011-2018	2010-2019
Setting	**UK (38%)**, remainder in Europe	**UK**
Clinical setting	UK: National Amyloidosis Centre	UK National Amyloidosis Centre
Assessment time	Not reported	1, 3, 6 months
1st line treatment	XXX bortezomib-based	100% bortezomib-based
Follow-up median	XX months	NR; OS to **125 months**

Source: ERG report post-FAC 3.2.1.2. **Abbreviations:** BORT, bortezomib; CR, complete response; CYC, cyclophosphamide; DEX, dexamethasone; N, number; NR, not reported; OS, overall survival; VGPR, very good partial response

Cost-effectiveness evidence recap

NICE National Institute for Health and Care Excellence

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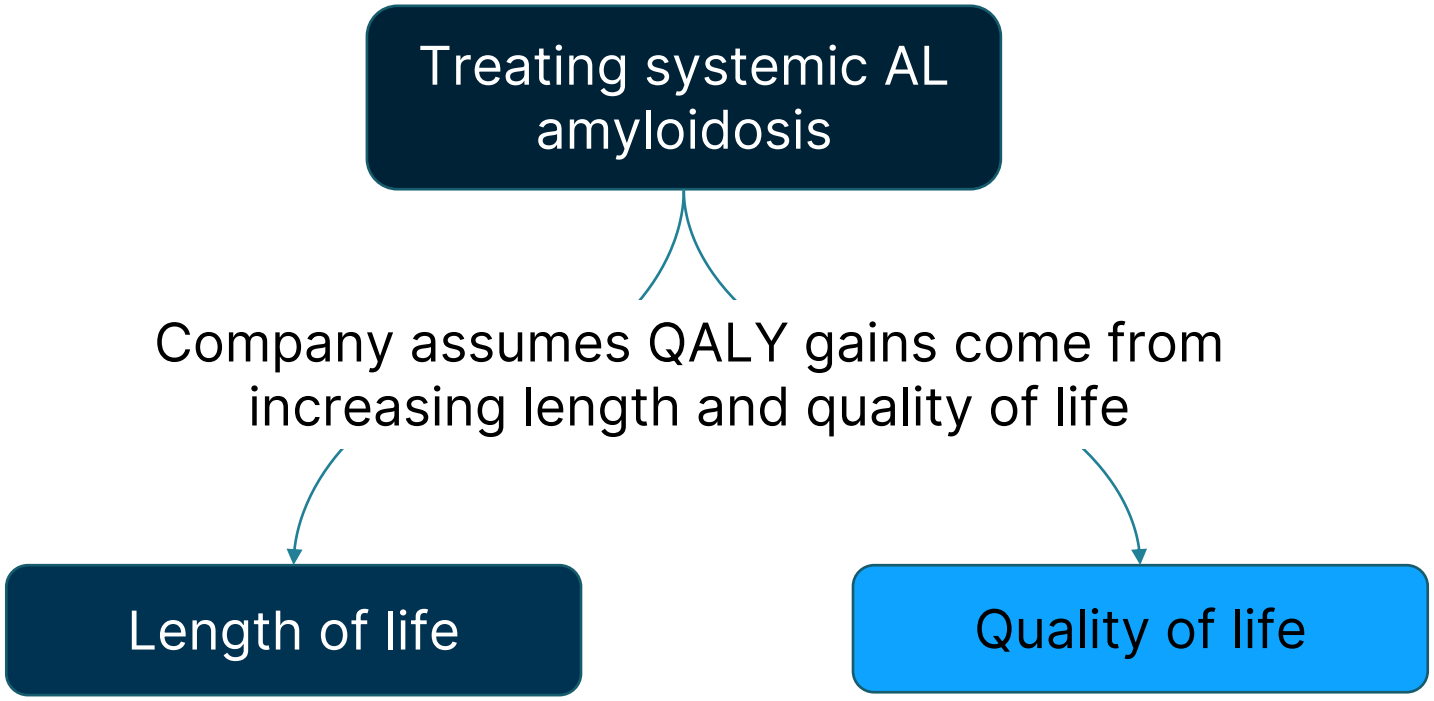
How quality-adjusted life years accrue in company's model

