NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

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3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Lymphoma Action
   b. Royal College of Pathologists-British Society of Haematology-British Association of Dermatologists
   c. United Kingdom Cutaneous Lymphoma Group - *endorsed by The Royal College of Physicians*
   d. British Association of Dermatologists

4. **Comments on the Appraisal Consultation Document from experts:**
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Kyowa Kirin Ltd.	Kyowa Kirin is committed to the NICE process and bringing mogamulizumab to eligible patients living with mycosis fungoides and Sézary syndrome. We welcome the opportunity to provide additional information to NICE and other relevant stakeholders and are optimistic we can find a positive way forward to ensure that patients in England and Wales can access this innovative medicine as quickly as possible. There is a high unmet need among people living with both mycosis fungoides and Sézary syndrome and they need better therapeutic options. Kyowa Kirin thanks NICE and the Committee for sharing their views on the evidence submitted to date in the Appraisal Consultation Document. Whilst we do not agree with the current conclusions the Committee has reached, we welcome the opportunity to address the areas of uncertainty highlighted. We will respond to all three questions posed by NICE and, more specifically, focus on the nature of these rare sub-types of Cutaneous T-Cell Lymphoma and the robustness of the clinical trial evidence. We will spell out the rationale for using vorinostat as a comparator, the choice of the trial population and the generalisability of the evidence to NHS clinical practice. We hope the Appraisal Committee reviews the requested evidence fairly and reconsiders its current evaluation of mogamulizumab for the treatment of people living with advanced mycosis fungoides and Sézary syndrome, two subtypes of Cutaneous T-Cell Lymphoma, who have had at least one prior systemic treatment and who are	Comment noted.

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			either clinically ineligible or refractory to brentuximab vedotin.	
2	Consultee	Kyowa Kirin Ltd.	Kyowa Kirin does not agree with the Committee's review of the clinical trial evidence taken from **MAVORIC, the largest phase III randomised control trial in Cutaneous T-Cell Lymphoma (n=372), which for the first time includes Sézary syndrome patients** We feel the rarity of Cutaneous T-Cell Lymphoma and the limited systemic treatment options for mycosis fungoides and Sézary syndrome have not been considered appropriately with regards to the design of this trial. To ensure heavily pre-treated patients were ethically recruited for this study, a new medicine not previously used was agreed to by the European Medicines Agency to be the chosen comparator. Generalisability of the trial evidence to the NHS population was supported by Cutaneous T-Cell Lymphoma clinical expert opinion and further analyses, which are referred to in the section below. Based on the evidence from the MAVORIC trial, mogamulizumab demonstrates significant benefits versus a licensed comparator in a patient population with very limited treatment options left.	Comment noted and summarised within ACM2 meeting slides. The committee recognised the rarity of disease. However, it was concerned about using the clinical effectiveness data because vorinostat was not licensed for use in the UK and did not represent NHS standard care. It concluded that the relative treatment effect compared with NHS standard care was uncertain (see section 3.4 of the FAD).
3	Consultee	Kyowa Kirin Ltd.	Kyowa Kirin recognises the Committee's **concerns about the uncertainty surrounding mogamulizumab as a result of treatment crossover/switching from comparator to active treatment and the use of vorinostat as a comparator** in the MAVORIC trial. Crossover was allowed for ethical reasons due to the poor prognosis for non-responding patients. Vorinostat was chosen as a comparator because it was licensed and widely used in several countries. To recruit ethically in a rare disease trial, a new medicine option was needed for this heavily pre-treated mixed mycosis fungoides and Sézary syndrome population and it was felt preferable to have a defined comparator rather than 'physician's choice'. The European Medicines Agency approved the MAVORIC	Comment noted. The additional analysis was appreciated and was considered by the committee in the second appraisal committee meeting. The new data is discussed in section 3.5 of the FAD.

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			study design. In order to address these uncertainties in the original submission, a number of analyses were conducted. These included a naïve indirect comparison between vorinostat and the physician's choice arm of the ALCANZA trial (which included methotrexate and bexarotene), bexarotene pivotal trials (phase II study with similar Cutaneous T-Cell Lymphoma population as done for vorinostat) and analyses that adjusted for treatment switching in the vorinostat arm of the MAVORIC trial. The results of the switching analysis were validated against data from the UK Hospital Episode Statistics and three published observational studies (one from the UK and two from the US). **As an additional analysis, at the recommendation of the Committee, Kyowa Kirin has now conducted an unanchored indirect comparison of mogamulizumab directly with data from patients (n=198) from the UK Hospital Episode Statistics database that matches well the mogamulizumab arm of the MAVORIC study.** This analysis benefits from the following: • Does not require any adjustment for treatment switching with its attendant uncertainties as no patients in the Hospital Episode Statistics database received mogamulizumab • Provides a direct comparison against current UK clinical practice rather than vorinostat as the Hospital Episode Statistics data is an administrative dataset including all patients treated in England • Reflects the current UK mycosis fungoides and Sézary syndrome population as the Hospital Episode Statistics data is an administrative dataset including all patients treated in England (NHS secondary care setting) The revised analyses, using the Evidence Review Group's base	

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			case for all other additional relevant aspects and [redacted], resulted in incremental cost-effectiveness ratios of £28,887 and £29,848 per quality-adjusted life-years depending on the carer utilities included for the delay in disease progression. Details of the analyses and the results are presented in the additional analyses document.	
4	Consultee	Kyowa Kirin Ltd.	Kyowa Kirin is concerned, that the **wording of the summaries of clinical and cost effectiveness does not provide an accurate summary view of the evidence regarding the efficacy of mogamulizumab.** The MAVORIC trial provides strong evidence of a benefit compared to vorinostat with respect to progression-free survival and response. The analysis of overall survival adjusting for switching from vorinostat to mogamulizumab provides evidence of a benefit in overall survival. Alongside this, there is evidence that the effectiveness of UK current treatment is not markedly superior to that of vorinostat. Based on these points we feel that the following comments in the Appraisal Consultation Document are potentially misleading: • Page 3: "*This means it is unclear how well mogamulizumab works*" • Page 8: "*concluded that its relative treatment effect compared with NHS standard care was unknown*" • Page 15: "*The relative treatment effect of mogamulizumab compared with NHS standard care was unknown*" • Page 9: "*But the company's analysis was unreliable because […] did not compare mogamulizumab with a relevant comparator*" The Appraisal Consultation Document also states on page 12: "*The Committee was not convinced that mogamulizumab provided an overall survival benefit compared with standard care*". However, even in the worst-case estimate using the 2-stage estimation for	Comment noted. The appraisal consultation document reflects conclusions made by the committee during part 1 and part 2 of the appraisal committee meeting and therefore the specific statements noted by the company are not considered to be misleading by NICE. However, the summary on Page 3 of the ACD (page 1 in the FAD) has been updated to reflect the committee's conclusion after the second committee meeting. The statements considered to be inaccurate by the company and described in the appendix have been addressed in the FAD.

