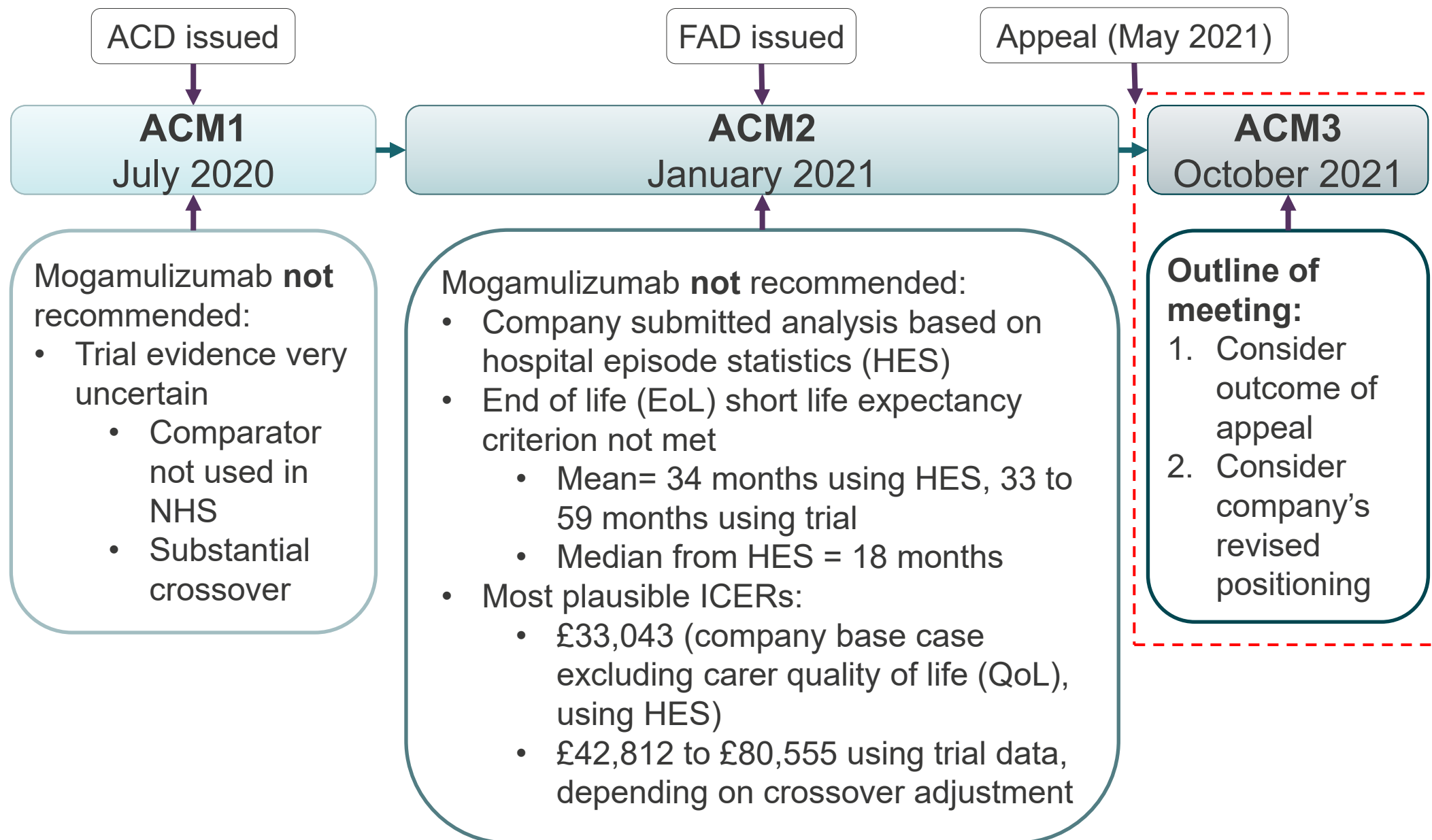


# Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

## **ACM 3 presentation – post-appeal**

14<sup>th</sup> October 2021

# History of appraisal



ACD: Appraisal consultation document; ACM: Appraisal committee meeting; EoL: End of life; FAD: Final appraisal document; HES: Hospital episode statistics; ICER: Incremental cost-effectiveness ratio; QoL: Quality of life