ANDROMEDA interim analyses have not shown that daratumumab in combination compared to standard care prolongs life and improves health-related quality of life



↑ QALYs from ↑ proportion of people whose condition shows complete haematological response and so have better quality of life; lower risk of progression to 2nd-line therapy and end-stage organ failure; longer life

Abbreviations: AL, amyloid light-chain; QALY, quality-adjusted life year

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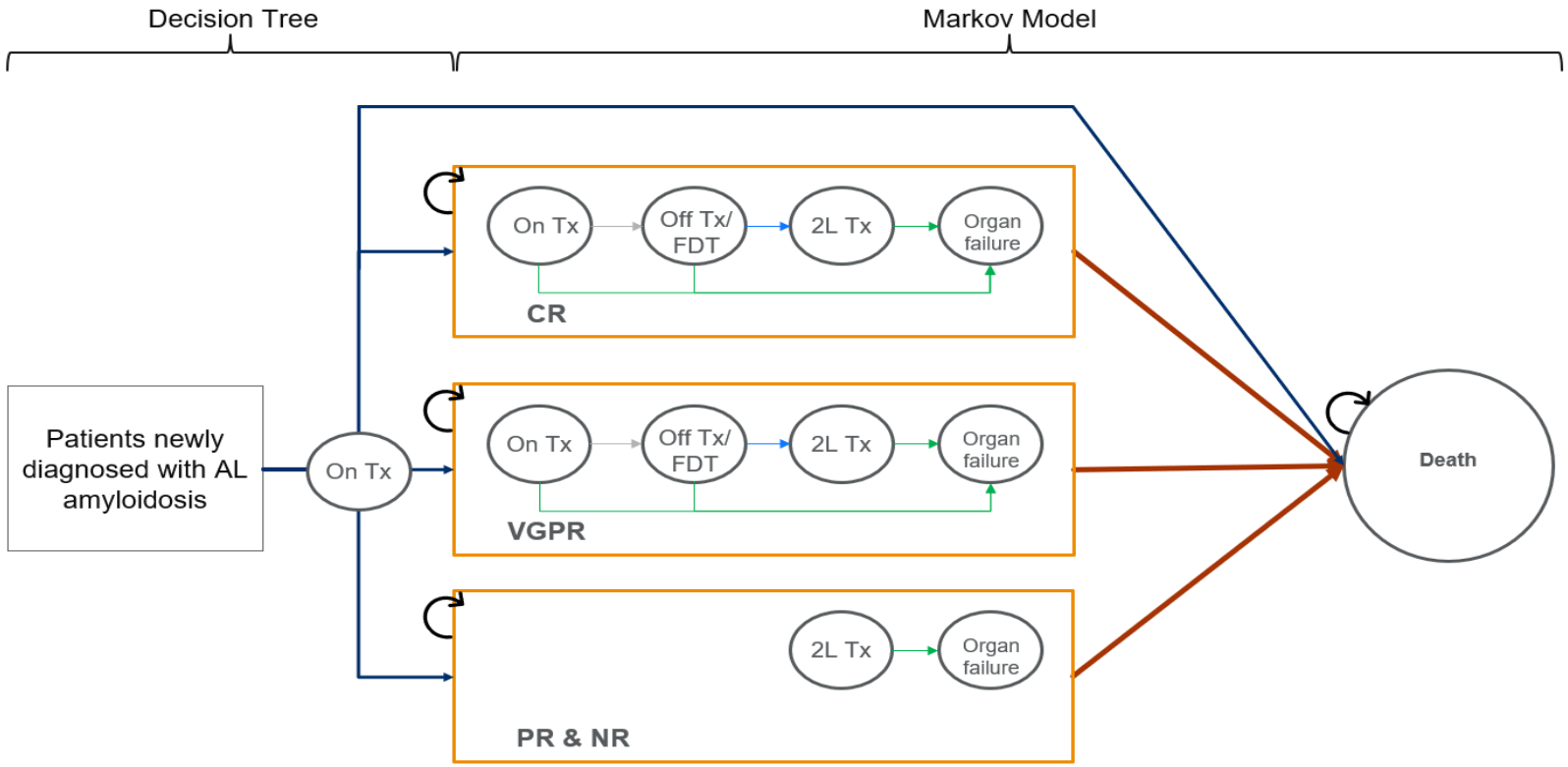
Company model overview at ACM 1

