NICE National Institute for Health and Care Excellence

Part 1	Contains no ACIC information
Slides for PUBLIC	

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

Lead team presentation

1st appraisal committee B meeting

Chair: Amanda Adler

Lead team: Charles Crawley, Sanjeev Patel, Tony Wootton

ERG: York CRD and CHE Technology Assessment Group

Technical team: Sharlene Ting, Carl Prescott, Henry Edwards

Company: Janssen-Cilag

8th December 2021

Issues: clinical and cost effectiveness

Treatment pathway	Would DARA/CYC/BORT/DEX be followed by DARA monotherapy to max 24 months? BORT/CYC/DEX a reasonable comparator?
Populations	Would clinicians wish to offer DARA/BORT/CYC/DEX to people with heart failure?
Haematological response	Clinically meaningful? How is response defined in the NHS? Is response assessment best done at 3 or 6 months?
Overall survival	Trial shows no benefit on overall survival; is modelling haematological response as a surrogate for survival appropriate?
	In absence of mature trial data, which study best reflects UK population and survival by haematological response in UK patients on chemotherapy? EMN23 post-2010 subset or ALchemy?
Adverse events	Reasonable to include only events that occur in >5% of patients in the model?
Model	Structurally appropriate?
Extrapolation	Overall survival extrapolated appropriately?
Utilities	Appropriate?
Costs	Would daratumumab monotherapy continue beyond 24 months? What is the correct way to model administration costs? Should costs of autologous stem cell transplant be included? Best source for costs of 2nd and 3rd line therapy?
End of life criteria	Met?

Amyloid light chain (AL) amyloidosis

- Severe form of amyloidosis
- UK annual incidence 1 in 100,000; increases with age; 4-year survival 54%
- In healthy people, plasma cells in bone marrow make ‘light chain proteins’
- In AL amyloidosis, light chain proteins form improperly, circulate, clump together into fibrils and deposits in organs: heart, kidneys and nerves
- Symptoms often non-specific e.g. weight loss + fatigue – delays diagnosis
- Death commonly from heart failure
- Mayo Clinic Staging System used
  - Stratifies patients by serum markers: NT-proBNP and troponin
  - Stage IIIb most severe cardiac involvement; ≅ 20% of UK patients, median survival 4.5 months vs cardiac stage IIIa 31.1 months
- Current treatment: chemotherapy; no licensed options
- Aim of treatment: rapid and durable haematological response to prolong survival + improve quality of life

Patient and carer perspectives

- Significant unmet need
  - Daratumumab combination is first licensed treatment
- Evidence from ANDROMEDA trial suggests that daratumumab combination can induce faster and deeper treatment response
  - Side effect profile similar to standard care
  - ANDROMEDA excluded cardiac stage IIIb disease
- Easy to administer: less time in hospital
- Patients with cardiac stage IIIb disease should be allowed to access treatment
  - Evidence from ALchemy suggests that patients who achieve an early deep haematological response have a significantly superior survival irrespective of cardiac involvement
  - Daratumumab has shown to be effective for patients with cardiac stage IIIb disease in other studies

Professional organisation perspective

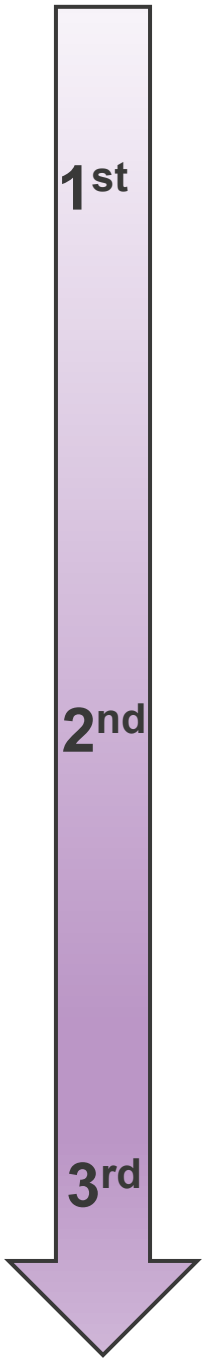
- AL amyloidosis differs from multiple myeloma, but treatment is the same, and does not account for disease-specific adverse effects
  - No ‘standard treatment’ as treatment needs to be individually tailored
  - Variable access to chemotherapy across UK
- Treatment with daratumumab combination is better than chemotherapy
  - 2nd and 3rd line treatments should remain available
- In NHS, testing for response occurs monthly
  - If no response at 3 months: consider switching to 2nd line therapy
- Company excludes people with Stage IIIb from trial – if the recommendation excludes patients with advanced cardiac and renal disease, this would affect patients who have the most to gain from treatment

Daratumumab (Darzalex, Janssen-Cilag) in combination with bortezomib, cyclophosphamide and dexamethasone

includes daratumumab monotherapy up to 2 years

Marketing authorisation	Adults with newly diagnosed systemic light chain amyloidosis
Mechanism	• Fully human monoclonal antibody • Binds to CD38 • Reduces native light chain production and organ toxicity
Administration and dose	**Daratumumab:** 1800 mg (15 mL vial; 120mg per mL) injected subcutaneously (subcut) over 3-5 minutes Week 1 to 8: every week Week 9 to 24: every 2 weeks Week 25 until progression or maximum of 2 years: every 4 weeks **Bortezomib:** 1.3mg/m^2 subcut – max 6 cycles **Cyclophosphamide:** 300mg/m^2 orally or IV – max 6 cycles **Dexamethasone:** 40mg orally or IV Weekly dose on Days 1, 8, 15 and 22 in every 28-day cycle
List price	£4,320 excluding VAT Patient access scheme discount in place

Treatment pathway and company's positioning



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/ BORT/CYC/DEX (DARA/BORT/ CYC/DEX)?