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			crossover adjustment, mogamulizumab resulted in 19 months survival benefit. The uncertainty described in the Evidence Review Group's report was not if mogamulizumab provided overall survival benefit, but rather how much this benefit was. Additionally, Kyowa Kirin has identified some instances of inaccurate description in the Appraisal Consultation Document including in the description of comparative effectiveness, and crossover adjustment. For detailed descriptions, please see accompanying Appendix with this response document.	
5	Consultee	Kyowa Kirin Ltd.	Kyowa Kirin is concerned about the **lack of justification provided for the Committee's preferred choice of crossover adjustment method**. This choice is the single most influential input and Kyowa Kirin has submitted 10-year data from the UK Hospital Episode Statistics database, one published UK observational study and two published US observational studies, which support the use of inverse probability of censoring weighting adjustment. This affects the following statements: • Page 10: "*The results from the crossover adjustment methods represent the upper and lower range of plausible overall survival in the standard care arm*" • Page 10: "*The Committee was not convinced that the IPCW-adjusted curve was clinically plausible for the average patient in the modelled population with severe disease*" • Page 12: "*The ERG preferred to use the 2-stage estimation crossover adjustment* • Page 17: "*But it recognised that the lower ICERs reflected the IPCW adjustment method, which it considered to be clinically implausible*" Kyowa Kirin does understand the uncertainty in the cross over	Comment noted. In section 3.8 of the ACD, it is explained that the committee did not consider the IPCW-adjusted curve to be clinically plausible for the average patient in the modelled population of severe disease. Section 3.8 also explains that the committee noted the large impact crossover method had on the cost-effectiveness results. Because of this the committee concluded that results of both methods (the two-stage estimation and the IPCW methods) represented the upper and lower range of plausible overall survival in the standard care arm. Further detail on the ERG's and committees' views on the crossover adjustment

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			adjusted overall survival analyses. Therefore, the additional analyses requested by the Committee, are based on the Hospital Episode Statistics data submitted together with this document. These analyses avoids this issue, as using the Hospital Episode Statistics database for comparison does not require any adjustment for treatment switching with its attendant uncertainties as no patients in the Hospital Episode Statistics database received mogamulizumab. Importantly, the Hospital Episode Statistics data represents current UK NHS clinical practice in advanced mycosis fungoides and Sézary syndrome patients. Additionally, the survival curve for the current standard of treatment in the NHS from the Hospital Episode Statistics analyses is in line with the survival curve from the MAVORIC trial using the inverse probability of censoring weighting adjustment method.	methods have been included in section 3.8 of the FAD. The committee considered the HES data submitted by the company during the second appraisal committee meeting. This is summarised in section 3.5 of the FAD.
6	Consultee	Kyowa Kirin Ltd.	Kyowa Kirin is concerned about the **inconsistent requirements in modelling mycosis fungoides and Sézary syndrome between this appraisal compared to the technology appraisal (TA 577) for brentuximab vedotin and the exclusion of allogeneic stem cell transplant after current treatment.** • Regarding the inclusion of allogeneic stem cell transplant: ▪ The Appraisal Consultation Document states on page 4: "it is acceptable to remove allogenic stem cell transplant after current treatment from the company's economic model because this was not allowed in the trial and reduces the risk of bias ".However, in TA577 a higher rate of allogeneic stem cell transplant than that than seen in the pivotal ALCANZA trial was accepted by the Committee. This was a key input in TA577. The additional allogeneic stem cell transplant not seen in the pivotal trial was kept in the model, and as a result influenced the treatment's cost-effectiveness and contributing significantly to the positive	Comment noted and summarised in ACM2 committee slides. Allogenic stem cell transplant The committee recognised that some patients may receive allogenic stem cell transplant in clinical practice. However, they also considered that inclusion of allogenic stem cell transplant could introduce double-counting and bias within the model. It was also noted that the inclusion of allogenic stem cell transplant only had a small impact on ICERs. More

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			recommendation. ▪ Additionally, the UK's Hospital Episode Statistics database demonstrated a 5.2% allogeneic stem cell transplant use after 2nd line treatment. Thus, the current UK clinical practice includes allogeneic stem cell transplant and the survival curves from the Hospital Episode Statistics database takes these into account and corroborates the UK specialist opinion on likely allogeneic stem cell transplant expected rates in this population. ▪ In the MAVORIC trial patients were treated to progression. Responding patients did not interrupt treatment in order to receive an allogeneic stem cell transplant. Upon progression they then switched to further treatments during which some patients received allogeneic stem cell transplant. In real life practice, a proportion of patients receiving mogamulizumab would interrupt treatment in order to receive allogeneic stem cell transplant. This was captured in the model as allogeneic stem cell transplant during current treatment and we believe this reduces the bias in the estimates of cost-effectiveness as it represents anticipated clinical practice. Similar adjustments were made in the modelling of brentuximab vedotin in TA577 in order to reflect differences between actual clinical practice and practice during the trial. ▪ We have concerns that by excluding aSCT after current treatment both is not representative of UK NHS clinical practice and does not consider the clinical governance advice given in the Summary of Product Characteristics for mogamulizumab, which is a regulatory document that is approved by the European Medicines Agency . ▪ While previously there were concerns about including the outcomes of patients who could have received aSCT	detail on this can be found in section 3.7 of the FAD. Mixed treatment population The use of mixed population analysis was accepted by the committee; however, it was noted that analyses such as these are associated with greater uncertainty than the single treatment analyses. Overall, the uncertainty of outcomes was due to a combination of factors, of which mixed treatment population was one. The wording in this section of the FAD has been updated to emphasise this (see section 3.6).

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			after current treatment, but the MAVORIC trial did not allow, In the additional HES data based analyses, we have double counted the health benefit of aSCT for patients who have received aSCT in the standard of care arm, thus biasing the results towards standard of care. • Regarding the analyses: On page 9 the Appraisal Consultation Document states: "the company's analysis was unreliable because it included a mixed population which grouped several lines of treatment together, did not differentiate between disease type and did not compare mogamulizumab with a relevant comparator". Mixed population analyses are very common in non-first line oncology diseases, especially in rare conditions including in mycosis fungoides and Sézary syndrome in the TA577 and are usually considered reliable if they reflect the potential clinical practice in the UK. Single line analyses would not reflect the potential place of mogamulizumab in the treatment pathway, which depending on the CD30 status, and the line of treatment brentuximab vedotin was given, can be second, or third or further line.	
7	Consultee	Kyowa Kirin Ltd.	Kyowa Kirin would like to highlight that the **summary sentence on page 18 stating that "Mogamulizumab is not innovative and all benefits are captured in the model" is not an accurate summary of the evidence.** With regards to innovation: mogamulizumab was granted Promising Innovative Medicine (PIM) designation from UK's The Medicines and Healthcare Products Regulatory Agency (MHRA) in March 2018 for the treatment of advanced refractory mycosis fungoides and Sézary syndrome. With regards to all benefits being captured in the model: this summary is inaccurate in light of the Evidence Review Group's preferred base case as described in the Appraisal Consultation Document. The model, on which the decision is based does not	Comment noted. The committee recognised that the mechanism of action of mogamulizumab is innovative (see section 3.17 of the FAD). However, the committee concluded that all benefits can be captured in the model.

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			capture important and relevant benefits. For example, carer burden is excluded, as stated in the Appraisal Consultation Document: "carer utility values had not been included in the model". (Please see more information and additional analyses in the additional document submitted with this form.)	
8	Consultee	Kyowa Kirin Ltd.	**While there are uncertainties, given the evidence, the assumption of equal efficacy for the physician's choice arm of the ALCANZA trial and the vorinostat arm of the MAVORIC trial is likely to be conservative.** Kyowa Kirin agrees with the Evidence Review Group on page 8, that "if vorinostat and the physician's choice were similar, patients in the physician's choice arm in ALCANZA would have longer progression-free survival and overall survival because patients had less severe disease. However, overall survival for the physician's choice arm was shorter than with vorinostat." ▪ Regarding the progression-free survival results, the MAVORIC vorinostat arm produced the same progression-free survival Kaplan-Meier curve as the ALCANZA physician choice arm, despite the ALCANZA trial including a better prognostic patient population (e.g., no Sézary syndrome, less advanced patients and less prior pre-treatments). This means, that vorinostat is likely be a more efficacious treatment than methotrexate/bexarotene, which were used in the ALCANZA physician choice arm. This, therefore, makes the assumption of similar efficacy conservative. Hence the incremental health benefit included in the cost-effectiveness model is conservative. Regarding the overall survival results, it is not possible to assess what the ALCANZA trial results would have looked like, since 46% of the patients on the physician's choice arm crossed over to brentuximab vedotin, while 73% of the patients on the vorinostat	Comment noted and acknowledged in the second appraisal committee meeting. However, the committee continues to take the view that the evidence is associated with uncertainties (as reflected in sections 3.4 and 3.5 of the FAD).