Model structure appropriate for decision making but partial and no response groups should be modelled separately to reflect NHS clinical practice



- Cohort model: 5 Markov health states, 28-day cycle, ½-cycle correction, 35-year time horizon, 3.5% discount rate
- People on daratumumab enter states based on response from ANDROMEDA 12-month landmark analysis after **3 cycles as per NHS practice (ERG base case)** or **6 cycles as per trial (company base case)**
- Treatment effect **not assumed** to be sustained over time
- **24-cycle stopping rule for daratumumab** as per trial (scenario)

Source: Company submission Figure 16. **Abbreviations:** 2L, 2nd-line; AL, amyloid light-chain; CR, complete response; FDT, fixed dose treatment; NR, no response; PR, partial response; Tx, treatment; VGPR, very good partial response

Committee preferences at ACM 1 (1)

ACD	Committee preferences	Company addressed?	ERG comments
3.9	Model partial and no response groups separately	Yes	Appropriate
3.4	Include people with end-stage cardiac and renal disease in modelled population	Yes. Primary source of data for standard care is EMN23-UK that includes people with end-stage cardiac and renal disease	• EMN23-UK suitable alternative to ALchemy (high overlap; similar baseline characteristics) • Unclear if outcomes are similar
3.11	Use ALchemy data for distribution of haematological response for standard care and use relative effectiveness from ANDROMEDA for daratumumab in combination	Partially. Used re-categorised EMN23-UK data as alternative to ALchemy because: • patient-level data for ALchemy not available • large overlap in EMN23-UK and ALchemy • need to re-categorise data to align with ANDROMEDA	• Substantial loss of data from re-categorisation of EMN23-UK • Unable to assess impact fully • Large effect on ICER

 Abbreviations: ICER, incremental cost-effectiveness ratio; NR, no response; PR, partial response

Committee preferences at ACM 1 (2)

ACD	Committee preferences	Company addressed?	ERG comments
3.11	Assess haematological response and adjust analyses for consistency in response categorisation between ANDROMEDA and ALchemy • Base case: 3 months • Scenario: 6 months	• Yes. Used EMN23-UK adjusted to align with ANDROMEDA in terms of response categorisation for people who had switched treatments and criteria used to define each response category • Assessment time points as preferred	• EMN23-UK appropriate source • Censored data: 0.5% at 3 months and 2.3% at 6 months
3.12	Provide estimates of association between haematological response and OS to account for confounding	• No. Provided multivariate analyses investigating potential confounders • Concluded no evidence of confounding	• Uncertainty remains as results suggest failure to adequately estimate parameters of interest
3.12	Use ALchemy to extrapolate OS, but explore fit compared with OS from ANDROMEDA	• Partially. Used re-categorised EMN23-UK instead of ALchemy to extrapolate OS by haematological response • Did not compare with ANDROMEDA OS curves	• EMN23-UK appropriate source • ANDROMEDA OS data too immature for comparison

 Abbreviations: OS, overall survival

Committee preferences at ACM 1 (3)

