Daratumumab in combination for treating newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

PART 1: for PUBLIC (contains **no ACIC** information)

Technology appraisal committee B

Chair: Charles Crawley

Lead team: Sanjeev Patel, Tony Wootton

External assessment group: York CRD and CHE Technology Assessment Group

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

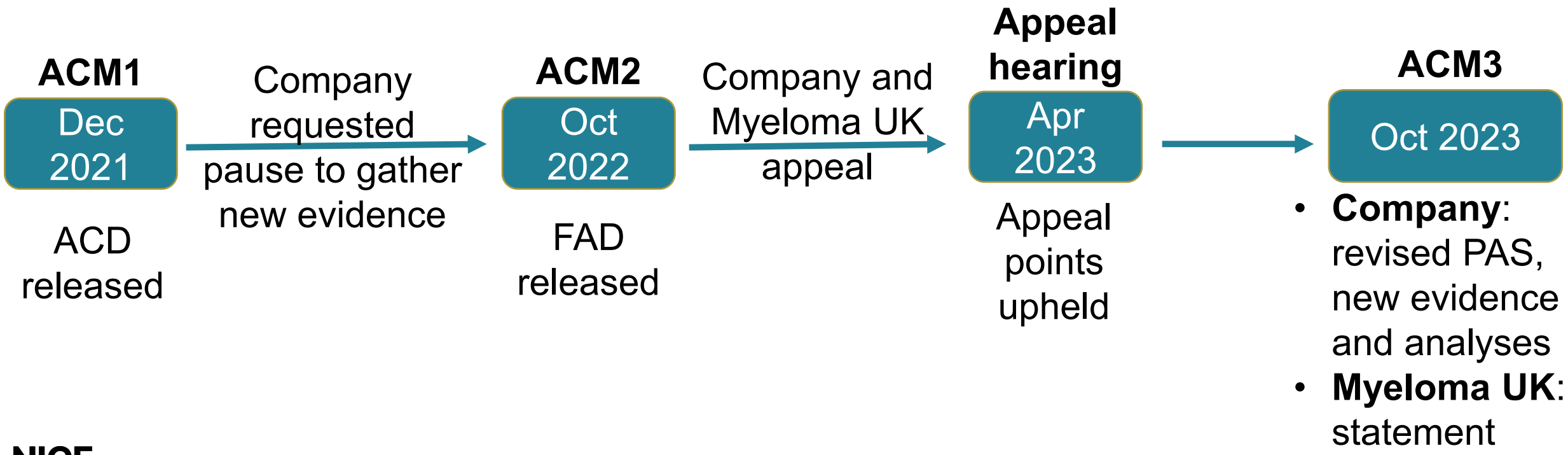
Company: Janssen-Cilag

13th October 2022: 3rd meeting (after appeal hearing)

Appraisal history

FAD recommendation

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



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Abbreviations: ACD, appraisal consultation document; ACM, appraisal committee meeting; FAD, final appraisal determination

Upheld appeal points

Relationship between haematological response and overall survival (Janssen 1a.2, 1a.3, 2.2; Myeloma UK 1a.1, 1a.2)

- Re-evaluate data on surrogate markers of OS, reconsider to what extent markers might inform judgement on OS. Seek advice from specialist haematologists, or specialists at National Amyloidosis Centre. Reconsider balance of evidence on effect of daratumumab on OS. Clearly explain committee's views in FAD

ALchemy and EMN23-UK dataset (Janssen 2.1; Myeloma 2.1)

- Reconsider whether both ALchemy and EMN23-UK may be representative of UK practice
- Clarify committee's preferred dataset for purpose of economic modelling

ICER threshold (Janssen 1a.1; Myeloma UK 1a.4)

- Reconsider significance and relevance of rarity and other factors in determining ICER threshold. Assess impact on recommendation. Adequately explain decision-making around ICER threshold in FAD

Abbreviations: FAD, final appraisal determination; ICER, incremental cost-effectiveness ratio; OS, overall survival