Relapsed refractory AL amyloidosis

- Melphalan with dexamethasone (MEL/DEX)
- Lenalidomide with dexamethasone (LEN/DEX)
- Carfilzomib with dexamethasone (CAR/DEX)
- BORT/CYC/DEX or BORT/DEX
- Autologous stem cell transplant

- LEN/DEX
- Panbinostat with bortezomib and dexamethasone (PAN/BORT/DEX)
- Pomalidomide with dexamethasone (POM/DEX)

Decision problem: Population Intervention Comparators Outcomes [8]

	NICE scope	Company submission + comments
P	Adults with newly diagnosed systemic amyloid light-chain amyloidosis	
I	Daratumumab with cyclophosphamide, bortezomib and dexamethasone DARA/CYC/BORT/DEX	DARA/CYC/BORT/DEX with DARA monotherapy thereafter up to 24 cycles reflecting key trial
C	Management without daratumumab • Bortezomib with dexamethasone, an alkylating agent +/-immunomodulatory drugs • Lenalidomide with dexamethasone • Melphalan and dexamethasone • Autologous stem cell transplant with high dose melphalan • Best supportive care	• Bortezomib + cyclophosphamide + dexamethasone BORT/CYC/DEX • ERG and Company UK clinical expert advisory board: BORT/CYC/DEX standard of care • Others rarely used • Best supportive care not appropriate
O	• Haematologic response rates • Organ response rates • Progression-free survival • Major organ deterioration progression-free survival (MOD-PFS) • Overall survival • Adverse effects of treatment • Health-related quality of life	• As scope but key trial did not collect PFS • MOD-PFS is defined as: death, haematological progression, major organ deterioration: - ***cardiac failure*** *i.e. need for cardiac transplant, left ventricular assist device, or intra-aortic balloon pump or* - ***renal failure*** *i.e. end-stage renal disease*

◉ *Would DARA/CYC/BORT/DEX be followed by DARA monotherapy to max 24 months?*
◉ *Is BORT/CYC/DEX a reasonable comparator for the NHS?*

Clinical evidence

	Intervention DARA/BORT/ CYC/DEX followed by DARA monotherapy	Comparator BORT/CYC/DEX	Includes people with cardiac stage IIIb
Trial	ANDROMEDA	ANDROMEDA	No
Observational studies		EMN23 ALchemy	Yes

ANDROMEDA trial – randomised open label

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

- **Excludes:** Mayo cardiac stage IIIb, NYHA IIIB or IV heart failure

DARA+ BORT/CYC/DEX n=195 Cycles 1 to 6

BORT/CYC/DEX n=193 Cycles 1 to 6

1º outcome

- Overall complete haematological response independently assessed – model

2º outcome

- MOD-PFS – model
- Overall survival – *not in model; data from ALchemy or EMN23 used*
- Adverse events – model
- HRQoL (EQ-5D-5L in model + SF36v2)

DARA monotherapy *for patients with partial or better response + stable or improved major organ failure after 6 cycles* 1800 mg 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 patient

◉ *Would clinicians wish to offer DARA/BORT/CYC/DEX to people with heart failure?*

ANDROMEDA definition of haematological response

Company uses response after 6 cycles in model; ERG uses 3 cycles based on National Amyloidosis Centre recommendations

Endpoint	Criteria
Complete haematological response (CR)	• Neg serum and urine immunofixation + normalised free light chain (FLC) levels and ratios • If involved FLC level lower than upper limit of normal, normalised uninvolved FLC
Very good partial response	• Baseline dFLC ≥50 mg/L: reduction in dFLC <40 mg/L • Baseline dFLC <50 mg/L: ≥90% reduction in serum M-protein + urine M-protein <100 mg/24 hours
Partial response	• Baseline dFLC ≥50 mg/L: a greater than 50% reduction in the dFLC • Baseline dFLC <50 mg/L: ≥50% reduction in serum M-protein plus reduction in 24-hour urine M-protein by ≥90% or to <200 mg/24 hours
No response	• <Partial response
Progression	• From CR, abnormal FLC ratio light chains must double • From any response, 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day - visible peak must be present • Involved free light chain increase of 50% to >100 mg/L

dFLC: difference between involved and uninvolved free light chain

◉ *Is the 1º outcome clinically meaningful? Are these defined as they would be in the NHS?*
◉ *When is or should response be assessed clinically? After 3 or 6 cycles?*