# Appeal summary

- Appeals submitted by company, Lymphoma Action/Leukaemia Care and the UK Cutaneous Lymphoma Group
- 18 points submitted, 4 upheld, 2 suggestions for clarification

<b>Committee asked to:</b>	Clarify how carer utilities were included in its decision making.
	Clarify how it decided on the appropriate ICER threshold, with particular reference to uncertainty and disease rarity.
	Make clear it considered there is likely to be a survival benefit for mogamulizumab compared to NHS standard care and how that impacts on its reasoning.
	Revisit decision on short life expectancy, clarifying that relevant period is survival from 2 <sup>nd</sup> line treatment, and what data it uses.
<b>Committee may wish to consider rewording FAD to:</b>	<ul style="list-style-type: none"><li>• More accurately reflect reasoning on why it concluded the HES database was not adequately matched to the trial data.</li><li>• Clarify that the uncertainty introduced by the vorinostat comparison concerns cost-effectiveness in an NHS setting rather than the clinical effectiveness of mogamulizumab.</li></ul>

FAD: Final appraisal document; HES: Hospital episode statistics; ICER: Incremental cost-effectiveness ratio

# Upheld appeal points

Appeal point	Summary	Slide
Point 1	Clarify how carer utilities were included in the committee's decision making.	10
Point 2	Clarify how the committee decided on the appropriate ICER threshold, with particular reference to uncertainty and disease rarity.	12
Point 3	Make clear the committee considered there is likely to be a survival benefit for mogamulizumab compared to NHS standard care and how that impacts on its reasoning.	14 to 15
Point 4	Revisit decision on short life expectancy, clarifying that relevant period is survival from 2 <sup>nd</sup> line treatment, and what data the committee uses.	17 to 18

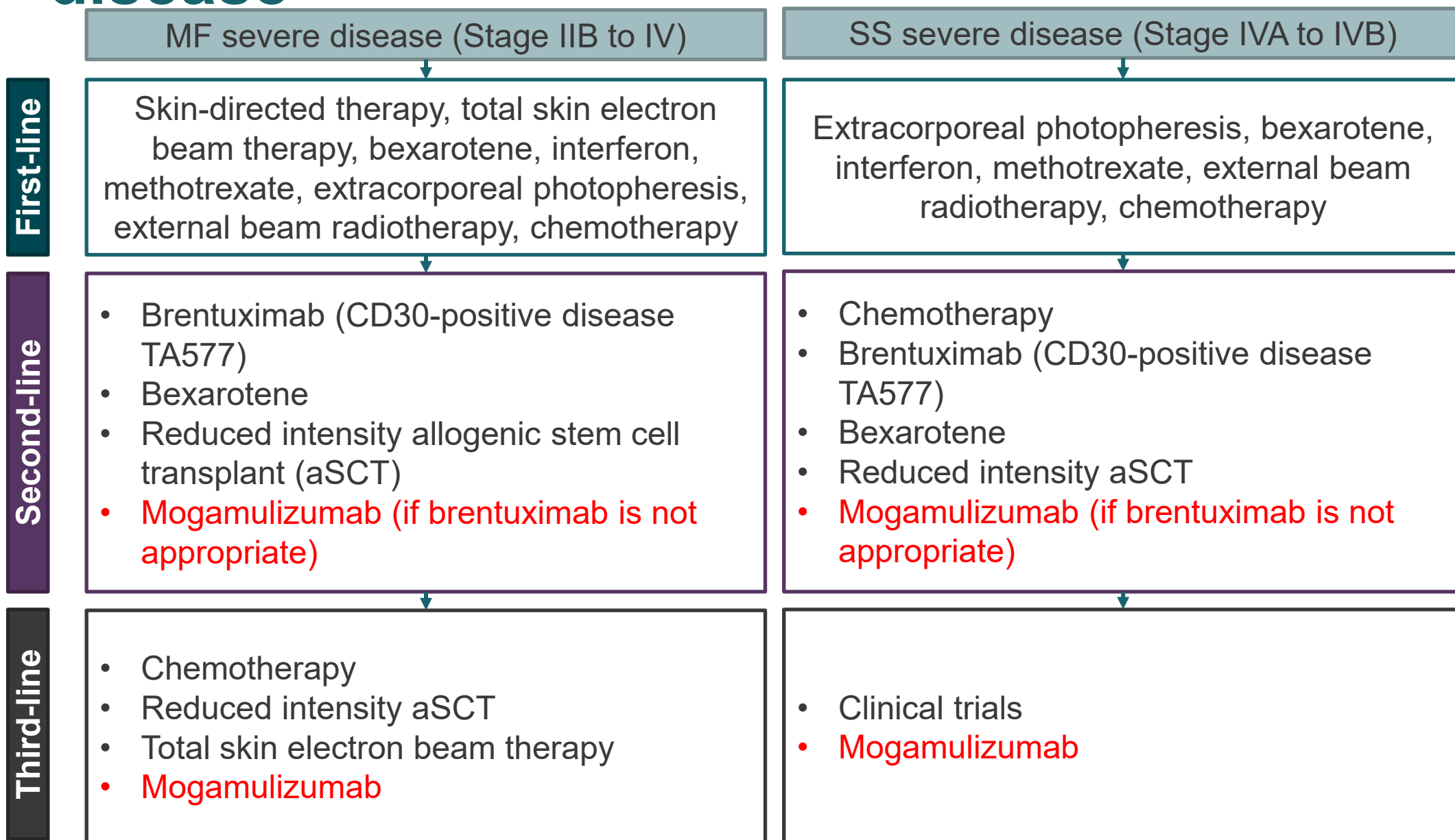
ICER: Incremental cost-effectiveness ratio

