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

ACM 2 presentation

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Company: Kyowa Kirin

13th January 2021

Key issues

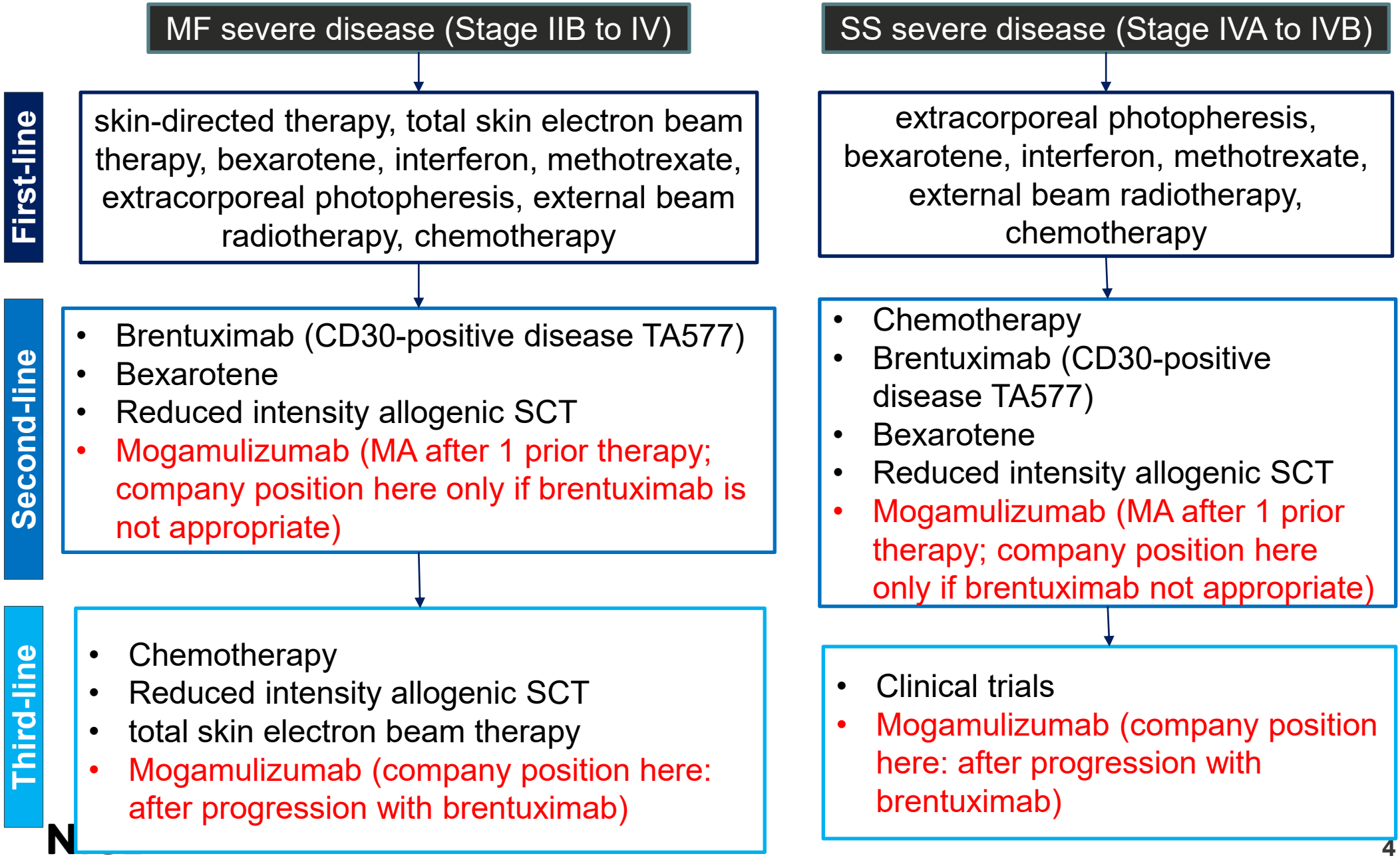
- Should decision-making be based on the original analysis using the MAVORIC trial data or the new analysis using hospital episodes statistics (HES) data?
  - If HES data is used, which extrapolation predicts the most plausible overall survival for established clinical management?
- Should the cost-effectiveness analyses include caregiver utilities?
- Are the end-of-life criteria met?