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			arm crossed over to mogamulizumab. The very different crossover rates and the lack of reliable crossover adjusted physician's choice arm makes predictions unreliable.	
9	Consultee	Kyowa Kirin Ltd.	**Appendix: Descriptions requiring amendment (Indirect comparison and comparators)** • The Appraisal Consultation Document states on page 7 that "an indirect treatment comparison using ALCANZA was not possible". While we agree, that an anchored indirect comparison using ALCANZA was not possible due to the lack of common comparator and crossover design, an unanchored indirect comparison was conducted by Kyowa Kirin using the ALCANZA trial and was submitted in the original submission for progression-free survival and during the clarification process for overall survival. • The Appraisal Consultation Document states on page 8: "The company assumed that vorinostat was a suitable proxy for standard care in the NHS because it showed similar progression-free survival to the physician's choice arm in ALCANZA". The assumption that vorinostat was a suitable proxy for standard of care in the NHS was also based on similar response rates as in the bexarotene pivotal trials and clinical expert opinion in this rare disease. • The Appraisal Consultation Document mentions on pages 3, 5, 7 interferon as part of standard of care, however "interferon alfa-2a has been withdrawn from the market and the stores are being used up, it is substituted with pegylated derivatives of interferon alfa (peginterferon)" (Evidence Review Group report Table 5.5). This should be clarified to represent current NHS clinical practice. • The Appraisal Consultation Document mentions on page 10: "the model did not include treatment costs that reflected clinical practice". The model included the treatment costs most relevant in the UK based on NHS England and UK	Comments noted. The FAD has been updated to specify that an anchored indirect comparison using ALCANZA was not possible (section 3.4) The FAD has been updated to explain the additional basis for the company assuming vorinostat is a suitable proxy for standard of care (section 3.4). The FAD has been updated to refer to peginterferon instead of interferon.

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			Hospital Episode Statistics data and UK clinical expert survey for this rare disease. While the MAVORIC trial comparator, vorinostat, is not available in the UK, the cost-effectiveness model comparator (bexarotene and a basket of other treatment options) and its treatment costs are representative of UK clinical practice.	The sentence stating "the model did not include treatment costs that reflected clinical practice" has been removed from the FAD.
10	Consultee	Kyowa Kirin Ltd.	**Appendix: Descriptions requiring amendment (Crossover adjustment and overall survival)** • The Appraisal Consultation Document states on page 10 "The company preferred the inverse probability of censoring weights (IPCW) method to adjust for crossover because it produced estimates in line with the company's clinical expert advice and accounted for a potential post-progression benefit of mogamulizumab". Kyowa Kirin preferred the inverse probability of censoring weights adjustment mainly because it was in line with UK Hospital Episode Statistics data with 10-year follow-up, and three large observational studies. The statement should therefore, read as "The company preferred the inverse probability of censoring weights (IPCW) method to adjust for crossover because it produced estimates consistent with UK Hospital Episode Statistics data and observational studies, in line with the company's clinical expert advice and accounted for a potential post-progression benefit of mogamulizumab". • The Appraisal Consultation Document discusses the representativeness of the Kaplan-Meier curve with the inverse probability of censoring weights crossover adjustment and the results with it on page 11. However, this curve is not used in the cost-effectiveness model. Only the	Comments noted. The FAD incorporates the additional reasons for the company preferring the IPCW method (section 3.8) Reference to the Kaplan-Meier curve has been removed in the FAD.

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			parametric survival model fitted to the adjusted patient level data is used, the representativeness of which is supported by the UK NHS Hospital Episode Statistics data and three observational studies. The Kaplan-Meier curve is only an interim result, not the final input. • The Appraisal Consultation Document states in the discussion about the 2-stage crossover adjustment on page 11: "The company suggested that the long-term predictions using the 2-stage estimation adjusted curve did not account for the potential disease-modifying effect of mogamulizumab". However Kyowa Kirin discounted this method mainly as it predicted more than double median survival than UK NHS Hospital Episode Statistics data, higher survival estimates at 1, 3 and 5 years and similar survival at 10 and 20 years from second-line as the observational data for a better patient population from diagnosis. • The Appraisal Consultation Document states on page 14: "It recalled that mogamulizumab could also be used after 2 previous treatments, but the HES database did not include these [survival values]". However, the Hospital Episode Statistics data included these and Kyowa Kirin had submitted this in the Technical engagement) stakeholder response form (for third line, the median survival was 1.1 years for mycosis fungoides and 1.0 year for Sézary syndrome). • The Appraisal Consultation Document states on page 14: "The Committee noted that median overall survival was around 1.3 years using the HES data for people who have had 1 treatment, but only a small number had Sézary syndrome". The 1.3 years is the result of survival from Hospital Episode Statistics data weighted for mycosis fungoides and Sézary Syndrome distribution in the MAVORIC trial, i.e., based on 45% of Sézary syndrome	The text referring to the company reasoning for discounting the 2-stage crossover adjustment has been updated as necessary (section 3.8). The statement referring to the HES data has been removed. The text "The Committee noted that median overall

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			patients.	survival was around 1.3 years using the HES data for people who have had 1 treatment, but only a small number had Sézary syndrome" has been updated to remove "but only a small number had Sézary syndrome" (see section 3.13).
11	Consultee	Kyowa Kirin Ltd.	**Appendix: Descriptions requiring amendment (Carer utility values)** • On page 13 the Appraisal Consultation Document states that "The Committee questioned if it was appropriate to include carer utility values for disease control (0.56) and subsequent treatment (0.37)". However, these utilities were not applied in the model. Only the utility advantage of the patient having controlled disease (0.19) was applied in the model. We welcome NICE's review of this as absolute values derived from the care giver burden study were NOT used in the cost-effectiveness model. • On the same page, the Appraisal Consultation Document states "However, the patient experts indicated that they mostly self-managed the condition" However, this only applied to the patient's current health state, controlled disease. The other patient indicated, that prior to achieving disease control with mogamulizumab, he was limited in everyday activities.	Comment noted. The relevant section of the FAD has been updated to accurately reflect the approach taken to carer utilities in the initial submission (see section 3.12). Reference to the patient expert has been removed.
12	Consultee	Patient expert	As a Sezary Syndrome patient I have been privileged to be set on a course of Mogamulizumab which has completely changed my life after suffering some fifteen years with the condition. I have been through all the usual treatments of drugs, light ECP, and progressed through three different chemotherapies treatments all of which made my condition worse. Having been set on a course of Mogamulizumab my whole skin condition miraculously improved to where I have no skin flaking, no	Comment noted. Real world benefit of mogamulizumab was presented to the committee during the appraisal committee meeting. However, based on the available clinical and cost-effectiveness evidence, the