ANDROMEDA statistical plan – trial ongoing

85% power to detect a 15% improvement; 2-sided alpha of 0.05

Analysis	Company	Comments
Interim analyses	1. For safety: After 1st 30 people complete ≥1 cycle 2. For efficacy: After 180 complete ≥6 cycles – median 11.4 months, **14 Feb 2020**	N.B: stop for benefit if $p \leq 0.0001$
'**Landmark analysis**'	**1. 12 months** – median 20.3 months, 13 Nov 2020 2. 18 months – planned (XXXXXX)	**Used in model, but not** in statistical plan Company: '12-month landmark analysis … was generated for conference purposes'
Final primary analysis	Everyone treated for ≥6 cycles **– done?**	Alpha 0.04999 (2-sided) Intention to treat
OS analysis	'Not confirmed' (XXXX)	ERG: 'analyses important to validate model'
2º endpoints: MOD-PFS, OS	If 1º endpoint positive, hierarchical testing to control for type 1 error; each alpha 0.05 (2-sided)	Inverse probability of censoring weight (IPCW) to adjust treatment effect in the presence of 2nd line therapy
Duration of post-treatment observation phase	Until 200 MOD-PFS events observed – anticipated XXXX	'≅80% power to detect a 33% reduction in risk of haematologic progression, major organ deterioration or death'; 2-sided alpha of 0.05

ANDROMEDA: baseline patient characteristics

Characteristic	DARA/BORT/ CYC/DEX (N=195)	BORT/CYC/DEX (N=193)
Mean age in years (SD)	62 (10.2)	64 (9.7)
Baseline ECOG score, n (%)		
0	XXXX	XXXX
1	XXXX	XXXX
2	XXXX	XXXX
Mean time since diagnosis in days (SD)	XXXX	XXXX
Mean number of organs involved (SD)	2 (1)	2 (1)
Cardiac stage based on Mayo Clinic Cardiac Staging System, n (%)		
I	47 (24)	43 (22)
II	76 (39)	80 (42)
IIIa	70 (36)	64 (33)
IIIb*	2 (1)	6 (3)
Chronic kidney disease stage, n (%)		
I	XXXX	XXXX
II	XXXX	XXXX
III	XXXX	XXXX
IV	XXXX	XXXX
V (end stage renal disease)	XXXX	XXXX

*Excluded but patients progressed between screening and 1st dose

- *Is ANDROMEDA generalisable to patients likely to use daratumumab in NHS practice?*
- *Is mean time to diagnosis likely to modify the treatment effect?*

ANDROMEDA results interim + 12-month landmark analyses

Company uses 12-month landmark analysis after 3 or 6 cycles in economic model

More patients achieved complete response at 12-month landmark analysis than interim analysis

	Response % (95% CI)			
	Interim analysis 14 Feb 2020		12-month landmark analysis 13 Nov 2020	
	median 11.4 months		median 20.3 months	
	DARA/BORT/ CYC/DEX (N=195)	BORT/CYC/ DEX (N=193)	DARA/BORT /CYC/DEX (N=195)	BORT/CYC/ DEX (N=195)
Complete haematological response	53% (46, 61)	18% (13, 24)	59% [redacted]	19% [redacted]
Odds ratio (95% CI)	*5.1 (3.2, 8.2)*		*5.0 (3.7, 9.4)*	
Very good partial response	[redacted]	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]	[redacted]
No response	[redacted]	[redacted]	[redacted]	[redacted]

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ANDROMEDA complete haematological response by cardiac stage

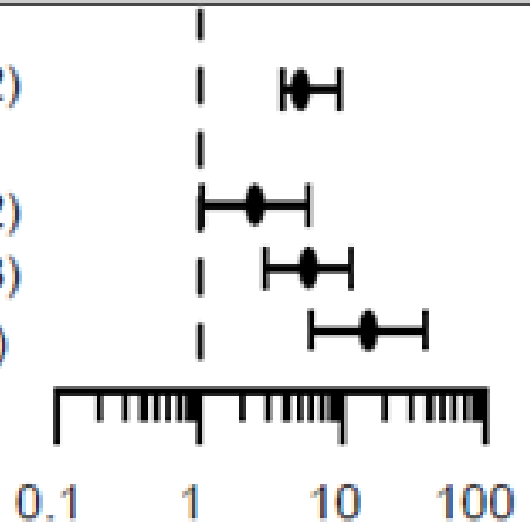
12-month landmark analysis

Company: *relative treatment effect of DARA/BORT/CYC/DEX increases with increasing disease severity*

ERG: *incorrect to assume larger treatment effect in stage IIIb; no data, poor prognosis may mean patients do not survive long enough to achieve complete response.*

True effect is uncertain

Subgroup	DARA/BORT/CYC/DEX n (% resp)	BORT/CYC/DEX n (% resp)	Odds ratio (95% CI)
Overall	115 (59.0)	37 (19.2)	5.0 (3.7–9.4)
Baseline cardiac stage			
I	24 (51.1)	13 (30.2)	2.4 (1.0–5.7)
II	46 (60.5)	17 (21.3)	5.7 (2.8–11.5)
III[a]	45 (62.5)	7 (10.0)	15.0 (6.0–37.5)



Favours BORT/CYC/DEX **Favours DARA/BORT/CYC/DEX**

◉ *Does ANDROMEDA provide evidence for cardiac stage IIIb?*

[A]**includes** [redacted] **patients who progressed to cardiac stage IIIb** between screening and 1st dose