Mogamulizumab (Poteligeo, Kyowa Kirin)

Company's proposed positioning is narrower than marketing authorisation (severe disease after brentuximab or if it's not appropriate)

Marketing authorisation	Treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.
Mechanism of action	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.
Administration	• 1 mg/kg administered as an intravenous infusion over at least 60 mins • Administration is weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every 2 weeks on Days 1 and 15 of each subsequent 28-day cycle until progression or unacceptable toxicity.
Price	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. Simple discount PAS approved **(updated post ACM1)**

Treatment pathway for severe disease



ACM1 – Preliminary recommendation

- Mogamulizumab is not recommended, within its marketing authorisation, for treating mycosis fungoides or Sézary syndrome in adults who have had at least 1 previous systemic treatment.

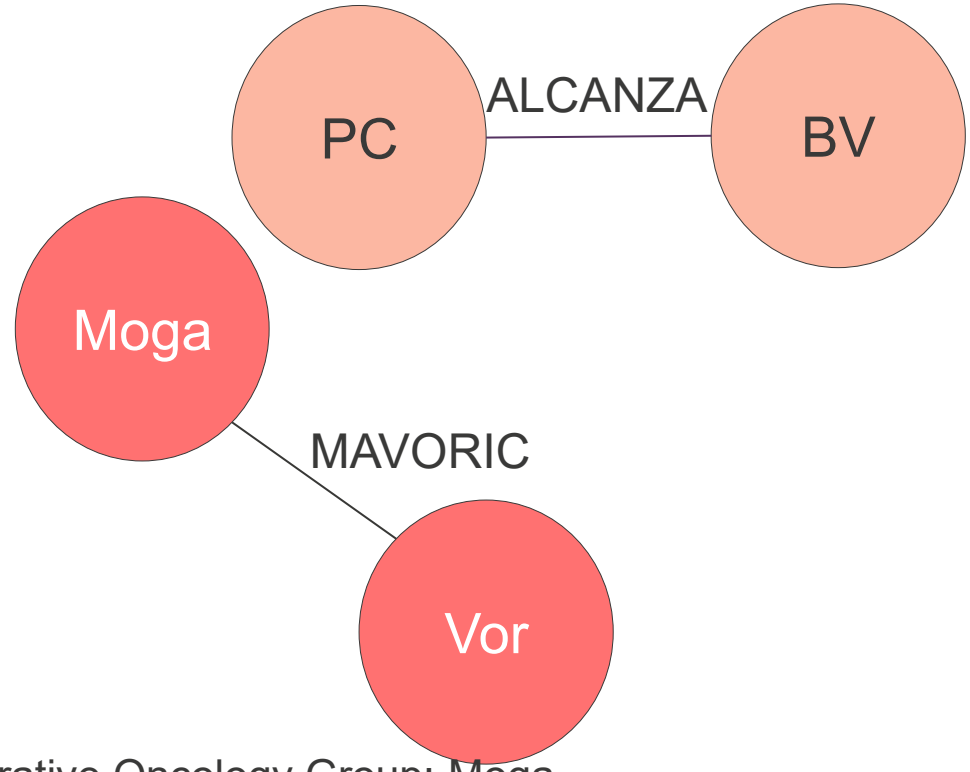
Company's original approach: vorinostat as a proxy for standard care

ACD states that clinical effectiveness of mogamulizumab is uncertain because:

- Standard care is most appropriate comparator, but mogamulizumab was compared with vorinostat in trial - vorinostat is not licenced or used in the UK
- The subgroup from MAVORIC based on severe disease included people at different stages in the treatment pathway and did not differentiate between MF and SS

ALCANZA trial was basis of TA577 brentuximab; differences between MAVORIC and ALCANZA include:*

- More heavily pre-treated patients in MAVORIC (3 median lines of therapy vs 2)
- Greater number with advanced disease in MAVORIC
- Patients with higher disease burden in MAVORIC (ECOG status 0: 56% vs. 70%; ECOG status 1: 43% vs. 27%, respectively)
- 55% MF and 45% SS patients in MAVORIC but no SS patients in ALCANZA



BV, Brentuximab vedotin; ECOG: Eastern Cooperative Oncology Group; Moga, mogamulizumab; PC, physician's choice; Vor, vorinostat

*See slides 31 and 32 for a further breakdown of differences

ACM1: Committee's preferred assumptions (resolved post-ACM1)

Issue	Committee conclusion	Company ACD response
Stopping rule	A two-year stopping rule is not acceptable	Removed stopping rule
Increase in utilities while on treatment	Preferred overall mean utilities for entire health state over cycle-specific utilities	Overall mean utilities used for health state
Time horizon	Extend to 45 years	Implemented

The company also fixed a linking mistake and corrected implementation of washout period costs.