Committee's requests to company after appeal

Request	Company
Relationship between haematological response, major organ deterioration and OS Evidence or analysis:	
• showing correlation between haematological response, MOD and OS	Meta-analysis
• assessing any potential confounding factors in relationship (e.g. definition of response; speed of, timepoint or duration of response)	Not provided
EMN23-UK dataset and potential bias introduced by missing data	
• OS Kaplan-Meier (KM) curves and extrapolations at 3 and 6 months for: - original EMN23 - unadjusted EMN23-UK (before re-categorisation to align with response criteria in ANDROMEDA) - ALchemy - unadjusted EMN23-UK with missing data from re-categorisation removed	KM curves but no extrapolations
• Additional information or analysis on missing data in EMN23-UK	Information

Abbreviations: KM, Kaplan-Meier; MOD, major organ deterioration; OS, overall survival

Relationship between haematological response, major organ deterioration and overall survival (1)

Background

- Company provided multivariate analysis exploring confounding factors in relationship between haematologic response and OS but analysis not appropriate or informative

Company post appeal

- Level 2 evidence: meta-analysis assessing prognostic utility of haematological response for OS in newly diagnosed AL amyloidosis (Kastritis et al. 2023)
  - 9 observational studies (inc. ALchemy) reporting CR or VGPR and OS hazard ratios
  - EMN23 excluded because of overlap with populations of other studies
  - Strong relationship between haematological response and improved OS
    - CR: HR 0.2 [95% CI 0.13–0.34]
    - VGPR: HR 0.2 [95% CI 0.17–0.26]
- Did not update ACM2 multivariate analysis for confounding factors (no new OS data)
  - Model failed to converge due to small sample size and few events

Abbreviations: ACM2, 2nd appraisal committee meeting; CI, confidence interval; CR, complete response; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; VGPR, very good partial response

Relationship between haematological response, major organ deterioration and overall survival (2)

ERG comments

- Agrees relationship between deep haematological response and improved OS biologically plausible and supported by evidence
- Accept that in the absence of a new data cut, company's ACM2 multivariate analysis cannot be updated

- Does the committee want to revise its view on the relationship between haematological response and OS?
- Has the company addressed the issue of potential confounding factors in this relationship?
- Has an OS benefit been demonstrated with daratumumab in newly diagnosed AL amyloidosis?

Abbreviations: ACM2, 2nd appraisal committee meeting; AL, amyloid light-chain; OS, overall survival

ALchemy and EMN23-UK (1)

Background

- Appeal panel:
  - Reconsider whether both ALchemy and EMN23-UK may be representative of UK practice
  - Clarify data source to be used for purpose of economic modelling

Company post appeal

- Missing data from EMN23-UK after re-categorisation:
  - Provided breakdown of 18-22% missing data (see slide 30)
  - Provided OS Kaplan-Meier curves at 3 and 6 months for unadjusted EMN23-UK (before re-categorisation to align with ANDROMEDA response criteria) and unadjusted EMN23-UK with missing data from re-categorisation removed (see slide 10)
- Provided OS Kaplan-Meier curves at 3 and 6 months for:
  - original EMN23 dataset, unadjusted EMN23-UK (before re-categorisation) and ALchemy for CR, VGPR, PR and NR response categories (see slides 12-15)
- Did not provide any OS extrapolation distributions

Abbreviations: CR, complete response; NR, no response; OS, overall survival; PR, partial response; VGPR, very good partial response

RECAP

Categorisation of haematological response

Haem. response	Original (Comenzo 2012)	Updated (Palladini 2021)	Algorithm used for response re-categorisation to align with ANDROMEDA
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 serum M−protein from baseline at XX mths

- What are the implications of the updated response criteria in UK 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