Source: Kastritis et al. (2021) Conference abstract

ANDROMEDA 2º endpoint ‘major organ deterioration progression-free survival’ interim analysis

Company uses outcome in model

ANDROMEDA 2º endpoint overall survival interim analysis

***Data immature**; another analysis planned* XXXX

To model survival, company: 1) used haematological response from ANDROMEDA as surrogate (2) obtained survival conditional on response from external observational evidence and (3) extrapolated long-term survival

ANDROMEDA	DARA/ BORT/ CYC/ DEX (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

◉ Does ANDROMEDA show survival benefit? With immature data, how best to model survival? Await final results? Surrogates? ◉ Is it reasonable to assume that life expectancy depends only on the depth of haematologic response achieved at the response assessment timepoint?

Choosing population to model

Key trial ANDROMEDA excludes cardiac stage IIIb; marketing authorisation does not exclude cardiac stage IIIb, company positions across marketing authorisation

Background

- **Company:** ANDROMEDA in original base case (b), EMN23 post-2010 subset in additional revised base case (a)
- **ERG base case:** ALchemy

Stakeholder comments

- Cardiac stage IIIb represents 20% of patients; high unmet need. Real world evidence of daratumumab effectiveness in this subgroup
- "UK ALchemy study is the best current data in the absence of a mandated registry for all patients diagnosed with AL amyloidosis. It does however only incorporate those well enough for a referral to the National Amyloidosis Centre"

ERG comments

- Company presents no evidence for cardiac stage IIIb disease. Relative effectiveness and safety are highly uncertain
- ALchemy most relevant data source for UK clinical practice

◉ *Should model include evidence for people with cardiac failure IIIb?*
◉ *If so, is it reasonable to look to observational data?*

Observational studies: EMN23 + ALchemy

Newly diagnosed patients with AL amyloidosis

Company models overall survival by haematological response using data from observational studies including cardiac stage IIIb for BORT/CYC/DEX, then applying ANDROMEDA relative treatment effect

Critique of ALchemy: survival curves for complete response and very good partial response cross

ERG comments: 'Source of overall survival data has a large impact on the cost-effectiveness results'. ALchemy is most relevant study to inform UK outcomes

Critique of EMN23: only XXX patients treated with 1st line bortezomib, different standard of care in other countries, 'looser' interpretation of response criteria, unable to critically appraise because company submitted limited data and only abstracts/posters

	EMN23 post 2010' subset – Company preferred	ALchemy – ERG preferred
N	XXXX 1156 UK based	1194 (ITT cohort); 1133 (1-month landmark cohort)
Design	Retrospective	Prospective
Recruitment	2011-2018	Feb 2010 - Aug 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	Bortezomib-based XXXX	Upfront bortezomib-based regimens
Follow-up median	XX months	Not reported; OS to **125 months**

◉ *Is modelling haematological response as a surrogate for survival appropriate?*

Baseline characteristics 3 clinical studies

	ANDROMEDA	EMN23	ALchemy
N	388	3065	1194
Mean (SD) age, years	XXXX	XXXX	-
Baseline ECOG score, n (%)			
0	XXXX	XXXX	
1	XXXX	XXXX	1117 (94)
2	XXXX	XXXX	
3	-	XXXX	
4	-	XXXX	77 (6)
Not reported	-	XXXX	-
Mean time since first diagnosis (SD)	XXXX	XXXX	-
Number organs involved			
1 organ, n (%)	XXXX	1123 (37)	-
2 organs, n (%)	XXXX	1224 (40)	-
≥3 organs, n (%)	XXXX	700 (23)	-
Not reported, n (%)	-	XXXX	-
Cardiac stage based on Mayo Clinic Cardiac Staging System[a], n (%)			
I	XX (23)	512 (17)	183 (15)
II	XXX (40)	1066 (35)	409 (34)
IIIa	XXXX	853 (28)	418 (35)
IIIb	XXXX	485 (16)	184 (15)
Not reported		XXXX	-

◉ *Which trial or cohort best reflects people in UK that would be treated with daratumumab?*

Survival BORT/CYC/DEX by haematological response after 3 cycles

Company prefers EMN23 blue

ERG prefers ALchemy orange 3 cycles 'most relevant to inform UK practice'

NI

Survival BORT/CYC/DEX by haematological response after 6 cycles

Company prefers EMN23 blue 6 cycles

ERG prefers ALchemy orange 3 cycles 'most relevant to inform UK practice'

NI

Predicted survival at 15 years by study

Haematologic response → Extrapolation based on ↓	Complete response	Very good partial response	Partial response	No response
ERG clinical advisors	~ 25-30%	Slightly lower	Few	Very few
Assessing response after 3 treatment cycles				
EMN23 (post-2010 subset)	XXXX	XXXX	XXXX	XXXX
ALchemy	31%	28%	12%	8%
Assessing response after 6 treatment cycles				
EMN23 post-2010 subset	XXXX	XXXX	XXXX	XXXX
ALchemy	35%	24%	9%	5%

ERG comments

- Main difference is in predictions for very good partial response – EMN23 predicts lower survival than ALchemy at 15 years
- Curves for complete response predict slightly higher survival using EMN23 than ALchemy
- ERG continues to prefer ALchemy