ACM1: Committee's preferred assumptions

	Committee conclusion	Company ACD response	ERG
Comparator	Standard care	ACM1: vorinostat (MAVORIC) ACM2: Established clinical management (HES data)	Prefer original MAVORIC analysis, with TSE and IPCW crossover adjustment as upper and lower ranges
Crossover adjustment methods	TSE and IPCW as upper and lower ranges	ACM1: IPCW ACM2: no adjustments needed with HES analysis	
Allogenic stem cell treatment costs	Exclude because this was not allowed in the trial	Include allogenic stem cell treatment costs based on HES data	Exclude allogenic stem cell treatment costs
Carer utilities	Exclude carer utilities	Include carer utilities	Exclude carer utilities

HES: Hospital episodic statistics; ECM: established clinical management; IPCW: inverse probability of censoring weighting; MAIC: matched adjusted indirect comparison; OS: overall survival; TSE: two-stage estimation

ACM1: End-of-life committee considerations

Criteria	ACM1 committee conclusion

Short life expectancy	• Not enough data to conclude that criteria had been met
	• HES data median overall survival: ~1.3 years but:
	  • Only included patients who had 1 previous treatment (mogamulizumab can be used after 2 previous treatments)
	  • Includes only a small number of people with SS
	• Short life expectancy may be met for people with SS (poorer prognosis), however there is no clear evidence to support this

Extension of life of at least an additional 3 months	• Uncertain due to use of inappropriate comparator (vorinostat)

Committee conclusion: mogamulizumab is not considered to be a life-extending treatment at the end of life

ACM1: Committee conclusions

Criteria	ACM1 committee conclusion
Most plausible ICER range (including all committee's preferred assumptions)	Between £48,533 and £94,250 per QALY gained • Lower ICERs: reflect IPCW adjustment (considered clinically implausible and optimistic) • Higher ICERS: reflect TSE method (considered overly pessimistic)
End-of-life criteria	Not met
Cancer Drugs Fund	Inclusion criteria not met
Innovation	All benefits are captured in the model

Mogamulizumab is not recommended, within its marketing authorisation, for treating mycosis fungoides or Sézary syndrome in adults who have had at least 1 previous systemic treatment.

ACD consultation responses

Consultation comments

- Patient Expert
- Lymphoma Action
- Royal College of Pathologists, British Society Haematology, British Association Dermatologists.
- University Hospital Birmingham
- United Kingdom Cutaneous Lymphoma Group
    - *Endorsed by British Association of Dermatologists and the Royal College of Physicians*

Web comments (14 received)

Comments from patients, carers and health care professionals individuals and teams, including:

- Cutaneous Lymphoma Clinical Nurse Specialists at St John's Institute of Dermatology
- Lymphoma specialist nursing team, The Christie NHS Foundation Trust
- Cutaneous Lymphoma Foundation
- Manchester Cutaneous Lymphoma Group
- Cutaneous Lymphoma Multidisciplinary Team, Queen Elizabeth Hospital Birmingham

All consultation comments disagreed with the ACD outcome. Key themes have been summarised over the next few slides

Summary of consultation comments (1)

Suitability of vorinostat as a comparator

- Vorinostat as comparator does not make effectiveness of mogamulizumab uncertain
- Most patients in MAVORIC had already been exposed to UK established care management treatments and had relapsed
- Clinical literature has shown vorinostat has equivalent activity to bexarotene and interferon

Available data in cutaneous T-cell lymphoma (CTCL)

- There are limited randomised controlled trials in CTCL (majority of data is anecdotal and single-arm and no other drug has shown marked improvement in PFS or ORR)
- MAVORIC is the largest randomised controlled trial for MF/SS and included advanced patients. Company should be commended for supporting this design in the knowledge it makes OS comparisons very difficult

Unmet need and disease prevalence

- There are limited available NICE recommend treatment options
- Rarity of disease has not been fully considered

Cost savings

- Financial cost of treating patients (and potential savings) has not been fully considered, e.g.:
  - Requirement for specialist tissue viability nurses to manage complex wound care
  - Cost of antibiotics, inpatient stays etc. due to risk of infection / sepsis

Summary of consultation comments (2)

Comments on quality of life

- Quality of life benefit is supported by clinical data, patients and clinical experts and has not been fully acknowledged

Patient quality of life:

- MF/SS are highly debilitating long-term conditions and patients can deteriorate rapidly. Care for patients who are not transplant-eligible is considered palliative

Carers quality of life:

- Impact begins at presentation and has not been fully appreciated
- Primary source of psychological support and provide complex, frequent and time-consuming topical skin management

"High degree of stress, exacerbated by sleep interruptions, in an attempt to alleviate their loved one's suffering e.g. topical application of creams during the night, pain control, temperature control, itch control"

Summary of consultation comments (3)

Comments on real world experience

Real world evidence shows mogamulizumab can:

- Improve disease related symptoms in cases where conventional therapies have failed
- Change course of disease and potentially extend life
    - Skin related complications (like sepsis) can be fatal. Controlling disease related symptoms may delay occurrence of fatal events

Data from Cutaneous Lymphoma Multidisciplinary Team, Queen Elizabeth Hospital Birmingham (n=8) shows similar response rates to the MAVORIC trial.