ACD	Committee preferences	Company addressed?	ERG comments
3.13	Use SF36v2 data from ALchemy to validate company's utility set	No. Unable to access patient-level data from ALchemy to validate utility values	-
3.14	Apply stopping rule for daratumumab (max 24 cycles)	Yes. Daratumumab given for maximum of 24 cycles	-
3.15	Increase daratumumab and bortezomib administration costs from £99 to £332	Partially. Base case: £99. Scenario: £332	-
3.18	Include autologous stem cell transplant in model	Yes. Included at second-line therapy	-
3.17	Apply estimates from UK expert advisory board for 2nd and 3rd line treatments	Yes. Included as per company's original submission	-
-	-	From cycle 7 onwards, increased relative survival benefit of daratumumab vs standard care by 4.4% (based on survival benefit of daratumumab monotherapy from ANDROMEDA at median 20 months follow-up)	• Increased applied to overall OS for daratumumab arm, to **all haematological response categories**

Abbreviations: ICER, incremental cost-effectiveness ratio; SF36, 36-Item Short Form Health Survey

ACD consultation responses

Responses received from:

- Company: Janssen-Cilag
- Clinical expert
- Patient group – Myeloma UK

Stakeholder comments

Patient group (Myeloma UK) and clinical expert

- **Lack of a haematologist among the clinical experts**
  - Important omission as haematologists would be lead consultants for this condition
  - Better placed to advise on generalisability of ANDROMEDA and timelines for assessing haematological response

- **Economic model did not include costs related to progression to end stage renal failure**
  - Dialysis costs between £15,000 to £60,000 per year. Benefit of delaying or preventing progression to end stage renal failure should be included in model

- **Unmet need with no recommended licensed options, step change in management**
  - If approved, daratumumab in combination would be the first treatment for newly diagnosed AL amyloidosis

ERG comments

Model includes progression to end-stage organ failure; assumes some people need:

- haemodialysis and peritoneal dialysis with related costs
- transplant or surgical intervention with related costs e.g. kidney transplant over £12k

Abbreviations: AL, amyloid light-chain

ACM1 issues surrounding observational studies

Marketing authorisation
Full licensed population

ANDROMEDA
- Excludes severe disease
- OS data immature

Observational study (ALchemy)
- Treatment switching: lack of consistency in categorising response between ANDROMEDA and ALchemy
- Long-term OS extrapolated based on haematological response only at 3 or 6 months
  - Possible confounding between better haematological response and living longer
  - Did not compare ANDROMEDA OS with ALchemy extrapolated OS curves
- Assume DARA relative effect in ANDROMEDA generalisable to severe disease

Company ACD response (EMN23-UK)
- Need patient-level data – only EMN23 available (UK cohort **~95%** overlap with ALchemy)
- Censored and re-categorised EMN23-UK based on people who had switched treatments **and** response criteria definitions
- Removed people who had switched treatments: **0.5% at 3 months and 2.3% at 6 months**
- In aligning response criteria definitions, lost data: **18% at 3 months and 22% at 6 months**

ERG comments
- EMN23-UK suitable alternative to ALchemy
  - Cannot check if outcomes similar (no unadjusted data for EMN23-UK)
- Unclear impact of censored data: no outcomes with only censoring for treatment switching
- Missing data from EMN23-UK likely to be at random
- Improved haematological response outcomes for EMN23-UK than ALchemy
- **Scenarios using unadjusted ALchemy to assess impact of re-categorised EMN23-UK**