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			itchiness and have a better feeling of well being. I have not had any adverse or side effects from the treatment. For me it has changed my whole social and home life and above all my expectations are beyond belief. I would thoroughly recommend and commend the use of the treatment to the low numbers of Sezary Syndrome patients to offer such relief of symptoms as I have experienced.	committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended
13	Consultee	Royal College of Pathologists, British Society Haematology, British Association Dermatologists.	The rarity of CTCL variants mycosis fungoides and Sézary syndrome has not been considered at around 6 per million for mycosis fungoides and <1 per million for Sezary syndrome so very few patients per year would need treatment in England (refractory to one systemic). Limiting the overall cost to the NHS. The health related quality of life in mycosis fungoides and notable Sézary syndrome is severely reduced and adds a huge burden to patients .	Comment noted. The committee recognised the rarity of the disease. The committee also discussed the impact of mycosis fungoides and Sézary syndrome on the quality of life of patients during both committee meetings. In addition, utility values for patients were included within the company's health economic model. However, based on the available evidence, the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended
14	Consultee	Royal College of Pathologists, British Society Haematology, British Association Dermatologists.	There is no clearly defined treatment pathway for patients with CTCL due to the rarity of the disease, and so the fact that there are differences in the trial population is just reflective of this fact and typical of any series of patients with CTCL.	Comment noted. The committee noted the rarity of the disease and the heterogeneity seen in clinical practice. However, based on the clinical and cost-effectiveness evidence, the committee concluded that mogamulizumab was not

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				cost-effective and therefore could not be recommended
15	Consultee	University Hospital Birmingham	We write this comment in response to NICE consultation response in relation to “Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome”. As key stakeholders in the management of patients with this disease, we wish to raise concerns in relation to the following items raised in the consultation process: 1. Section 1 Recommendations, Subsection (Why the committee made these recommendations), Paragraph 2: “The clinical trial evidence is very uncertain because mogamulizumab is compared with vorinostat, a treatment that is not used or licensed in the UK. Also, many people switch treatments and there are a lot of differences among the trial population. This means it is unclear how well mogamulizumab works.” 2. Section 3 Committee Discussion, Subsection 3.3 “It concluded that standard care was the most appropriate comparator, which includes treatments such as methotrexate, bexarotene, interferon and chemotherapy.” We disagree with these recommendations and conclusions and present our experience at our Specialist Skin Lymphoma Service of treating this complex patient group with cutaneous T-cell lymphoma on a compassionate basis with mogamulizumab over the past 1 year. We have treated 8 patients (3 males, 5 females) with a mean (+/- SEM) age of 61.38 (+/- 4.07) years with mogamulizumab on a compassionate basis since July 2019. These included 4 patients with advanced mycosis fungoides (IIIB – IVA2 disease), two patients with Sezary syndrome (IVA2) and two patient with HTVL1	Comment noted. The committee acknowledged the real world experience with mogamulizumab during the second appraisal committee meeting. However, based on the clinical and cost-effectiveness evidence the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended

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			lymphoma (one MF-like and the other Sezary syndrome-like). These patients were all heavily pre-treated and had received a median of 6.625 (+/- 0.98) previous treatments of which 1.125 (+/- 0.39) were skin directed therapies and 5.5 (+/- 0.65) systemic therapies. Previous systemic therapies in these patients included methotrexate (n=4), bexarotene (n=4), interferon (n=4), gemcitabine (n=4), CHOP (n=3), interferon (n=4), ECP (n=3), resminostat (n=3) and brentuximab (n=2). In this cohort, 6/8 achieved an overall response rate (OR) in skin of 50% (complete response, CR, n=1; partial response, PR, n=2; stable disease, SD, n=2; and progressive disease PD, n=1). In these same six patients nodal disease remained stable and it was not possible to assess skin/lymph node follow-up status in 2/8 patients as they only received mogamulizumab for one month at the time of our review. Blood response assessment was possible in 7/8 patients and demonstrated an OR of 71.4% (CR, n=3; PR, n=2 and SD, n=2) with a reduction in peripheral blood absolute Sezary cell counts of 77.40 (+/- 8.95)% with a mean time to response of 0.76 (+/- 0.24) months. None of our patients had visceral disease and therefore no visceral response assessment following mogamulizumab was possible. Mogamulizumab was well tolerated with similar safety profile to the MAVORIC Trial and the most common treatment-emergent adverse events were grade 1-2 (97.5% of all TEAEs) and only one episode of grade 3 TEAEs was observed (2.5%). The most common TEAEs included skin infection (n=4), rash (n=2), fever (n=2), nausea (n=3), lethargy (n=3) and diarrhoea (n=2). In our real world experience of treating patients in a Specialist Lymphoma Centre we observed similar response rates with mogamulizumab those observed in the MAVORIC trial, in our heavily pre-treated group of cutaneous T-cell lymphoma patients. These included similar response rates of 71.4% in blood (MAVORIC = 68%) and 50% in skin (MAVORIC = 42%). Given our experience in treating these patients we argue strongly that	

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			mogamulizumab, a drug which has shown significant and measurable benefits in clinical trials has been unfairly dismissed and denies patients with this rare disease an effective durable treatment.	
16	Consultee	United Kingdom Cutaneous Lymphoma Group	The UK Cutaneous Lymphoma Group is an organisation that represents clinicians across the UK who are involved in the diagnosis, treatment and support of patients with skin lymphomas. We were highly disappointed as a group of Cutaneous Lymphoma Specialists with the decision by NICE to not recommend mogamulizumab CTCL patients refractory to at least one previous systemic treatment. On behalf of the UK Cutaneous Lymphoma Group (UKCLG), we would like to respond to this recent NICE recommendation, and make particular reference to the following comment made by NICE regarding the largest randomised controlled trial in CTCL (MAVORIC). As the specialist UK Cutaneous Lymphoma Group we felt that it was most appropriate to prepare one unanimous response from our Group in response to the NICE recommendations. NICE recommendations: “The clinical trial evidence is very uncertain because mogamulizumab is compared with vorinostat, a treatment that is not used or licensed in the UK. Also, many people switch treatments and there are a lot of differences among the trial population. This means it is unclear how well mogamulizumab works” UKCLG response:	Comment noted. The committee noted the rarity of the disease and commended the company on its efforts to obtain clinical data. The committee considered results of the MAVORIC study. However, it was concerned about the clinical effectiveness data because vorinostat is not licensed for use in the UK and does not represent NHS standard care. The company submission also compared data for vorinostat with data from the ALCANZA study (which included standard therapies, such as bexarotene). However, the committee noted that there were significant differences between the MAVORIC and ALCANZA trial populations and the ALCANZA trial had a high level of crossover (see section 3.4 of the FAD). Overall, based on the clinical and cost-effectiveness evidence available, the

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			This response reflects the UKCLG responsibility to advise on the management of CTCL patients and to publish multi-disciplinary treatment guidelines for UK CTCL patients (see BJD, Gilson et al 2018). The historical evidence base for much CTCL treatment is weak, not due to failures in the approach of researchers, or due to lack of engagement in the treating community, but reflecting the rarity of CTCL, and the difficulty of researching an unusual condition, the principle difficulties of which NICE will be well versed in. The recent publication of two large randomised controlled trials (RCTs) ALCANZA and MAVORIC, has provided impressive efficacy data for Brentuximab and Mogamulizumab in advanced stages of disease, and has offered a unifying platform for international approaches to a debilitating, life-changing and dangerous disease. The MAVORIC trial is the largest RCT study completed in CTCL to date (n=372) and is the first to address progression free survival (PFS) as a primary endpoint. This is a highly relevant endpoint in CTCL, which has a huge symptom burden which detrimentally affects quality of life, and increases burden on healthcare systems. In addition, the patient population recruited is entirely representative of the UK CTCL patient cohort, namely stage IB-IV MF/SS patients refractory to at least 1 systemic treatment, consisting of methotrexate, bexarotene, alpha interferon or chemotherapy, all of which are in current use and/or approved for CTCL in the UK, and are recommended in the published joint UKCLG/BAD guidelines already referenced. Furthermore, the 3 main supra-regional centres for CTCL all contributed patients to MAVORIC, and have, since EMA approval, treated patients with mogamulizumab on the Compassionate Use Scheme. The trial design with vorinostat as a comparator was approved by	committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.