◉ *In absence of mature trial data, which study best reflects survival in UK patients on chemotherapy? EMN23 post-2010 subset or ALchemy?*

ANDROMEDA adverse events interim analysis

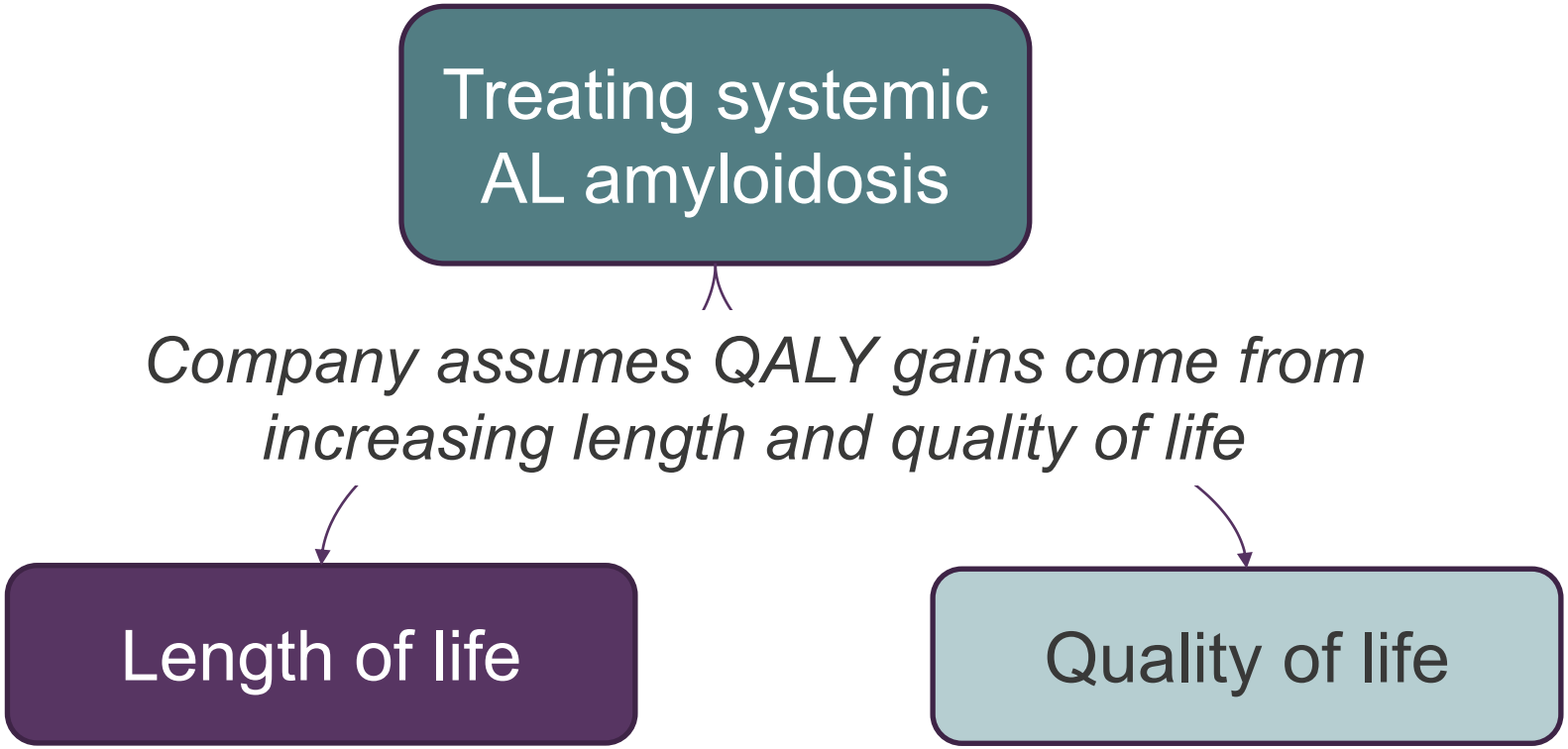
	DARA/BORT/CYC/DEX (N=193), n (%)	BORT/CYC/DEX (N=188), n (%)
Any treatment emergent adverse event	[redacted] (98)	[redacted] (98)
≥1 related to treatment	[redacted]	[redacted]
≥1 related to daratumumab	[redacted]	[redacted]
≥1 related to bortezomib	[redacted]	[redacted]
≥1 related to cyclophosphamide	[redacted]	[redacted]
≥1 related to dexamethasone	[redacted]	[redacted]
Any serious	[redacted] (43)	[redacted] (36)
≥1 related to treatment	[redacted]	[redacted]
≥1 related to daratumumab	[redacted]	[redacted]
≥1 related to bortezomib	[redacted]	[redacted]
≥1 related to cyclophosphamide	[redacted]	[redacted]
≥1 related to dexamethasone	[redacted]	[redacted]
leading to stopping daratumumab	[redacted]	[redacted]
leading to stopping bortezomib	[redacted]	[redacted]
leading to stopping cyclophosphamide	[redacted]	[redacted]
leading to stopping dexamethasone	[redacted]	[redacted]
leading to stopping study treatment	8 (4)	8 (4)
Deaths	27 (14)	[redacted]
≥1 grade 3 or 4 treatment emergent adverse event, >5%	[redacted] (57)	[redacted] (59)