"To not recommend Mogamulizumab will deny this rare cohort of patients one of the only drugs in 21 years of practice as a cutaneous lymphoma specialist which has shown rapid and measurable improvement in clinical symptoms, disease burden and PFS"

"To date Mogamulizumab is by far the best drug I have received in terms of keeping me well. I am functional, with little side effects."

"Have witnessed first-hand the dramatic improvement Mogamulizumab has had on patients' skin condition/appearance, disease symptoms and overall quality of life, where often multiple previous lines of systemic treatment have failed in this very difficult to treat condition"

ACD consultation: company comments (1)

Issues	Comment
MAVORIC study design	• Rarity of MF/SS and limited systemic treatment options have not been considered appropriately • Vorinostat was used as comparator for ethical recruitment of heavily pre-treated patients (European Medicines Agency approved) • Clinical opinion, ALCANZA and Hospital episodic statistics (HES) data supports generalisability to UK • Crossover was allowed for ethical reasons
Crossover adjustment	• HES data, UK observational study and two US observational studies support use of IPCW in original analyses

Inconsistency with TA577	• ACD states the mixed population analyses are unreliable, however this was accepted for MF/SS in TA577
	  • This is common in non-first line oncology diseases and usually considered reliable if they reflect potential clinical practice
	  • Mogamulizumab can be used second-line or third line or further so single line analyses would not reflect potential place in treatment pathway
	• ACM1 concluded allogenic stem cell treatment costs should be excluded to be consistent with MAVORIC. However in TA577, a higher rate of allogenic stem cell treatment than seen in the pivotal trial was accepted

ACD consultation: company comments (2)

Issues	Comment
Innovation	• Mogamulizumab was granted Promising Innovative Medicine (PIM) designation from MHRA in March 2018 • ERG base-case model does not capture important and relevant benefits (e.g. carer burden)

Vorinostat efficacy	• Assuming equivalence with standard care is a conservative approach because:
	  • Vorinostat in MAVORIC trial produced same PFS results as physician choice in ALCANZA trial (despite ALCANZA including a better prognostic population). This means vorinostat is likely to be more efficacious than methotrexate/bexarotene
	  • Overall survival predications are unreliable due to different rates of crossover in both trials

New analysis: hospital episodic statistics (HES) data overview

Data from an administrative dataset that includes all MF/SS patients treated in secondary care in England; observation period (1st October 2010 to 31st March 2019)

Comparison of inclusion criteria for MAVORIC and HES analysis

MAVORIC trial	HES population (n=198)
• Histologically confirmed MF/SS (55%:45%)	• At least one ICD-10 diagnosis of MF/SS (85%:15%)
• Stage IB–IVB (mostly advanced)	• Staging not recorded in HES database • Patients treated in secondary care with systemic treatments assumed to be mostly advanced according to clinical experts
• Failed at least 1 previous systemic therapy	• Had one prior systemic therapy recorded in the HES database
• ECOG performance score of 1 or less and adequate haematological, hepatic, and renal function	• ECOG score and haematological, hepatic, and renal function not recorded in HES database • Patients eligible for systemic therapy selected (suggests ECOG score of 1 or less and adequate haematological, hepatic, and renal function)

Overall, HES data includes information on all patients treated with MF/SS with secondary care activity tracked from first diagnosis in secondary care to the end of the study or death

New analysis: (HES data) overview

Background: ACD requested "scenario analyses using HES data to model OS in the standard care arm"

Company submitted unanchored MAIC analysis using 10-year HES data. MAVORIC data was reweighted to match UK population for second-line, advanced MF/SS