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			the EMA even though Vorinostat is not EMA approved for CTCL, and the significant UK patient numbers recruited to the study is testament to the clinical need for patient access to novel treatments in CTCL in view of the poor prognosis for advanced disease and lack of effective standard therapies. This RCT is the largest study of sezary syndrome (SS) patients (n=168) to date, and provides invaluable evidence of treatment responses for this rare aggressive leukaemic CTCL variant. The trial recruited patients resistant or refractory to current UK standard SS treatments. Specifically, the trial stratified patients according to stage and CTCL subtype (MF vs SS). This is especially important as SS has a poor OS (median 32 months from diagnosis) and controlled trial data on current standard first line treatment options such as combination therapy consisting of photopheresis, pegylated alpha interferon and bexarotene, is lacking despite the high cost of such therapies. Furthermore, the trial results for Mogamulizumab show an improved PFS compared to Vorinostat as the primary endpoint, and this was most striking in the SS patient cohort which is also reflected in the improved PFS for stage III-IV. In addition ORR for SS was excellent at 37% with a median duration of response of 17.3 months. The efficacy data is supported by the ORR (31%) of patients on Vorinostat who crossed over to Mogamulizumab after progression (136/186). Serious adverse reaction were rare and the safety profile is wholly acceptable. The UK recruitment into MAVORIC coupled with the high usage on compassionate basis since August 2019 (n=23 across 5 centres) provides further evidence that mogamulizumab is a much needed addition to our anti CTCL therapies.	

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			In conclusion the efficacy of Mogamulizumab in terms of PFS and ORR/duration of response is clear and especially impressive for the SS cohort which is a rare and difficult to treat CTCL subtype with no published controlled trial data. As such Mogamulizumab represents an important treatment option for CTCL patients which is reflected in both FDA and EMA approval. As a group of clinicians representing all nations of the UK, we cannot tolerate another drift further from our European and worldwide counterparts in our ability to access appropriate and effective treatment for patients with a disease as damaging as CTCL including sezary syndrome.	
17	Consultee	British Association of Dermatologists (BAD)	The British Association of Dermatologists would like to support the submission made by the UKCLG	Comment noted. See UKCLG response above.
18	Consultee	Royal College of Physicians	We have liaised with the British Association of Dermatologists (BAD) and we would like to endorse the response submitted by UK Cutaneous Lymphoma Group (UKCLG).	Comment noted. See UKCLG response above.
19	Consultee	Lymphoma Action	We are concerned that the rarity of mycosis fungoides (MF) and Sezary syndrome (SS) has not been given sufficient consideration. It is unreasonable to demand the same standards of trial evidence in rare subtypes of cancers as in more common cancers. In the MAVORIC trial, mogamulizumab was not directly compared with the committee's defined UK options for MF/SS because it would have been unethical to use a comparator agent that many of the trial participants had already been treated with unsuccessfully. Patients recruited into the trial had already received a median of 3 previous treatments and most had already had bexarotene and/or interferon. Excluding patients who had already received these treatments would have significantly affected trial recruitment which,	Comment noted. The committee considered results of the MAVORIC study. However, it was concerned about the clinical effectiveness data because vorinostat is not licensed for use in the UK and does not represent NHS standard care. Overall, the committee considered the evidence for mogamulizumab to be limited

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			for such a rare condition, would have led to an inadequately powered trial. Instead, an alternative comparator was selected that has been proven in clinical trials to be effective and well tolerated in CTCL and has been widely used in other countries for several years.	and concluded that the size of the relative benefits was uncertain (see sections 3.4 and 3.5 in the FAD). The committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.
20	Consultee	Lymphoma Action	We feel the clinical evidence supporting mogamulizumab has been unreasonably dismissed. Many treatments currently used for people with MF/SS have only been studied in single-arm trials or are not specifically licensed for the condition and are prescribed off-label. However, mogamulizumab is supported by robust data from a randomised phase 3 trial involving 370 patients – the largest trial ever conducted in cutaneous T-cell lymphoma (CTCL). It is unreasonable to dismiss the positive data from this large trial because it does not directly compare mogamulizumab with treatments currently used as NHS standard – especially since most patients recruited into the trial had already been treated with many of these standard options but had failed to respond or had experienced relapse. Despite this, mogamulizumab provided significant, measurable benefits against an active comparator in this difficult-to-treat, heavily pretreated population.	Comment noted. The committee considered results of the MAVORIC study. However, it was concerned about the clinical effectiveness data because vorinostat is not licensed for use in the UK and does not represent NHS standard care. Overall, the committee considered the evidence for mogamulizumab to be limited and concluded that the size of the relative benefits was uncertain (see sections 3.4 and 3.5 in the FAD). The committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.
21	Consultee	Lymphoma	We are concerned that this recommendation does not acknowledge	Comment noted. The

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		Action	the impact of advanced stage MF and SS on patients. These are long-term conditions that cause significant symptoms and can be aggressive. Existing treatments do not, in general, produce durable responses and patients are keen for treatment options that give them longer disease control. In the MAVORIC trial, the primary outcome measure of progression-free survival (PFS) supports a longer duration of response with mogamulizumab treatment. Patients treated with mogamulizumab reported improvements in disease-related symptoms and functioning. Delaying disease progression is important for these chronic conditions and there is a clear unmet need for an effective, durable treatment. We believe the recommendations do not give sufficient consideration to the impact of MF and SS on quality of life. This can be difficult to capture adequately using clinical scoring systems but has a considerable impact on the day-to-day lives of patients. Even small improvements can be beneficial and can make a disproportionate difference to patients' lives. The benefit of mogamulizumab on quality of life is supported by clinical data and by the testimony of clinical experts and patients alike.	committee discussed the impact of mycosis fungoides and Sézary syndrome on the quality of life of patients during both meetings. In addition, utility values for patients were included within the company's health economic model. However, based on the clinical and cost-effectiveness evidence the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.
22	Consultee	Lymphoma Action	We consider the recommendation underestimates the potential impact of MF/SS on carers. It can have a significant psychological, emotional and financial impact beyond the patient themselves and can negatively affect work, leisure activities, relationships and emotional wellbeing due to caring responsibilities, frequent appointments, anxiety and stress. An effective treatment such as mogamulizumab therefore has the potential to benefit not just the patient but also the carer – psychologically, emotionally and financially.	The committee recognised the impact of mycosis fungoides and Sézary syndrome on carers and discussed this at both meetings. The company submitted carer utility data, however the committee did not consider the company's approach appropriate for use in decision-making (see section 3.12). Overall, based on the clinical and cost-effectiveness evidence available, the committee

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				concluded that mogamulizumab was not cost-effective and therefore could not be recommended.
23	Web comment	Patient 1	**Has all of the relevant evidence been taken into account?** "No, mogamulizumab is compared to a drug not used in the UK (Vorinostat).Mycosis Fungoides and Sezary Syndrome are both very rare diseases. We have very little in our treatment armoury (NICE approved), in order to be able to treat patients with this awfully debilitating condition(s). Refusing NICE approval of Mogamulizumab on the basis of the recommendations given is unreasonable due to the following reasons. -Trial evidence available in more common cancers will be much more readily obtainable, and due to the rarity of the disease it is unfair to expect the same volume of available data." "Mycosis Fungoides and Sezary Syndrome are both very rare diseases. We have very little in our treatment armoury (NICE approved), in order to be able to treat patients with this awfully debilitating condition(s). Refusing NICE approval of Mogamulizumab on the basis of the recommendations given is unreasonable due to the following reasons. -Trial evidence available in more common cancers will be much more readily obtainable, and due to the rarity of the disease it is unfair to expect the same volume of available data. - In your review of trial data Mogamulizumab is compared to a drug not used in the UK (Vorinostat).	Comment noted. The committee noted the rarity of the disease and commended the company on its efforts to obtain clinical data. The committee recognised the burden placed on some carers; however, the committee was not convinced that the company's approach to modelling carers utility values was appropriate and therefore chose to remove carer utilities from the model (see section 3.12). However, it concluded that mogamulizumab was not cost-effective and therefore could not be recommended.