**NICE**

# Company's revised positioning

<b>Marketing authorisation (MA)</b>	Treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.
<b>Mechanism of action</b>	Mogamulizumab is a defucosylated, humanized IgG1 kappa immunoglobulin that selectively binds to C-C chemokine receptor type 4 (CCR4), a G-protein-coupled receptor for C-C chemokines that is involved in the trafficking of lymphocytes to various organs including the skin, resulting in depletion of the target cells.
<b>Positioning at ACM1 and ACM2</b>	Severe disease after brentuximab or if it's not appropriate i.e. 2 <sup>nd</sup> line+.
<b>Positioning post-appeal</b>	<p>Severe disease after <b>2 prior therapies</b> for MF and 1 prior therapy for SS.</p> <p><b>Rationale:</b></p> <ul style="list-style-type: none"> <li>• From 3<sup>rd</sup> line, mogamulizumab would be the only treatment option that has not been recycled.</li> <li>• For SS treatment options are limited even from 2<sup>nd</sup> line, as SS patients have minimal CD30 positivity (required for brentuximab).</li> </ul>
<b>List price</b>	<p>The list price is £1,329 per vial (20mg mogamulizumab in 5ml or 4mg/ml), the average cost of a course of treatment is £57,109.</p> <p>Simple discount PAS approved (<b>updated post appeal</b>)</p>

# Original treatment pathway for severe disease



# Updated treatment pathway for severe disease

MF severe disease (Stage IIB to IV)

SS severe disease (Stage IVA to IVB)

First-line

Skin-directed therapy, total skin electron beam therapy, bexarotene, interferon, methotrexate, extracorporeal photopheresis, external beam radiotherapy, chemotherapy

Extracorporeal photopheresis, bexarotene, interferon, methotrexate, external beam radiotherapy, chemotherapy

Second-line

- Brentuximab (CD30-positive disease TA577)
- Bexarotene
- Reduced intensity allogeneic stem cell transplant (aSCT)

- Chemotherapy
- Brentuximab (CD30-positive disease TA577)
- Bexarotene
- Reduced intensity aSCT
- **Mogamulizumab (if brentuximab is not appropriate)**

Third-line

- Chemotherapy
- Reduced intensity aSCT
- total skin electron beam therapy
- **Mogamulizumab**

- Clinical trials
- **Mogamulizumab**

# Upheld appeal points



# Upheld appeal points

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ICER: Incremental cost-effectiveness ratio

**NICE**

# Upheld appeal point 1 – carer utility

Committee discussion	Appeal panel discussion
Carefully considered the data on carer utilities and expressed a view that a utility gain for carers greater than that for people with the disease was implausible.	The committee consideration was fairly expressed and not unreasonable.
Carer utilities were not included in the modelling.	The decision not to include carer utilities in the modelling was not unfair.
The committee recognised the burden of this condition on care-givers.	Having recognised the burden on care-givers the committee should have considered this issue qualitatively in their decision-making.
<b>Company</b> <ul style="list-style-type: none"><li>Company revised modelling <b>excludes</b> carer utilities.</li></ul>	<b>Appeal panel conclusion</b> <ul style="list-style-type: none"><li>The failure to show greater consideration of carer burden in the decision-making, and/or to have given more reasoning around what consideration may have taken place, amounted to unfairness.</li></ul>

How will committee consider carer burden in its decision making?