Company uses in model

◉ *Is it reasonable for company to include only events that occur in >5% of patients in the model?*

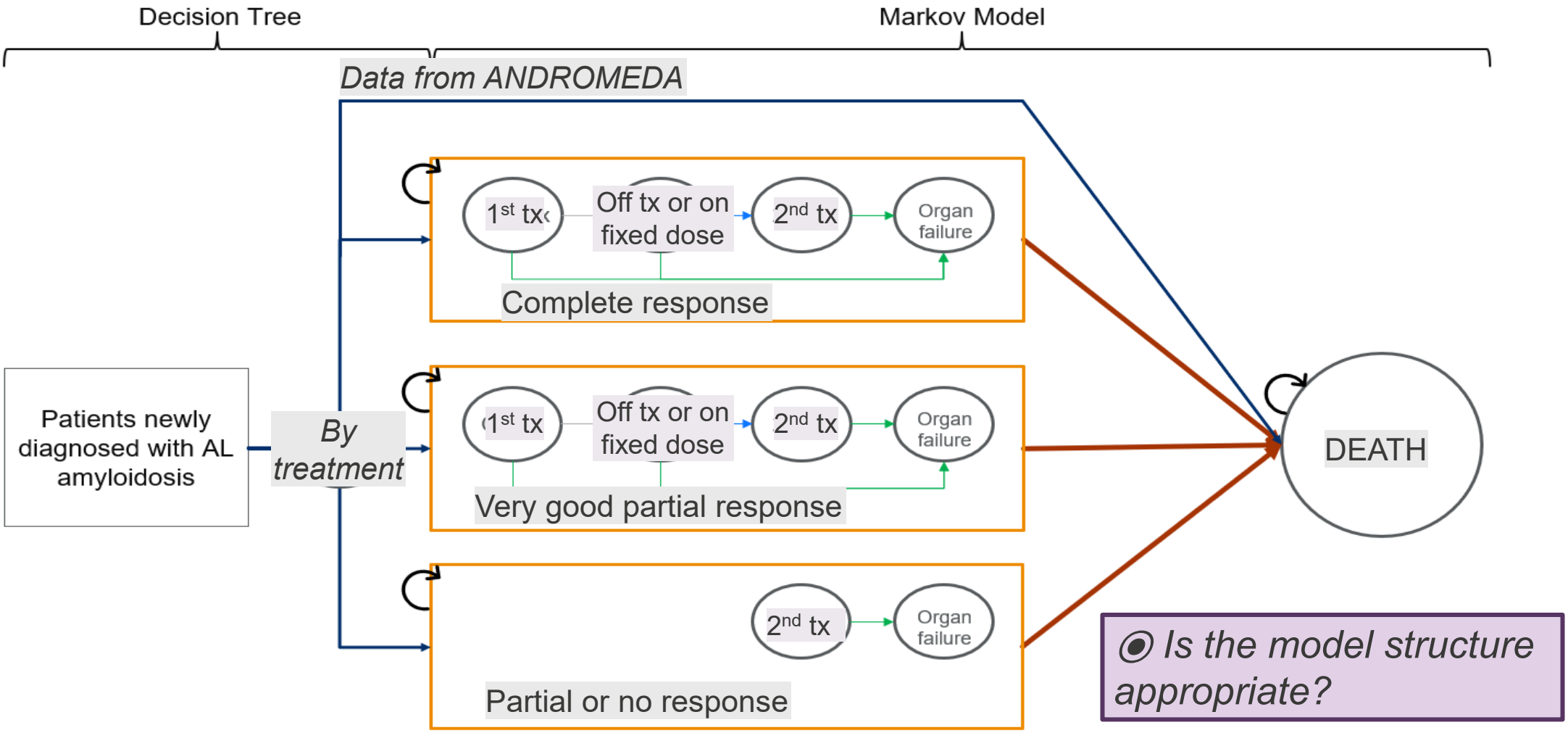
Cost-effectiveness evidence

Where do QALY gains come from?



↑ *QALYs from ↑ proportion of patients who achieve complete haematological response and so better quality of life; lower risk of progression to 2nd-line therapy and end-stage organ failure; longer life*

Company model structure



- Cohort model: 5 Markov health states, 28-day cycle, ½ -cycle correction, 35-year time horizon, 3.5% discount rate
- Company does not assume that treatment effect is sustained over time; **24-cycle stopping rule for DARA as per trial**
- Patients on DARA 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)

Structure: Combining partial + no response

Background

- **Company:** assumes patients whose disease respond sub-optimally (partial or none) are treated the same clinically. Combines response groups in model
- **ERG:** patients who achieve partial response are expected to survive longer. Calculating survival as weighted average of 2 response groups underestimates survival in combined group. May favour DARA/BORT/CYC/DEX
- **Company:** did not revise model structure within technical engagement time frame. Did an exploratory analysis by calculating survival for response groups separately and by treatment arm; similar results to pooling. Considered separating PR and NR may favour DARA/BORT/CYC/DEX