Abbreviations: DARA, daratumumab; OS, overall survival

Haematological response criteria

Haem. Response	Original (Comenzo 2012)	Updated (Palladini 2021)	Algorithm used for response re-categorisation
CR	Neg. serum and urine immunofixation and normal FLC ratio	• No amyloid light chain (free and/or part of complete immunoglobulin): neg. immunofixation electrophoresis of serum and urine **AND** • **Either** FLC ratio in reference range **or** uninvolved FLC > iFLC ± abnormal FLC ratio	• Neg. serum IFE + iFLC=κ + κ≤19.4 at XX mths + neg. urine IFE at 6 mths **OR** • Neg. serum IFE + iFLC=λ + λ≤26.3 at XX mths + neg. urine IFE at 6 mths **OR** • Neg. serum IFE + 0.26 ≤κ/λ ≤1.65 + 3.3 ≤κ FLC ≤19.4 + 5.7 ≤λ ≤26.3 at XX mths + neg. urine IFE at 6 mths
VGPR	dFLC concentration <40mg/L	dFLC concentration <40mg/L	• Baseline dFLC ≥50 + dFLC <40 at XX mths **OR** • Baseline dFLC <50 + ≥90% decrease in serum M–protein from baseline at XX mths
PR	dFLC decrease >50% from baseline	dFLC decrease >50% from baseline	• Baseline dFLC ≥50 + >50% decrease in dFLC from baseline at XX mths **OR** • Baseline dFLC <50 + ≥50% decrease in

- Which criteria were used in ALchemy?
- Are the haematological response criteria applied in ANDROMEDA used in NHS clinical practice?

Source: Company ACD response Tables 9 and 10. **Abbreviations:** CR, complete response; dFLC, difference between amyloidogenic (involved) and non-amyloidogenic (uninvolved) free light chain concentrations; FLC, free light chain; haem., haematological; iFLC, involved FLC; iFE, immunofixation electrophoresis; mths, months; neg., negative; PR, partial response; VGPR, very good partial response

Haematological response: EMN23-UK vs ALchemy

Improved haematological response using censored and re-categorised EMN23-UK data than uncensored and unadjusted ALchemy data

		3 months					6 months				
		CR	VGPR	PR	NR	Dead	CR	VGPR	PR	NR	Dead
ANDROMEDA (Palladini 2021)	DARA	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
	SC	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
EMN23-UK: censored for treatment switching and re-categorised	DARA	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
	SC	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
ALchemy (Comenzo 2012): no censoring, not re-categorised	DARA	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
	SC	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Change in haematological response (DARA – SC)											
ANDROMEDA		XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
EMN23-UK		XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
ALchemy		XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Source: ERG critique of company ACD response Tables 1 and 2. **Abbreviations:** CR, complete response; DARA, daratumumab; NR, no response; PR, partial response; SC, standard care (bortezomib/cyclophosphamide/dexamethasone); VGPR, very good partial response

Extrapolated overall survival: EMN23-UK vs ALchemy

Relative difference in OS between CR and VGPR, PR and NR greater in EMN23-UK. OS for CR higher at 3 months and crosses general population survival curve sooner in EMN32-UK than ALchemy

Source: ERG critique of company ACD response Figures 3 and 4.
Abbreviations: CR, complete response; KM, Kaplan-Meier; NR, no response; OS, overall survival; PR, partial response; VGPR, very good partial response

Which data provides credible OS extrapolations? Re-categorised EMN23-UK or unadjusted ALchemy?

Modelled sustained response of daratumumab monotherapy on overall survival

Additional survival benefit included for all response states in daratumumab arm

Background

- Model did not assume survival benefit from sustained response to daratumumab monotherapy

Company ACD response

- ANDROMEDA 18-month landmark analysis (median 25.8 months)
  - Sustained response at 24 months observed in people with CR on daratumumab than standard care (XXX vs XXX at 3 months and XXX vs XXX at 6 months)
- Revised base case: includes expected survival benefit of daratumumab monotherapy, calculated by:
  - ratio of OS of daratumumab vs standard care from 12-month ANDROMEDA landmark analysis (1.066) and equivalent ratio from EMN23-UK data (1.021)
  - multiplying per-cycle OS probabilities for **all response states in daratumumab arm from Cycle 7** onwards by **1.044** (=1.066/1.021)

ERG comments

- Increased survival benefit (4.4%) applied to **all haematological response states including no response** in daratumumab arm

- Is it appropriate to model a sustained response for daratumumab monotherapy compared with standard care and extrapolate its effect on overall survival in the longer term?
- Is it appropriate to apply an expected survival benefit to all haematological response states?