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			- The benefit of Mogamulizumab on quality of life is supported by clinical data, patients and clinical experts and It feels that the impact this condition has on patients and their carers has not been acknowledged in this decision making process. The debilitating symptoms of this disease (a few as an example… constant itching, unable to sleep, unable to maintain/ control own body temperature, pain, regular dressing changes, bleeding skin, unable to work/ hold a job down) that our patients suffer with means many of them do not wish to continue living if they do not have access to adequate treatment in order to help with their ongoing suffering. It makes life for most unbearable. These patients need treatment to improve comfort and quality of life as symptoms in turn severely have an effect on psychological and emotional well-being. Improving quality of life must be paramount in this decision making process, to make sure the time the patient has, has some quality. - It seems the impact on carers has not been fully appreciated in the decision making process. Carers and family often have to take lots of time off work to assist and even may not be able to work themselves due to the negative impact this condition has on their loved one. All of this in turn will have an impact on their relationships and increases anxiety and stress beyond the patient."	
24	Web comment	Web commentator 1	**Has all of the relevant evidence been taken into account?** "There are very few randomised studies in CTCL, and the evidence base for then majority of treatments used are from anecdotal series and single-arm studies. The evidence for MAVORIC is from a large scale multicentre trial, which is a real rarity in this context." **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**	Comment noted. The committee discussed the impact of mycosis fungoides and Sézary syndrome on the quality of life of patients during both meetings. In addition, utility values for patients were included within the company's health economic model. However,

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			"Highlighting the use of vorinostat as a comparator, in the context of very limited UK experience in this setting, is fully valid. However it must also be acknowledged that many patients in the study had already been exposed to most of the agents that are routinely used in UK practice. Furthermore, quality of life considerations are crucial in CTCL, as many patients can live for years but with very considerable and life-affecting symptoms." **Are the recommendations sound and a suitable basis for guidance to the NHS?** "Advanced stage CTCL is a significant area of unmet need for the reasons stated above. The data for mogamulizumab are derived from a robust large-scale international trial with significant crossover. I would be grateful if this could be considered" **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** "Not that I'm aware of."	based on the clinical and cost-effectiveness evidence the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.
25	Web comment	Web commentator 2	**Has all of the relevant evidence been taken into account?** "The committee have discounted the use of Vorinostat in the Mavoric trial largely because it is not available in the UK. Studies show that it's effectiveness is similar to that of Bexarotene and interferon. Most of the UK patients had already received multiple therapies (median 3) including methotrexate, bexarotene and interferon, so these would not have been a suitable comparator. In such a rare disease this trial is the largest RCT for MF/SS and in particular the largest cohort of SS published to date. It shows	Comment noted. The company submission compared data for vorinostat with data from the ALCANZA study (which included standard therapies, such as bexarotene). However, the committee noted that there were significant differences between the MAVORIC and

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			marked improvement in PFS, ORR and duration of response, particularly of blood burden. No other drug has shown similar improvements in a RCT in SS. As clinicians looking after patients with this condition we have seen dramatic and lasting control of distressing symptoms for the first time, when our usual 'standard' therapies have not worked. Very few therapies are available for this disease and our patients should not be denied the option of Mogamulizumab which has shown significant effectiveness in this difficult to treat group." **Are the recommendations sound and a suitable basis for guidance to the NHS?** "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. There has never been a trial which has documented this sort of response in the SS cohort; the largest to date in CTCL history. There is also data on improved quality of life and carer burden for the first time. It will be a tragedy for individual patients and the clinical teams who have to look after them if this drug is not approved; in particular for SS"	ALCANZA trial populations and the ALCANZA trial had a high level of crossover (see section 3.4 of the FAD). Overall, based on the clinical and cost-effectiveness evidence available, the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.
26	Web comment	Cutaneous Lymphoma Clinical Nurse Specialists at St John's Institute of Dermatology	**Has all of the relevant evidence been taken into account?** "As a team of Cutaneous Lymphoma Clinical Nurse Specialists at St John's Institute of Dermatology, we were incredibly saddened and disappointed with NICE's recommendation not to consider mogamulizumab for CTCL patients. We are in full agreement with the comments made by the UKCLG with regards to the success of mogamulizumab in our patient group, which is reflected in the MAVORIC and ALCANZA trials. We feel it is difficult to fully portray the importance of mogamulizumab	Comment noted. Please see comment 16 addressed to UKCLG.

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			due to the rarity of the disease, and it is unreasonable to demand the same standards of trial evidence in rare subtypes of cancers as in more common cancers. Our first-hand experience in nursing patients with CTCL has shown us how invaluable mogamulizumab is. Patients with severe disease are overwhelmingly debilitated and have limited treatment options. We feel that it goes against humanity to deny patients of this option when their quality of life is so low. We feel that is it our duty as nurses to advocate for our patients and implore you to reconsider your decision. We look forward to hearing your response.	
27	Web comment	Web commentator 3	“I feel these recommendations are not taking into account that MF and SS are long term conditions having a strong impact on patients' quality of life. the MAVORIC trial https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30379-6/fulltext shows that Mogamulizumab significantly prolonged progression-free survival and could provide a new, effective treatment for patients with MF and SS, a subtype that represents a major therapeutic challenge in cutaneous T-cell lymphoma. These patients' clinical conditions can deteriorate rapidely and Mogamolizumab can improve disease related symptoms in cases where conventional treatment has not been successful. Also, these patients often die for complications related to the skin disease (like sepsis) and controlling disease related symptoms/skin deterioration may delay the occurence of fatal events.”	Comment noted. The committee discussed the impact of mycosis fungoides and Sézary syndrome on the quality of life of patients during both meetings. In addition, utility values for patients were included within the company’s health economic model. However, based on the clinical and cost-effectiveness evidence the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended
28	Web comment	Lymphoma specialist nursing team, The Christie	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** "As a lymphoma specialist nursing team working within a UK NHS	Comment noted. The committee noted the rarity of the disease and commended the company on its efforts to