Stakeholder comments

- Aim is for at least very good partial response

◉ *Does combining categories reflect clinical care?*

Modelling when to assess response

Background

- **Company base case:** uses haematological response instead of – and to inform – overall survival, after 6 cycles
  - Response improves over time
  - Suggests conservative because patients on BORT/CYC/DEX would stay on 1st line treatment longer
  - Company clinical expert: 6 cycles reflects clinical practice
- **ERG base case:** after 3 cycles reflects NHS clinical practice

Stakeholder comments

- "ALchemy trial suggests that the response assessment should be at 3 months and in fact demonstrates a benefit for a 1 month assessment"
- "Patients may have an assessment of response at 3 months, but the potential for switching to second line treatment does tend to happen at around the 6 month point unless the patient is not tolerating treatment ... response at both 3 and 6 months would have been a better approach"

ERG comments

- Survival curves that inform probability of death are stratified by response at the specific time point. Therefore, survival curves at 3 cycles reflect deepening of response over time

◉ *When should response be assessed?*

Extrapolating survival by haematological response after 6 cycles using EMN23 post-2010 subset data – Company

Depth of haematologic response	Parametric survival model
Complete response	Exponential
All other responses	Weibull

[redacted]

◉ *Has overall survival been modelled appropriately?*

Utility values

Background

- **Company:** used EQ-5D-5L data from ANDROMEDA by haematological response at 6 cycles
  - Considers HRQoL related to:
    - Which haematological response
    - Decreases with progression to 2nd-line therapy, organ failure and haemodialysis
    - Decreases for treatment-related adverse events grade 3 and 4 reported in >5% –
      - assumes decrements depend on response to 1st-line treatment but company does not provide a justification
  - Revised base case by applying age-adjusted utilities
- **ERG:**
  - Considers EQ-5D-5L utility values by haematological response highly uncertain because:
    - values lack face validity for very good partial response
    - short follow-up period of 6 cycles to inform long-term utility values
    - limited data during 2nd line treatment + end-stage organ failure
  - Scenario: utility values on 2nd line treatment + end-stage organ failure do not differ by haematological response – small impact on ICER
  - Consider ALchemy SF-36 data (baseline, 3, 6 and 12 months) to inform utilities

Stakeholder comments

- Impact of organ involvement on utility values underestimated

ANDROMEDA mean EQ-5D-5L interim analysis

Open label trial

used in model

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◉ *Face validity? Missing data?*

Utility values chosen by company by health state

Based on ANDROMEDA EQ-5D-5L valued with UK tariff van Hout et al (2012)

Item	Values	Sources
Response 'On 1st line therapy' and Off treatment or on fixed daratumumab therapy'		
Complete	XXXX	Note: Very/good partial: mean values for other categories, because value for very good partial (XXXX) lower than partial and no response
Very good partial	XXXX	
Partial + no	XXXX	
Health state 'On 2nd line therapy'		
Complete	XXXX	Utility on '1st line therapy', reduced by disutility of 2nd line therapy of XXXX
Very good partial	XXXX	Disutility associated with 2nd line therapy estimated as difference between mean baseline utility score (XXXX) and mean utility value associated with 'progressive disease'
Partial + no	XXXX	
Health state 'End-stage organ failure		
Complete	XXXX	Based on utility on '1st line therapy', reduced by the disutility due to end-stage organ failure (XXXX) and disutility from haemodialysis (0.10) and proportion of patients who have haemodialysis (XXXX; from modified Delphi panel of expert clinicians)
Very good partial	XXXX	
Partial + no	XXXX	Disutility end-stage organ failure difference between mean baseline utility (XXXX) and patients with chronic heart failure assessed for heart transplant (0.5)
One-off reduction in quality-adjusted life years because of adverse events		
DARA/BORT/CYC/DEX	0.0029	Based on disutility related to ANDROMEDA specific adverse events assuming that they affect utility over 21 days
BORT/CYC/DEX	0.0020	

◉ *Face validity?*

Maximum duration for daratumumab monotherapy

Background

- **Company:** assumes daratumumab given up to 24 cycles (XXXX patients reached 24 cycles in landmark analysis)
  - Company UK expert clinicians: treatment beyond 2 years highly unlikely
  - Scenario: daratumumab treatment duration 24 cycles (rather than mean XX cycles)
- **ERG:** Summary of product characteristics does not include 24-cycle stopping criterion
  - If patients continue monotherapy past 24 cycles, daratumumab costs underestimated
  - Model structure not flexible to permit monotherapy >24 cycles
  - ERG clinical advisors: If option available, patients with no disease progression may choose to continue with monotherapy

Stakeholder comments

- "Stipulating a maximum timeframe for daratumumab would take away the option of carrying on with treatment.'
- 'This is especially pertinent for the small proportion of patients with concomitant multiple myeloma with a high proportion of plasma cells in their bone marrow"