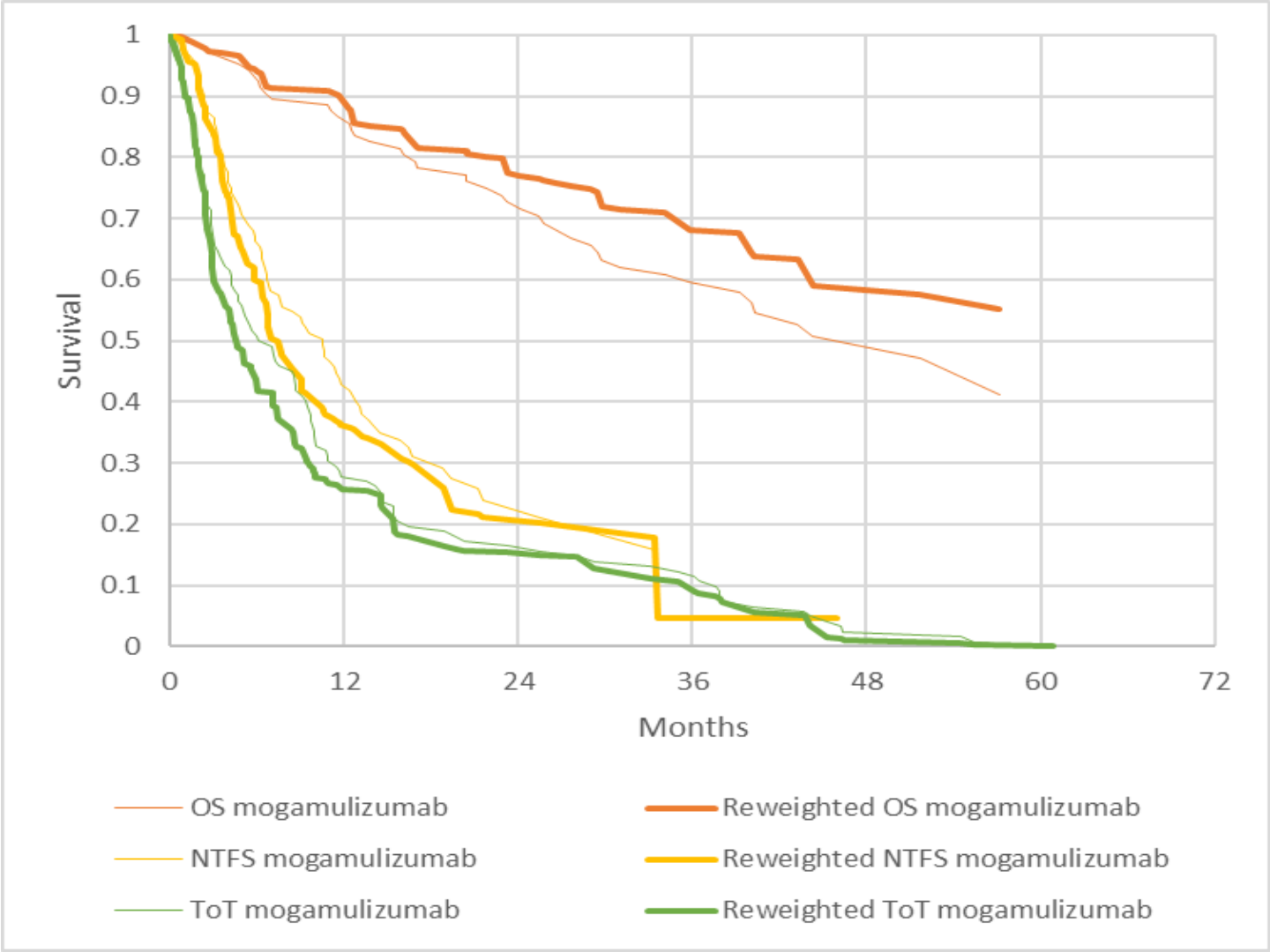
Inclusion/exclusion criteria	Stage, number and type of prior therapies
Not available in HES data	ECOG status, race and time from diagnosis
Considered for matching	Age, gender and disease type

Age (a prognostic factor) and gender (which can potentially affect survival) were similar and so not matched to avoid reducing sample size unnecessarily. Age difference increased by 2.5 years and gender difference decreased by 3.4% in the post-matched population. This was not expected to influence results

ERG preference: company's original analysis based on MAVORIC data

- Age and gender should have been matched (differences in mean age were larger in post-matching population)
- **DSU TSD 18** states all effect modifiers and prognostic factors should be accounted for because "failure of this assumption leads to an unknown amount of bias in the unanchored MAIC"
- Unanchored MAIC should be regarded with a "considerable degree of caution"

New analysis: impact of re-weighting MAVORIC mogamulizumab arm



- Increasing weight of MF patients slightly lowered time on treatment and next-treatment free survival and slightly increased overall survival in the mogamulizumab arm
- Reweighting had very limited impact on time on treatment and next-treatment free survival in the vorinostat arm (not shown here)

ERG

Reweighting was not well-explained and estimated increase in overall survival in the mogamulizumab arm is uncertain

Is the new HES analysis or the original MAVORIC analysis preferred?