# Upheld appeal points

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ICER: Incremental cost-effectiveness ratio

**NICE**

# Upheld appeal point 2 – threshold, uncertainty and rarity

Committee conclusion in FAD (section 3.14)	Appeal panel conclusion
High level of uncertainty associated with the MAVORIC analysis.	The uncertainty in the appraisal was not about the effectiveness of mogamulizumab (for which there was robust data) but about the cost-effectiveness in an NHS setting → distinction not clear in FAD.
HES analysis addressed some of the issues associated with MAVORIC but was also associated with uncertainty. The committee had been aware of the issue of rarity.	The committee was not obliged to discount uncertainty in the data solely because of the rarity of the condition. However, rarity is a relevant factor to consider when committees weigh the importance of uncertainty in modifying the ICER threshold.
An acceptable ICER would be no higher than the middle of the range normally considered cost-effective (£20,000 to £30,000 per QALY gained).	There was insufficient discussion and transparency about how the appropriate ICER threshold had been decided upon ... in particular about how rarity had been weighted. Because this issue was of such importance in this appraisal, this lack of reasoning was unfair.

**How has the committee weighed uncertainty and rarity in determining an acceptable ICER? Does committee wish to revisit its conclusion?**

# Upheld appeal points

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# Upheld appeal point 3 – survival benefit (1)

Committee conclusion in FAD (section 3.9)	Appeal panel conclusion
<p>The committee was not convinced that mogamulizumab provided an overall survival (OS) benefit compared with standard care.</p>	<ul style="list-style-type: none"><li>• The panel were aware that the MAVORIC trial did not show an OS benefit for mogamulizumab but also that it was not designed to show this.</li><li>• The magnitude of the difference between OS in the MAVORIC trial and the HES data was striking, and it would therefore have been unreasonable to conclude that there was no OS benefit from mogamulizumab.</li></ul>
<p>The committee had relied on models with an OS benefit in the appraisal.</p>	<ul style="list-style-type: none"><li>• At the hearing the committee said it accepted a mogamulizumab OS benefit. However, the FAD clearly states <i>“the committee was not convinced that mogamulizumab provided an overall survival benefit compared with standard care”</i> which seemed to the panel an unreasonable statement.</li><li>• The panel noted the committee’s comments about the context of this statement, but did not think this would be clear to people reading the FAD.</li></ul>

FAD: Final appraisal document; HES: Hospital episode statistics; OS: Overall survival

# Upheld appeal point 3 – survival benefit (2)

## Additional text from appeal decision

- Prof O'Brien, for the appraisal committee, said that although the MAVORIC trial did not show a significant difference in OS between treatment and control arms (which was an active treatment not used in the NHS), the committee accepted that there may well be an OS benefit when compared to NHS current practice.
- It considered a number of scenarios with an OS benefit, and did not ask for a scenario without OS benefit.
- He said that the statement in the FAD should be considered in following context; this paragraph was specifically considering the issue of how to adjust for cross-over, so the statement was explaining why it was appropriate to consider the ERG approach to this issue (which showed a lower OS benefit).

**How should the FAD be revised to reflect above?**

FAD: Final appraisal document; OS: Overall survival

# Upheld appeal points

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# Upheld appeal point 4 – short life expectancy (1)

## Committee conclusion in FAD (section 3.13)

- Concerned about differences between the median results from HES and the mean results when it is used in the model → cost-effectiveness results and decisions are based on mean QALYs and costs.
- Other sources of data such as that from Cutaneous Lymphoma International Consortium (CLIC), the model outputs using the trial data and professional organisation submissions all suggested survival >24 months.
- Overall, not robust evidence that the short life expectancy criterion had been met.