◉ *Would NHS treatment stop at 24 cycles? Treatment waning?*

Treatment administration costs underestimated

Background

- **Company:** originally underestimated costs of subcut administration of DARA and BORT
  - Revised costs (**£99.30**) to align with NICE appraisal ID1510 (daratumumab in untreated multiple myeloma)
  - Used NHS Reference Costs 2019/20. N10AF: **Specialist Nursing**, Cancer Related, Adult, Face to face
- **ERG:**
  - Company revised costs are lower than national cost collections **£241-£332**
  - ERG clinical advisors: DARA and BORT need preparation; DARA needs observation after administration. Administration conducted as day case or outpatient visit
  - HRG code for **procurement of chemotherapy** for average cycle. Includes all costs related to procuring each drug cycle and costs of supportive drugs. For bortezomib-based regimens, HRG codes are:
    - SA10Z for procurement per cycle: average cost weighted by activity is £2,110.10
    - SB12Z for 1st delivery of cycle: average cost weighted by activity is £241.12
    - SB15Z for deliveries in same cycle: average cost weighted by activity is £332

Stakeholder comments

- Incremental administration costs of adding DARA to BORT/CYC/DEX unlikely to be great

◉ *How would DARA and BORT be administered? Specialist nursing or chemotherapy administration?*

Impact of treatment on autologous stem cell transplants (ASCT)

Background

- **Company:**
  - **Base case:** excludes cost of ASCT although some patients received in trial
  - Original scenario: used ALchemy to inform distribution of patients by 2nd and 3rd line therapy that included ASCT, included unit cost of ASCT £15,065
  - Additional scenario: used EMN23 data, XXX of patients have ASCT as 2nd line treatment; impact on costs only, not health outcomes
- **ERG:** excluded ASCT costs from 1st line because impact of DARA/BORT/CYC/DEX on patients having ASCT is uncertain → likely small impact on ICER
  - Considers should include ASCT to reflect UK clinical practice
  - Company's scenario using ALchemy more likely to reflect UK practice
  - If DARA/BORT/CYC/DEX affects having ASCT, would likely impact health outcomes, not only costs

Stakeholder comments

- No data available. More patients may be eligible for ASCT if there are better responses to DARA/BORT/CYC/DEX
- Organ involvement excludes ASCT – would take months for significant improvements in cardiac and renal parameters

◉ *Should model include autologous stem cell transplants?*

Costs of 2nd and 3rd line treatments

Background

- **Company base case:** used UK clinical expert opinion on type of treatment and distribution of patients by 2nd and 3rd line therapies
  - Scenario: used distributions from ALchemy
- **ERG base case:** used ALchemy as considers it a more relevant source of evidence

Principle agent	Proportion receiving 2nd-line therapy		Proportion receiving 3rd-line therapy	
	UK clinical experts	ALchemy	UK clinical experts	ALchemy
Bortezomib	10%	8%	-	2%
Lenalidomide	75%	55%	30% DARA/BORT/CYC/DEX 20% BORT/CYC/DEX	58%
Melphalan	5%	11%	-	2%
ASCT	-	11%	-	12%
Panabinostat	-	0%	-	5%
Pomalidomide	-	2%	70% DARA/BORT/CYC/DEX 80% BORT/CYC/DEX	13%
Carfilzomib	10%	1%	-	2%
Bendamustine	-	8%	-	6%
Thalidomide	-	4%	-	0%
Cyclophosphamide	-	2%	-	0%

◉ *What is the best source of 2nd line treatments? Trial? UK clinical experts? ALchemy?*

End-of-life criteria

Short life expectancy of 24 months, treatment extends survival by average >3 months

Background

- **Company:**
  - Considers patients with **cardiac stage IIIb** meet NICE's end-of-life criteria:
    - expected overall survival is about 6 months (source not provided)
    - model predicts that DARA/BORT/CYC/DEX extends their life by >3 months ([redacted] years in base case A and [redacted] years in base case B)
- **ERG:** Considers company did not present evidence to support conclusion
    - Company estimates refer to entire patient population in whom company seeks recommendation, of which patients with stage IIIb disease are about 15%
    - In the entire patient population, estimate of overall survival with current **standard of care** (BORT/CYC/DEX) is [redacted] years, well above end-of-life criterion of 24 months
  - Satisfied end-of-life criteria **not** met

◉. *Has company demonstrated end of life criteria across marketing authorisation?*

Company and ERG base case

Parameter	Company base case	ERG base case
Modelled population	**Base case A:** EMN23 post-2010 subset **Base case B:** ANDROMEDA	ALchemy
Timing of response assessment	6 cycles	3 cycles
Source of data for overall survival by response	EMN23 post-2010 subset	ALchemy
Approach to costs of 2nd and 3rd line therapies: source of data on regimens and associated proportions	UK clinical advisory board	ALchemy

Innovation and equality considerations

Innovation

- Substantial unmet need for a novel, effective and well-tolerated treatment for newly diagnosed AL amyloidosis
- First licensed option for AL amyloidosis
- Daratumumab significantly improves haematological and organ responses

Equality considerations

- ANDROMEDA excluded cardiac stage IIIb disease as they are not typically candidates for BORT/CYC/DEX at the specific dose and dosing schedule used in trial
- These patients have most severe degree of cardiac involvement, poor prognosis and a significant unmet need

◉ *Is DARA/BORT/CYC/DEX innovative?*

◉ *Are there any equality issues to consider?*

End of Part 1

Results will be presented in Part 2 because of confidential price discounts