New analysis (HES data): OS extrapolations

Best-fits: exponential for mogamulizumab arm and generalised gamma for ECM arm

Company base case: exponential for both arms

Generalised gamma is not clinically reasonable for ECM arm because:

- it predicts a plateau in survival
- OS curves predict better survival for ECM arm compared with those who received mogamulizumab in the long-term.

Lognormal (2nd best fit) is not clinically reasonable for ECM because:

- OS curves cross and slightly higher proportion of patients on current treatments are predicted to survive than patients receiving mogamulizumab after 30 years
- it predicts 21% are available at 5 years (clinical expert [ACM1 slides] predicted only 10% of patients to be alive at 5 years).

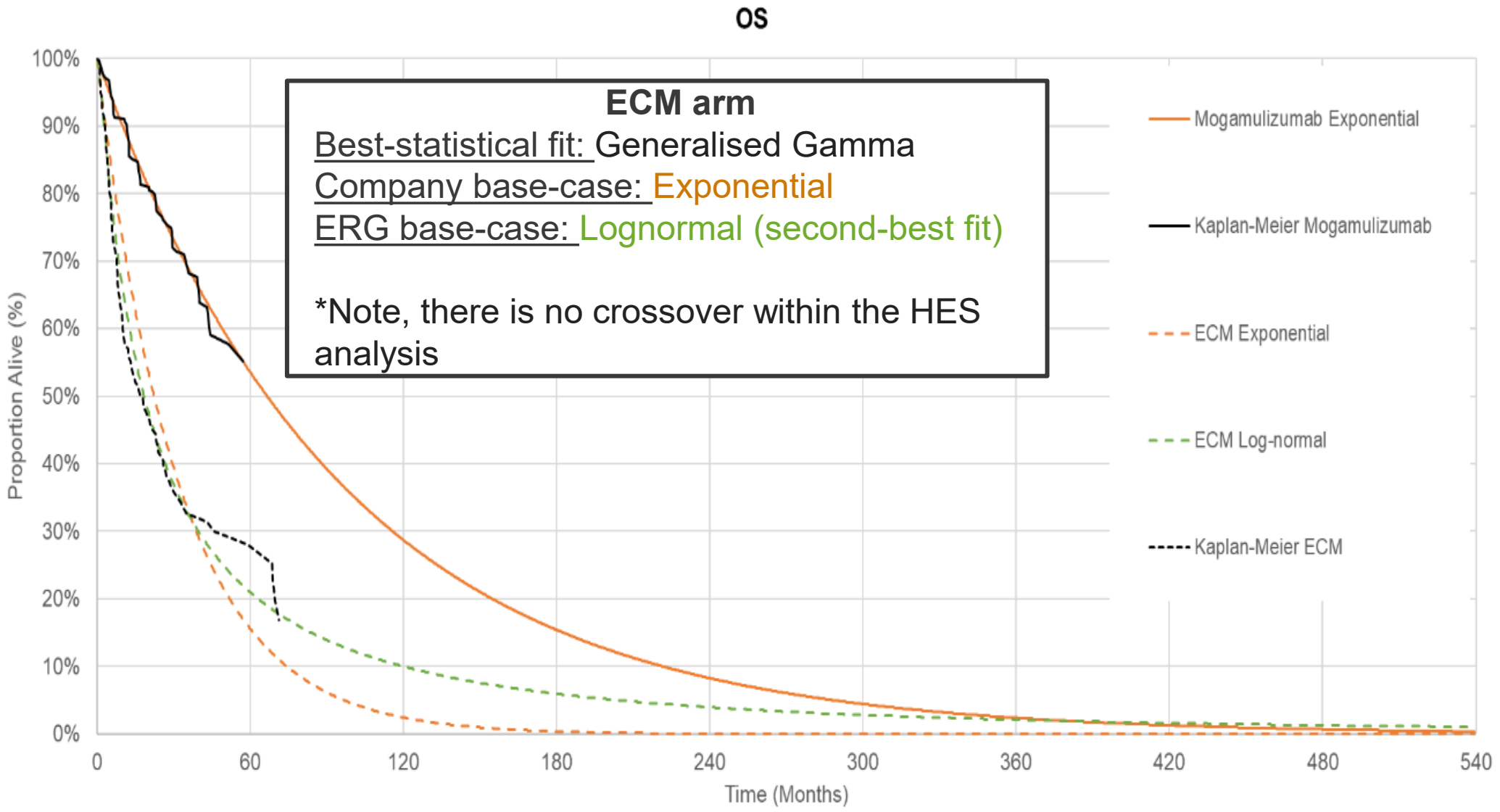
Consistency with ACD/ACM1:

- ACD stated that strong justification was needed to use different parametric curves in each arm. If there is now sufficient evidence to support the use of different distributions in the two treatment arms, the original analyses need to be updated also

ERG base case: exponential for mogamulizumab arm; lognormal for ECM

Agrees with company concerns regarding generalised gamma for ECM arm but considers second-best fit (lognormal) to be more appropriate for ECM arm

New analysis: HES data OS extrapolations



Does the exponential or log-normal produce more plausible estimates of survival for established clinical management?