RECAP

Extrapolated overall survival: adjusted EMN23-UK vs ALchemy

- Company did not present original unadjusted EMN23-UK data
- Relative difference in OS between CR and VGPR, PR and NR greater in adjusted EMN23-UK
- OS for CR higher at 3 months and crosses general population curve sooner in adjusted EMN23-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

KM curves: overall survival for unadjusted EMN23-UK before re-categorisation and unadjusted EMN23-UK with cases removed because of missing data during re-categorisation at 3 and 6 months

ERG comments

- Graphs show considerable similarity and overlap
- Impact of missing data from reclassification likely to be negligible

3 months

6 months

Return to slide 7

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Source: Company post-appeal addendum Figures 9 and 10. **Abbreviations:** CR, complete response; KM, Kaplan-Meier; NR, no response; PR, partial response; VGPR, very good partial response

ALchemy and EMN23-UK (2)

ERG comments

- In principle, original unadjusted EMN23-UK (before re-categorisation) suitable alternative to ALchemy: ~95% overlap; expect near equivalent outcomes
  - Comparison of OS for unadjusted EMN23-UK and ALchemy most relevant to check that EMN23-UK similar to ALchemy before re-categorisation → expect KM curves to have substantial overlap, but:
    - Differences greater than might be expected
      - No reassurance OS curves from 2 datasets are equivalent
      - In some cases, ALchemy OS closer to full EMN23 than to EMN23-UK only
    - Company unable to investigate reasons for apparent differences
    - ERG unable to comment without access to either dataset; unexplained discrepancy concerning
- Company did not provide extrapolation of KM curves or comparison of haematological response rates at 3 and 6 months for unadjusted EMN23-UK with ALchemy or ANDROMEDA and re-categorised EMN23-UK

Abbreviations: KM, Kaplan-Meier; OS, overall survival

KM curves: overall survival for people showing CR in original EMN23 dataset, unadjusted EMN23-UK and ALchemy at 3 and 6 months

ERG comments

- At 3 and 6 months, OS for CR in ALchemy noticeably higher relative to unadjusted EMN23-UK

3 months

6 months

Source: Company post-appeal addendum Figures 1 and 5. **Abbreviations:** CR, complete response; KM, Kaplan-Meier; OS, overall survival

KM curves: overall survival for people showing VGPR in original EMN23 dataset, unadjusted EMN23-UK and ALchemy at 3 and 6 months

ERG comments

- At 3 months, OS for VGPR appears well aligned up to 35 months, some divergence afterwards, with higher OS in ALchemy up to around 60 months
- At 6 months, OS for VGPR in ALchemy higher relative to EMN23-UK during ~35 to 60-month period

3 months

6 months

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Source: Company post-appeal addendum Figures 2 and 6. **Abbreviations:** KM, Kaplan-Meier; OS, overall survival; VGPR, very good partial response

KM curves: overall survival for people showing PR in original EMN23, unadjusted EMN23-UK and ALchemy at 3 and 6 months

ERG comments

- At 3 months, OS for PR in ALchemy lower relative to unadjusted EMN23-UK
- At 6 months, OS for PR higher in EMN23-UK relative to ALchemy until 35 months

[redacted]

3 months

[redacted]

6 months

Source: Company post-appeal addendum Figures 3 and 7. **Abbreviations:** KM, Kaplan-Meier; OS, overall survival; PR, partial response

KM curves: overall survival for people showing NR in original EMN23, unadjusted EMN23-UK and ALchemy at 3 and 6 months

ERG comments

- At 3 months, OS for NR in ALchemy is lower relative to unadjusted EMN23-UK
- At 6 months, OS for NR in ALchemy is noticeably higher relative to EMN23-UK

3 months

6 months

- Given 95% overlap between ALchemy and **unadjusted** EMN23-UK, what are reasons for differences in OS curves? Does the committee consider using EMN23-UK dataset to inform decision making acceptable?