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		NHS Foundation Trust	supra-network cutaneous lymphoma service in the North West of England we have extensive experience caring for patients with all types of cutaneous lymphoma including MF and SS, including patients who are receiving Mogamulizumab. We currently provide support to patients who are receiving Mogamulizumab and 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. Mogamulizumab, although not without its potential but overall manageable side effects, has been well tolerated and integrated into lymphoma treatment service delivery within our haematology/oncology day services without any challenges. We feel it was unreasonable to dismiss the results of the MAVORIC phase 3 randomised controlled trial on the basis that the comparator arm is not licenced for use in the UK for patients with MF or SS. MF and SS are rare types of cancer and systemic treatments currently used in the UK to treat these cancers have not been subject to such a large robust randomised controlled trial as the MAVORIC study demonstrated, or patients are prescribed treatments off label. The data from the patients treated on the Mogamulizumab arm demonstrated superior results compared to the comparator arm. In addition, many of the patients in this study had already received and relapsed following standard UK treatments." **Are the recommendations sound and a suitable basis for guidance to the NHS?** "MF and SS are rare and aggressive diseases that have a significant negative impact on all aspects of a patients' quality of life. This recommendation does not adequately reflect the impact that advanced stage MF and SS has on patients with these rare	obtain clinical data. The committee considered results of the MAVORIC study. However, it was concerned about the clinical effectiveness data because vorinostat is not licensed for use in the UK and does not represent NHS standard care. The company submission also compared data for vorinostat with data from the ALCANZA study (which included standard therapies, such as bexarotene). However, the committee noted that there were significant differences between the MAVORIC and ALCANZA trial populations and the ALCANZA trial had a high level of crossover (see section 3.4 of the FAD). The committee recognised the impact of mycosis fungoides and Sézary syndrome on carers and discussed this at both meetings. The company submitted carer utility data, however the committee did not consider the company's approach appropriate for use in decision-making. Overall, based on the clinical and cost-effectiveness evidence

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			and aggressive diseases, and that other existing treatments do not produce meaningful or durable responses. Although the comparator arm treatment in the MAVORIC trial is not used in the UK, the treatments accessed by trial patients previously (and failed) are treatments currently used in the UK. In the MAVORIC study Mogamulizumab demonstrated longer duration of responses and these results have been reflected in our real-world experience of patients receiving this treatment. We do not feel that the recommendation adequately reflects the significant impact MF and SS has on patients' quality of life. Where a patient is not transplant eligible (either due to performance status, age, comorbidities or progressive disease), all treatment options are considered palliative and aim to improve the patient's quality of life. Quality of life is of paramount importance in this patient group and this concept is being supported by NHS England who are carrying out quality of life questionnaires in the hope to show the importance of quality of life alongside survival (https://www.england.nhs.uk/cancer/living/). We see first-hand in our clinical practice the poor quality of life this patient group experience prior to access to Mogamulizumab. The impact on carers, including carer burden modelling, does not adequately reflect 'real world' observations during day to day clinical practice in supporting both patients and carers with MF and SS. We have witnessed the positive impact Mogamulizumab has had on the lives of both patients and carers receiving this treatment at our centre. The burden on carers often starts from the presentation of the disease, including the often many years of uncertainty before a diagnosis of this rare condition is confirmed. Carers witness patients suffering due to intractable symptoms such as pain, pruritus, loss of temperature control as well as the disfiguring skin appearances with patches, plaques and tumours that require dressing changes. Carers often express helplessness and	available, the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.

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			hopelessness in their attempts to alleviate their loved ones' suffering. Carers are often the primary source of psychological support for patients, and indeed the only source of support before a cutaneous lymphoma diagnosis is made. Healthcare professionals, such as ourselves, provide professional holistic support to patients and carers, in reality we only have a limited period of time with patients and carers and the burden of care falls to the carer who is with the patient the majority of the time. Practically, carers assist patients with their often complex, frequent and time-consuming topical skin management regimens including application of whole body topical applications. This can include areas patients cannot reach, including intimate areas, often both during the day and the night. Patients requiring systemic treatments are required to attend hospital appointments on frequent basis, spending many hours in a hospital setting for assessment and treatment. Patients and carers often travel a long distance to a specialist cutaneous lymphoma treatment centre.. This can make it difficult for carers to maintain their employment, often relying on the goodwill of their employers to work flexible hours to be able to support their loved one. Carers can often be the single source of income due to the nature of MF/SS and treatment side effects of treatment resulting in patients with advance stage disease often being unable to continue to work. This can have significant financial impact on the whole family, including costs of transport, increased utility bills due to frequent requirements to wash bedding and clothing and heating for temperature control comfort. Carers' own physical and mental health and well-being can be neglected as they focus on their loved ones at the expense of their own needs. Carer can experience a high degree of stress, exacerbated by sleep interruptions, in an attempt to alleviate their loved ones suffering e.g. topical application of creams during the night, pain control, temperature control, itch control. Relationships, including sexual relationships can be affected due to the condition and treatment side effects. The financial cost of resources required to treat skin tumours or	

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			erythroderma for patients with MF or SS has not been reasonably considered. These include time and expertise of specialist tissue viability nurses and district nursing teams to assess and manage complex wound care, often requiring frequent and complex dressings. With the high risk of infection and sepsis due to the break in skin integrity there is also the additional financial cost of anti-microbial antibiotics, hospital inpatient stays and associated costs. Unlike standard goals of wound care management, caring for patients with MF or SS presents major challenges. Wound care can only provide partial relief to this group of patients as it is the effective treatment of the underlying cutaneous lymphoma that allows the tumours to heal. Mogamulizumab can provide such effective treatment, not only providing physical and emotional relief to patients but also reducing the financial burden on NHS services as described above."	
29	Web comment	Cutaneous Lymphoma Multidisciplinary Team, Queen Elizabeth Hospital Birmingham	On behalf of:  Cutaneous Lymphoma Multidisciplinary Team, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, Birmingham, B15 2TH The aforementioned respondents write this comment in response to NICE consultation response in relation to “Mogamulizumab for	Comment noted. The committee acknowledged the real world experience with mogamulizumab during the second appraisal committee meeting. However, based on the clinical and cost-effectiveness evidence the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended

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			previously treated mycosis fungoides and Sézary syndrome". As key stakeholders in the management of patients with this disease, we wish to raise concerns in relation to the following items raised in the consultation process: 1. Section 1 Recommendations, Subsection (Why the committee made these recommendations), Paragraph 2: "The clinical trial evidence is very uncertain because mogamulizumab is compared with vorinostat, a treatment that is not used or licensed in the UK. Also, many people switch treatments and there are a lot of differences among the trial population. This means it is unclear how well mogamulizumab works." 2. Section 3 Committee Discussion, Subsection 3.3 "It concluded that standard care was the most appropriate comparator, which includes treatments such as methotrexate, bexarotene, interferon and chemotherapy." Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? "We disagree that there is uncertainty regarding the clinical trial evidence regarding the effectiveness of mogamulizumab. In the MAVORIC trial, mogamulizumab was not directly compared with standard of care treatments (e.g., methotrexate, bexarotene, interferon and chemotherapy) as many of the trial participants had already been treated with unsuccessfully with these agents. We have treated 8 patients (3 males, 5 females) with a mean (+/- SEM) age of 61.38 (+/- 4.07) years with mogamulizumab on a compassionate basis since July 2019. These included 4 patients with advanced mycosis fungoides (IIIB – IVA2 disease), two patients with Sezary syndrome (IVA2) and two patients with HTLV-1 lymphoma (one mycosis fungoides and the other Sezary	