Company ACD response: carer utility

Background	
Company approach	• Data source: EQ-5D-3L data (MAVORIC) and vignette study (n=100) • Utility gain only applied in disease control health state
ACM1	• Committee preferred to remove carer utilities

	Company response
1	**Base-case:** Carer utility applied as a utility gain (0.19; the difference between the direct carer utilities for disease control and subsequent treatment states) only in the incremental length of time spent in the Disease Control state when treated with mogamulizumab compared with standard care.
2	Directly includes carer utility values for disease control (0.56) and subsequent treatment (0.37) for the respective health states in the model

ERG: exclude carer utilities

- Base-case excludes carer utilities because there remains a lack of methodological guidance on inclusion on carer utilities
- If carer utilities are included, scenario 1 is preferred and is considered a conservative approach

NICE

Should carer utilities be included or excluded?

Original (MAVORIC) analysis: crossover method

ACM1: company preferred IPCW, ERG preferred TSE.
Committee considered IPCW and TSE to reflect upper and lower bounds of OS

Company: HES data supports use of IPCW; use of TSE is not justified. IPCW and TSE should both be used as base-cases (reflecting upper and lower bounds)
ERG: HES analysis using MAVORIC data reweighted based on 1 variable is not methodologically sound enough to lead to IPCW preference. Clinical expert considered TSE most plausible

NICE

Which crossover method is preferred for the MAVORIC analysis?

End-of-life criteria (HES data)

Background ACM1: end-of-life criteria not met

Company response: end-of-life criteria is met	
Short life expectancy (less than 24 months)	• Median life expectancy in UK current clinical practice in the HES database is 17.83 months • Mean extrapolated discounted and undiscounted life-years in the established care management arm of the cost-effectiveness model is 2.87 and 3.31 years respectively
Extension of life of at least an additional 3 months	• The mean additional discounted and undiscounted months from the cost-effectiveness model compared to current NHS treatments are 44.6 and 61.9 months.

ERG: End-of-life criteria is met with new HES data ("*The data obtained from the HES database can be considered the best source of evidence*")	
Short life expectancy	• Data from the HES database can be considered the best source of evidence and suggest criteria is met
Extension of life	• Criteria is met with available data

Summary of company and ERG preferences

HES analysis: company base-case	HES analysis: ERG preferences
• Carer utilities (additional disease control only) • Allogenic stem cell treatment after current treatment for both arms • OS: ECM, exponential / moga, exponential • NTFS: ECM gen gamma / moga, gen gamma	• No carer utilities • No allogenic stem cell treatment after current treatment for either arm • OS: ECM, lognormal / moga, exponential • NTFS: ECM, gen gamma / moga, lognormal
MAVORIC analysis: company preferences	**MAVORIC analysis: ERG preferences (ERG base-case)**
• Cross-over adjustment method: IPCW • Carer utilities (additional disease control only) • Allogenic stem cell treatment after current treatment • OS: ECM, exponential / moga, lognormal • NTFS: ECM, gen gamma / moga, gen gamma	• Cross-over adjustment method: TSE • No carer utilities • No allogenic stem cell treatment after current treatment • OS: ECM, exponential / moga, exponential • NTFS: ECM, gen gamma / moga, lognormal

For NTFS, company chose gen gamma for both treatment arms (best fit for ECM, 2nd best for mogamulizumab). ERG considers better-fitting lognormal more appropriate for mogamulizumab.

HES: Hospital episodic statistics; ECM: established clinical management; NTFS: next-treatment free survival

Company and ERG ICERs based on HES data (PAS for mogamulizumab included*)

Moga vs. established clinical management (ECM)	Incremental costs	Incremental QALYs	ICER (£/QALY)
All company preferences (company base-case)	£88,034	2.84	£31,030
Company preferences, but with no carer utilities	£88,034	2.66	£33,043
Company preferences, but with direct carer utilities**	£88,034	3.71	£22,214
Company preferences, but no allogenic SCT after current treatment	£92,178	2.94	£31,353
Company preferences, but ECM OS lognormal	£82,663	2.40	£34,375
Company preferences, but both OS lognormal	£93,544	3.15	£29,695
ERG preferences	£86,864	2.27	£38,274
ERG preferences, but ECM OS exponential	£92,536	2.72	£33,961
ERG preferences, but with allogenic SCT after current treatment	£82,995	2.21	£37,590
ERG preferences, but with incremental carer utilities	£86,864	2.40	£36,233
ERG preferences, but with direct carer utilities**	£86,863	3.41	£25,471