Data considered at ACM2	Median	Mean from model
MAVORIC IPCW	-	33 months
MAVORIC 2 stage-estimation	-	59 months
HES data	18 months	34 months
CLIC	63 months	-
Expert response to TE	36 to 60 months	-

**At appeal it was discussed that median from CLIC and expert response to technical engagement (TE) was from diagnosis, not 2nd line treatment**

# Upheld appeal point 4 – short life expectancy (2)

Appeal panel discussion	Appeal panel conclusion
<ul style="list-style-type: none"><li>• Agreement that survival from time of initiation of 2<sup>nd</sup> line treatment (not time from diagnosis) is the relevant parameter for decisions about the EoL criteria.</li><li>• Data on this is less robust than data on survival from diagnosis.</li></ul>	<p>The panel were persuaded by the ERG’s own view that the HES data provide the best available source of evidence on this.</p>
<ul style="list-style-type: none"><li>• The committee were not obliged to prefer the HES data because of the advice from the ERG.</li></ul>	<p>The committee did not provide reasons in the FAD or during the hearing for why it had not agreed that this was the best source of evidence.</p>
<ul style="list-style-type: none"><li>• The FAD suggests that the data from the CLIC and the professional organisations’ response to TE had been relied upon in reaching a decision about the EoL criteria.</li></ul>	<p>The final decision about the short life expectancy criterion “did not add up”.</p>

**How should the FAD be revised to reflect above?**

EoL: End of life; FAD: Final appraisal document; HES: Hospital episode statistics; TE: Technical engagement

# Additional company analyses

# Additional company data – matched adjusted indirect comparison (MAIC) scenario

## Company – post-appeal submission

- Included a scenario analysis including age and sex.
- This had a negligible effect on the hazard ratio for overall survival.

Adjusted for:	Hazard ratio for overall survival (95% confidence interval)
MF/SS	0.36 (0.24 to 0.53)
MF/SS, age, sex	0.38 (0.25 to 0.59)

## ERG

- Agree with company that the sensitivity analysis including age and sex had a negligible effect on the hazard ratio compared to the base case analysis.
- However, the uncertainty of the MAIC remains given the likelihood that not all prognostic factors were employed for the adjustment.

MAIC: Matched adjusted indirect comparison; MF: Mycosis fungoides; OS: Overall survival; SS: Sézary syndrome

# Additional company data – survival analysis (1)

OS extrapolation: company	OS extrapolation: ERG
Mogamulizumab: exponential curve	Mogamulizumab: exponential curve
<ul style="list-style-type: none"> <li>Statistically best fitting, provides a good visual fit, clinically plausible.</li> </ul>	<ul style="list-style-type: none"> <li>ERG agreed with the company's choice of distribution for OS in the mogamulizumab arm.</li> </ul>
ECM: exponential curve	ECM: lognormal
<ul style="list-style-type: none"> <li>Gen. gamma was best fitting but predicts a plateau in survival: not clinically reasonable.</li> <li>Many of the HES extrapolations predict better survival than for moga: not clinically reasonable.</li> <li>Lognormal predicts clinically implausible 20% alive at 5 years.</li> </ul>	<ul style="list-style-type: none"> <li>Second best fit (for both arms).</li> <li>Exponential best fit for moga, but worst fit for HES.</li> <li>Gen. gamma is best fit for HES and could be clinically plausible. Suggests more than 10% of patients cured, but company also notes the long survival of ~10% of people who have aSCT in the HES data.</li> <li>Different curves → large differences in extrapolated survival.</li> </ul>

## FAD conclusions (section 3.10):

- Company/ERG used exponential for moga (best statistical fit); for ECM, ERG preferred lognormal
- Gen gamma was best fit for ECM, but company and ERG agreed not clinically plausible
- “...using different extrapolations in each arm needs strong justification”*
- “...the company's approach was acceptable for decision making”.*

# Additional company data – survival analysis (2)

## AIC and BIC statistics OS

Model	AIC HES	BIC HES	AIC moga	BIC moga
Exponential	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Generalised Gamma	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Log-normal	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

## Comparison of OS extrapolations



**What is the most appropriate model for extrapolating OS?**

# End of life

Updated positioning of mogamulizumab – company base case (exponential both arms)

Criterion	Mean (months)	Median (months)
<b>Short life expectancy:</b> life expectancy less than 24 months for people having treatment with any standard care	28	13
<b>Extension to life:</b> the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared to current NHS treatment	52.6	-

All other extrapolations of the HES data lead to a mean life expectancy greater than 28 months

Original positioning of mogamulizumab

	Mean (months)	Median (months)
<b>Short life expectancy (ECM)</b>	34.4	17.8
<b>Extension to life</b>	44.6	-

**Are the end of life criteria met?**

ECM: Established clinical management; HES: Hospital episode statistics

# Dismissed appeal point – mean vs median

## Appeal panel conclusion

- On the specific issue of whether it was unreasonable of the committee to prefer median rather than mean figures in reaching a decision about survival about the EoL criteria, the appeal panel concluded:
  - The committee had not disregarded median survival and gave a reasoned explanation for why it had preferred to use mean survival data.
  - It is possible that a different committee could have reached a different decision, but the panel did not judge that this decision was unreasonable.