Abbreviations: CR, complete response; OS, overall survival

Association between haematological response and overall survival

Company considers multivariate analyses show no evidence of confounding. ERG considers results are not reliable

Company ACD response

- Conducted multivariate analyses of ANDROMEDA interim analysis data (median 11.4 months) on impact of baseline patient characteristics on OS for people with CR at 3 and 6 months for whole population and per treatment
  - Results only available for whole and daratumumab population; model instability in standard care
  - No confounding identified
- UK clinical expert: haematologic response is a consistent, reliable and independent predictor of survival in amyloidosis; expect confounding between haematological response and OS in ANDROMEDA not meaningfully impactful

ERG comments

- Cannot comment on company's results as they do not appear to be adequately estimated
  - Many hazard ratios do not have appropriately estimated confidence intervals, almost all are estimated at 0 or extremely high
- Given lack of reliable results from statistical analysis, area of uncertainty

Abbreviations: CR, complete response; OS, overall survival

Company's multivariate analysis on impact of baseline characteristics on overall survival at 11.4 months median follow up for full population with complete response at 3 months

Has the issue of confounding in the relationship between haematological response and overall survival been adequately addressed?

Remaining uncertainties: Validating utility dataset

Company cannot access ALchemy data to validate utilities derived from ANDROMEDA EQ5D-5L data, some of which lacked face validity

Table. Utilities used in base case derived from ANDROMEDA EQ5D-5L data

Haem. response	Response on '1st-line therapy; off treatment or fixed DARA therapy'	State 'on 2nd-line therapy'	State 'End-stage organ failure'
CR	XXXX	XXXX	XXXX
VGPR	XXXX (mean values for other categories, because VGPR value XXXX lower than PR and NR)	XXXX	XXXX
PR and NR	XXXX	XXXX	XXXX
One-off reduction because of adverse events: DARA 0.0029; SC 0.0020			

Are the utility values plausible?

Source: ERG report Table 19; Company submission Table 53. **Abbreviations:** CR, complete response; DARA, daratumumab; EQ5D, EuroQol-5 dimensions; NR, no response; PR, partial response; SC, standard care; VGPR, vey good partial response

Key issue: Administration cost for daratumumab and bortezomib

Company prefers specialist nursing tariff for cancer treatment, £99. Committee preferred £332. ICER increases when admin cost increases

Background

- Company preferred £99 (specialist nursing costs for cancer treatment N10AF) as used in TA763
- Committee preferred £332 (deliver subsequent elements of chemotherapy cycle HRG code SB15Z)

Company ACD response

- HRG code SB15Z not appropriate:
  - IV or SC admin of cancer treatment cost the same
    - IV treatments need complex monitoring, extended chair time and pharmacist input
    - DARA SC needs 3-5 minute injection
- Evidence from UK micro-costing exercise on treatment delivery in hospital setting
  - Data on hospital capacity, time for treatment and patient characteristics from survey of 60 healthcare professionals in various settings. Simulations for typical NHS hospital over 5 years and 27 new patients treated annually with DARA SC
  - Average cost £123 per dose
- Base case: **£99**. Alternative scenarios: **£123** (micro-costing tool) and **£332** (committee preferred)

ERG comments: cannot comment on micro-costing exercise (tool/details not presented by company)

Which estimate best reflects likely NHS administrative cost of daratumumab and bortezomib?

Abbreviations: CDF, Cancer Drugs Fund; IV, intravenous; SC, subcutaneous

End-of-life criteria

Background

- Company: daratumumab meets EOL criteria for cardiac stage 3b
- Committee considered company:
  - positioned daratumumab for full population
  - did not present evidence that life expectancy on standard care <24 months

Company ACD response

- Large proportion of eligible population is at EOL: 18-20% cardiac stage 3b
  - Median survival on bortezomib-based therapies 5 months (EMN23 post-2010 data)
  - Phase 2 study on daratumumab monotherapy in newly diagnosed stage 3b: median survival 9 months

ERG comments

- EOL criteria not met in full population: life expectancy with standard care >24 months
- Phase 2 study (off-label daratumumab monotherapy use in 27 people with stage 3b): no comparative effectiveness evidence of daratumumab in combination vs standard care in stage 3b

NICE

Has any new evidence been presented to change the committee's views on whether daratumumab meets EOL criteria for full population?