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

***The company used direct carer utilities (scenario 2 slide 22) to demonstrate that base case carer utilities reflected a conservative approach. ERG does not consider direct carer utilities used in this scenario to be plausible*

Company and ERG ICERs: MAVORIC (PAS for mogamulizumab included*)

Moga vs. established care management (ECM)	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company preferences	£93,300	2.86	£32,634
Company preferences, but with mogamulizumab OS exponential	£83,870	2.23	£37,690
Company preferences, but with no carer utilities	£93,300	2.68	£34,809
Company preferences, but with no allogenic stem cell treatment after current treatment	£97,311	2.93	£33,185
ERG preferences (ERG base case)	£68,547	0.85	£80,555
ERG preferences, but with IPCW cross-over adjustment	£87,218	2.04	£42,812
ERG preferences, but with incremental carer utilities and IPCW	£87,218	2.21	£39,382
ERG preferences, but with direct carer utilities**	£68,547	1.27	£54,055
ERG preferences, but with IPCW and direct carer utilities**	£87,218	3.09	£28,226

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

***The company used direct carer utilities (scenario 2 slide 22) to demonstrate that base case carer utilities reflected a conservative approach. ERG does not consider direct carer utilities used in this scenario to be plausible*

Innovation and Equality

- **Is mogamulizumab innovative?**
- **Has the change in health-related quality of life been adequately captured in the model?**
  - TA577 notes “The committee acknowledged the limitations of the EQ-5D-3L as an assessment tool for advanced CTCL because it may not be sensitive to skin-related diseases, but noted that it should capture depression and pain…”

- **Are there any equality issues?**

Key issues

- Should decision-making be based on the original analysis using the MAVORIC trial data or the new analysis using hospital episodes statistics (HES) data?
  - If HES data is used, which extrapolation predicts the most plausible overall survival for established clinical management?
- Should the cost-effectiveness analyses include caregiver utilities?
- Are the end-of-life criteria met?

Back-up slides

Baseline demographic and disease characteristics of patients in the MAVORIC and ALCANZA studies (1/2)

	ALCANZA		MAVORIC	
	Brentuximab vedotin (n=64)	Physician's choice*(n=64)	Mogamulizumab (n=186)	Vorinostat (n=186)
Age, median years (range)	62 (51–70)	59 (48-67)	63 ([redacted])	65 (56-72)
Male, n (%)	33 (52)	37 (58)	109 (59)	107 (58)
Race, n (%)				
White	56 (88)	53 (83)	125 (67.2)	135 (73)
Other	5 (8)	10 (16)	[redacted]	[redacted]
ECOG performance status, n (%)				
0	43 (67)	46 (72)	106 (57.0)	104 (56)
1	18 (28)	16 (25)	78 (41.9)	82 (44)
2	3 (5)	2 (3)	2 (1.1)	0
Time from initial diagnosis, median months (range)	42.2 (12.8–87.4)	37.0 (12.3-102.7)	41.0 (17.4–78.8)	35.4 (16.2-68.2)

NICE *methotrexate or bexarotene

Baseline demographic and disease characteristics of patients in the MAVORIC and ALCANZA studies (2/2)

	ALCANZA		MAVORIC	
	Brentuximab vedotin (n=64)	Physician's choice*(n=64)	Mogamulizumab (n=186)	Vorinostat (n=186)
Disease type, n (%)				
MF	48 (75)	49 (77)	105 (56.5)	99 (53)
SS	N/A	N/A	81 (43.5)	87 (47)
Disease stage, n (%)				
IB-IIA	15 (31)	18 (37)	36 (19.4)	49 (26)
IIB	19 (40)	19 (39)	32 (17.2)	23 (12)
IIIA-IIIB	4 (8)	2 (4)	22 (11.8)	16 (9)
IVA1	0	1 (2)	73 (39.2)	82 (44)
IVA2	2 (4)	8 (16)	19 (10.2)	12 (6)
IVB	7 (15)	0	4 (2.2)	4 (2)
Lines of prior systemic therapy, median (range)	2 (1-4)	2 (1-3)	3 (2–5)	3 (2-5)

NICE *methotrexate or bexarotene

From ACM1: Cross-over adjusted OS (severe disease from MAVORIC)

NICE

Data source: Figure 5.4 in ERG report