## Company

- Mean is: “*skewed by ‘super-survivors’, the long survival of ~10% of patients receiving the only potentially curative treatment, aSCT after current and subsequent treatment in HES*”.
- FAD section 3.7, committee prefers removing aSCT after current treatment from the moga arm of the cost-utility analyses → ECM arm includes some benefits and no costs of aSCT.

## ERG

- ‘Super-survivors’ are part of the same cohort for which life expectancy is estimated and so their life expectancy is not a bias but part of the life expectancy of the whole cohort.
- Removing aSCT in the FAD was intended to remove potential bias in the estimate of the *difference* between mogamulizumab and standard care in QALYs and costs, not to imply that the *absolute* estimate of life expectancy was biased by the inclusion of asCT.



# Cost-effectiveness estimates

# Key modelling assumptions

Assumption	Company base case	ERG base case
Positioning	Severe disease after 2 prior therapies for MF and 1 prior therapy for SS	
Data source for comparator	HES data	
Carer utilities	Excluded	
aSCT	aSCT excluded after current treatment	
OS extrapolation	Exponential for both arms	Lognormal for ECM
NTFS and PFS extrapolation of ECM	Log-logistic	
NTFS and PFS extrapolation of mogamulizumab	Lognormal	
TTD	Kaplan-Meier curves	
MAIC	Matched on histology, age and gender	

aSCT: Allogenic stem cell transplant; ECM: Established clinical management; HES: Hospital episode statistics; MF: Mycosis fungoides; MAIC: Matched adjusted indirect comparison; NTFS: Next-treatment-free survival; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation; SS: Sézary syndrome

# Company revised base case results\* *Updated PAS*

## Deterministic results (PAS price for mogamulizumab)

	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Established clinical management	XXXXXXXXXX	1.60			
Mogamulizumab	XXXXXXXXXX	4.68	£86,998	3.08	£28,233*

## Probabilistic results (PAS price for mogamulizumab)

	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Established clinical management			
Mogamulizumab	£86,147	3.06	£28,116

\*There is a confidential discount for bexarotene. Including this increases all ICERs by less than 1%

\*\*Adjusting the baseline characteristics to match the refined population has a minimal impact on the cost-effectiveness results (less than £50)

ICER: Incremental cost-effectiveness ratio; PAS: Patient access scheme; QALY: Quality-adjusted life year

# ERG revised base case results\* *Updated PAS*

## Deterministic results (PAS price for mogamulizumab)

	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Established clinical management	XXXXXXXXXX	2.10			
Mogamulizumab	XXXXXXXXXX	4.68	£81,292	2.58	£31,475

## Probabilistic results (PAS price for mogamulizumab)

	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Established clinical management			
Mogamulizumab	£80,663	2.56	£31,509

\*There is a confidential discount for bexarotene. Including this increases all ICERs by less than 1%  
 ICER: Incremental cost-effectiveness ratio; PAS: Patient access scheme; QALY: Quality-adjusted life year

# ERG scenario analysis *Updated PAS*

## Deterministic results

Overall survival	ICER (£/QALY)
Exponential for both arms (company preferred)	£28,233
Lognormal for ECM (ERG preferred)	£31,475
Generalised gamma for HES arm	£36,720
Lognormal for both arms	£26,859

ECM: Established clinical management; HES: Hospital episode statistics; ICER: Incremental cost-effectiveness ratio; PAS: Patient access scheme; QALY: Quality-adjusted life year

# Innovation and equality

## Innovation:

- Is mogamulizumab innovative?
  - Mogamulizumab is a CCR4 monoclonal antibody.
- Any uncaptured benefits in model?
  - Company notes benefits of aSCT for 5.2% of patients captured in ECM arm, but not the costs.
  - Carer burden not captured.

## Equality:

- Are there any equality issues?

aSCT: Allogenic stem cell transplant; CCR4: C-C chemokine receptor type 4; ECM: Established clinical management