Source: Company post-appeal addendum Figures 4 and 8. **Abbreviations:** KM, Kaplan-Meier; NR, no response; OS, overall survival

Modelled sustained response of daratumumab monotherapy on overall survival

Background

- Company used data from ANDROMEDA 18-month landmark analysis (median 25.8 months follow-up) to justify modelling sustained response of daratumumab monotherapy
  - Sustained response at 24 months observed in people with CR on daratumumab than standard care ([redacted] vs [redacted] at 3 months and [redacted] vs [redacted] at 6 months)
- Company base case at ACM2: included expected survival benefit of daratumumab monotherapy for **all response states in daratumumab from Cycle 7** onwards by **1.044**

Company post appeal

- Revised base case: 4.4% efficacy uplift applied to CR and VGPR only

ERG comments

- Company assumes long-term survival benefit even after daratumumab monotherapy is stopped up to 24 cycles

- Is it plausible that people will continue to have a survival benefit after daratumumab maintenance monotherapy is stopped?

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Abbreviations: ACM2, 2nd appraisal committee meeting; CR, complete response; OS, overall survival; VGPR, very good partial response

Key questions (1)

Relationship between haematological response, major organ deterioration and overall survival (slide 5 and slide 6)

- Does the committee want to revise its view about the relationship between haematological response and OS?
- Has the company addressed the issue of potential confounding factors in this relationship?
- Has an OS benefit been demonstrated with daratumumab in newly diagnosed AL amyloidosis?

Categorisation of haematological response (slide 8)

- What are the implications of the updated response criteria in UK clinical practice?

Abbreviations: CR, complete response; OS, overall survival; VGPR, very good partial response

Key questions (2)

ALchemy and EMN23-UK (slides 11 to 15)

- Given 95% overlap between ALchemy and unadjusted EMN23-UK, what are reasons for differences in OS curves?
- Does the committee consider using EMN23-UK dataset to inform decision making acceptable?

Modelled sustained response of daratumumab monotherapy on overall survival (slide 16)

- Is it plausible that people will continue to have a survival benefit after daratumumab maintenance monotherapy is stopped?

Other factors

- Are there any other factors that require additional consideration, for example, rarity, unmet need, innovation of daratumumab, first licensed treatment?

Abbreviations: OS, overall survival

Company revised base case

Committee preferred assumption after ACM2	ERG comment
Include end-stage cardiac and renal disease	Included
Confounding factors in relationship between haematological response and OS	Company provide level 2 evidence to support relationship
Assess haematological response at 3 months in base case; explore scenario using 6 months	Included
Distribution of haematological response for standard care may lie between ALchemy and adjusted EMN23-UK	Company consider adjusted EMN23-UK the only appropriate data source
Extrapolated OS in longer term may lie between ALchemy and adjusted EMN23-UK	Company use EMN23-UK to extrapolate OS by haematological response
Company's approach of applying expected increased survival benefit for daratumumab maintenance monotherapy not appropriate	Company applied additional benefit to CR and VGPR response categories only, but assumed benefit continues after daratumumab stops
Some utility data lack face validity	Company's scenario using utilities from UK clinicians are not appropriate
Stopping rule for daratumumab monotherapy of a maximum of 24 cycles	Included
Apply appropriate chemotherapy administration costs	Included

Abbreviations: ACM2, 2nd appraisal committee meeting; CR, complete response; OS, overall survival; VGPR, very good partial response

Drivers of cost-effectiveness results

Table. Impact of varying assumptions on company base case results

No.	Scenario	Inc. Costs	Inc. QALYs	ICER, £/QALY
1	No additional survival benefit with daratumumab monotherapy (factor of 1.044 set to 1.0)	↓	↓	↑
2	Haematological response assessment at 6 months	↑	↑	↓
3	Combination of scenarios 1 & 2	↑	↓	↑
4	Use of ALchemy dataset	↓	↓	↑

Abbreviations: ICER, incremental cost-effectiveness ratio; inc, incremental; QALY, quality-adjusted life years

Cost-effectiveness results

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

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Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

NICE National Institute for Health and Care Excellence

Thank you