Abbreviations: BORT, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; EOL, end-of-life

Innovation, uncaptured HRQoL benefits and Cancer Drugs Fund

Company ACD response

- HRQoL benefits of daratumumab not fully captured in model
- Clinical experts at UK NAC: HRQoL improvements for CR or VGPR not usually seen before 1 year after start of treatment (ANDROMEDA: 11.4 months median follow up)
- Introduction of daratumumab in UK practice: increase disease awareness, shorten diagnosis, improve outcomes
- Psychological benefit; increased benefit for people who also have multiple myeloma; improvement in outcomes related to daratumumab in combination post-autologous stem cell transplant

ERG comments

- No new HRQoL data
- ERG clinical advisors: HRQoL improvements may peak at ~9-12 months from start of treatment and continue to improve for 2-3 years at slower pace before stabilising
- ANDROMEDA utilities by haematological response: validity is highly uncertain and also extrapolated over long term (survival also stratified by distribution of response at specific assessment time point)
- No data to support additional claims
- Company added additional survival benefit for daratumumab monotherapy

Are there any additional benefits not captured in the model?
Could further data collection reduce uncertainty in the model?

Abbreviations: CR, complete response; HRQoL, health-related quality of life; VGPR, very good partial response; UK NAC, UK National Amyloidosis Centre

Company and ERG base case

ACD	Committee preferences	Company and ERG base case
3.9	Model partial and no response groups separately	Yes
3.4	Include people with end-stage cardiac and renal disease in modelled population	Yes, EMN23-UK
3.11	Use ALchemy data for distribution of haematological response for standard care and use relative effectiveness from ANDROMEDA for daratumumab in combination	Used EMN23-UK
3.11	Assess haematological response at 3 months in base case and explore a scenario using 6 months, adjusting analyses to ensure consistency in response categorisation between ANDROMEDA and ALchemy	Yes
3.12	Use ALchemy to extrapolate overall survival, but explore fit compared with overall survival from ANDROMEDA	Used EMN23-UK
3.13	Validate utility values using ALchemy SF36v2 data	-
3.14	Apply stopping rule for daratumumab monotherapy (max. 24 cycles)	Yes
3.15	Increase daratumumab administration costs from £99 to £332	No
3.18	Include autologous stem cell transplant in model	Yes
3.17	Apply estimates from UK experts for 2nd- and 3rd-line treatments	Yes

Abbreviations: SF36, 36-Item Short Form Health Survey

Drivers of cost-effectiveness results

Company's base case and ERG's analyses result in ICERs higher than what would usually be considered cost-effective use of NHS resources

Table. Impact of varying assumptions on company base case results

No.	Scenario	Inc. Costs	Inc. QALYs	ICER, £/QALY
1	Haematological response assessment at 6 months	↑	↑	↓
2	ALchemy: source to inform baseline haematologic response distribution for standard care	↑	↓	↑
3	ALchemy: source to inform overall survival, stratified by haematologic response (CR, VGPR, PR, NR: Weibull)	↓	↓	↑
4	Administration cost of daratumumab and bortezomib of £123 (micro-costing tool)	↑	–	↑
5	Administration costs daratumumab and bortezomib of £332 (committee preferred)	↑	–	↑
6	No additional survival benefit with daratumumab from cycle 7 onwards (factor of 1.044 set to 1.0)	↓	↓	↑

Abbreviations: CR, complete response; ICER, incremental cost-effectiveness ratio; inc, incremental; NR, no response; PR, partial response; QALY, quality-adjusted life years; VGPR, very good partial response

Cost-effectiveness results

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

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

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Thank you