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			syndrome like). These patients were all heavily pre-treated and included 6.625 (+/- 0.98) previous treatments of which 1.125 (+/- 0.39) were skin directed therapies and 5.5 (+/- 0.65) systemic therapies. Previous systemic therapies in these patients included methotrexate (n=4), bexarotene (n=4), interferon (n=4), gemcitabine (n=4), CHOP (n=3), interferon (n=4), ECP (n=3), resminostat (n=3) and brentuximab (n=2). In this cohort, 6/8 achieved an overall response rate (OR) in skin of 50% (complete response, CR, n=1; partial response, PR, n=2; stable disease, SD, n=2; and progressive disease PD, n=1). In these same six patients, nodal disease remained stable. It was not possible to assess skin/lymph node follow-up status in 2/8 patients as they only received mogamulizumab for one month at the time of our review. Blood response assessment was possible in 7/8 patients and demonstrated an OR of 71.4% (CR, n=3; PR, n=2 and SD, n=2) with a reduction in peripheral blood absolute Sezary cell counts of 77.40 (+/- 8.95)% with a mean time to response of 0.76 (+/- 0.24) months. None of our patients had visceral disease and therefore no visceral response assessment following mogamulizumab was possible. Mogamulizumab was well tolerated and the most common treatment-emergent adverse events (TEAEs) were grade 1-2 (97.5% of all TEAEs) and only one episode (2.5%) of grade 3 TEAE was observed. The most common TEAEs included skin infection (n=4), rash (n=2), fever (n=2), nausea (n=3), lethargy (n=3) and diarrhoea (n=2). In our real-world observations of treating patients with mogamulizumab, we found similar response rates to those observed in the MAVORIC trial. These included similar response rates of 71.4% in blood (MAVORIC = 68%) and 50% in skin (MAVORIC = 42%)." **Are the recommendations sound and a suitable basis for guidance to the NHS?**	

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			"Given our experience in treating these patients we argue strongly that mogamulizumab, a drug which has shown significant and measurable benefits in clinical trials has been unfairly dismissed and denies patients with this rare disease an effective durable treatment." **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** "No"	
30	Web comment	Patient 2	"Having been diagnosed with MF (CTCL) back in 1999 and endured every treatment available resulting in going through two Allogeneic Stem Cell Transplants ANY new drug that can delay or even stop the need for enduring Stem Cell Transplant can only be positive and in the long run much more cost effective as Stem Cell Transplant is in its self expensive but the long term post treatment support and medical complications just adds to the costs. I full support the adoption of this new drug"	Comment noted. Overall, based on the clinical and cost-effectiveness evidence available, the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.
31	Web comment	Web commentator 4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** "Rare skin disease" "I read this paper with interest as I believe it is very relevant to the patients I care for in the South West Skin Lymphoma clinic. This is a rare condition that patients and their carers find bewildering and utterly miserable. Current treatment options are limited and development of new medicines should be a priority. This trial has	Comment noted. Overall, based on the clinical and cost-effectiveness evidence available, the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.

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			involved an astonishing number of patients and produced clearly significant results in support of Mogamulizumab as an option for patients with refractory disease. The cost of the treatment reflects the in depth research that has gone into this breakthrough which is reminiscent of the immune targeting treatments in Melanoma which have developed over the past 10 years. It is essential to allow these new treatments to be used and ultimately refined in clinical practice. I would ask NICE to carefully reconsider its decision to allow this progress to take place for Cutaneous Lymphoma."	
32	Web comment	Manchester Cutaneous Lymphoma Group	**Has all of the relevant evidence been taken into account?** "The Results of the Mavoric trial have been considered but the committee have expressed concerns regarding the validity of comparator arm. This concern is misplaced (as detailed below). The committee did not have access to the real world data demonstrating efficacy outside a clinical trial. Our experience has been outlined below. The Committee did not compare the survival of the Sezary Syndrome patients who have received Mogamulizumab (in and outside clinical trials) with the consistent historical evidence showing a median survival of 36 months" **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** "We recognise the cost effectiveness of any intervention is very difficult to measure due to so many complexities. The situation of aggressive CTCL and Sezary Syndrome is a good example. This is a rare disease and the published evidence regarding the efficacy of any treatment is sparse. We recognise that Overall Survival (OS) is a key element to be considered by NICE. The Mavoric trial design was cross over, which offers the patients the advantage of always having access to Mogamulizumab irrespective of the initial treatment arm. The	Comment noted. The committee noted the rarity of the disease and commended the company on its efforts to obtain clinical data. The committee considered results of the MAVORIC study. However, it was concerned about the clinical effectiveness data because vorinostat is not licensed for use in the UK and does not represent NHS standard care. The company submission also compared data for vorinostat with data from the ALCANZA study (which included standard therapies, such as bexarotene). However, the committee noted that there were significant differences between the MAVORIC and ALCANZA trial populations and the ALCANZA trial had a high level of crossover (see

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			company should be commended for supporting this trial design in the knowledge that it makes OS comparisons very difficult. As the longer term follow up from Mavoric emerges and in combination with the increasing real world experience, clinicians looking after these patients are becoming ever more confident that Mogamulzimab changes the course of the disease not only in terms of an improvement in PFS but in the stiking observation that it leads to a more indolent behaviour post Mogamulzimab. In time, this will translate into patients living longer as a result of Mogamulizumab. A very important issue to take into account in terms of cost effectiveness is the impact any intervention has on a patient's quality of life. Nowhere is this more evident than in this very distressing disease where patients can live for several years with relentless symptoms including progressive weeping wounds, unbearable itch and disfigurement. The Movoric trial and our real world experience with Mogamulizumab shows a dramatic reduction in the suffering of our patients and a transformative improvement in they way in which they can live their lives including returning to work and caring for their families. In this disease, the impact on quality of life should have equal importance to the possibility of prolongation of lifespan as a consequence of Mogamulizumab therapy." **Are the recommendations sound and a suitable basis for guidance to the NHS?** “We strongly reject the recommendations of NICE in this case and the current guidance to the NHS will increase suffering of our patients and will deny them the opportunity for a longer lifespan.” **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation,**	section 3.4 of the FAD). The committee also discussed the impact of mycosis fungoides and Sézary syndrome on the quality of life of patients during both meetings. In addition, utility values for patients were included within the company’s health economic model. Overall, based on the clinical and cost-effectiveness evidence available, the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.

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			age, gender reassignment, pregnancy and maternity? “We are not aware of any such considerations in this case” "Response to NICE re the recent decision regarding Mogamulizumab in CTCL and Sezary Syndrome On behalf of the Manchester supra regional cutaneous lymphoma service we wish to register our challenge to the recent decision by NICE. The Manchester supra regional cutaneous lymphoma service comprises a multidisciplinary team of dermatologists, oncologists, haematologists, histopathologists and specialist nurses responsible for the care of this rare group of patients drawn from a population of over 5 million. We have one of the largest number of patients with advanced Cutaneous Lymphoma in the UK and have extensive experience with the use of Mogamulizumab. We participated in the international Mavoric trial and we have 5 patients currently receiving this therapy in the patient access programme. All 5 patients have experienced a dramatic improvement in their skin and associated Quality of Life. In addition, we have a further 2 patients due to commence in the near future. The data from the Mavoric trial shows a clear benefit in terms of PFS and quality of life. We however note the concern expressed by the NICE committee regarding the comparator arm of Vorinostat which is not licenced in the UK. The current literature is very clear that Vorinostat has equivalent activity in phase II studies to Bexarotene which was one of the comparator arms in the Alcanza trial, the results of which led to NICE approving Brentuxmab in advanced CTCL. (The other comparator arm in this study was methotrexate which has been used as first line systemic therapy for over 50 years and for which	

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			there is little recently published evidence for efficacy). In contrast to the Alcanza trial, the Mavoric study included many more patients with advanced disease, particularly with blood involvement, diagnosed as Sezary syndrome. The literature for Sezary syndrome has been very consistent over many years showing an obstinate median survival of 36 months. Up to now, there has been no treatment available which has had an impression on this dismal prognosis. Mogamulizumab in contrast, in the Mavoric study has shown the highest response rate and the longest PFS ever recorded. In addition we now have clear evidence from the Mavoric study that Mogamulizumab therapy led to a sustained improvement in the quality of life for these patients for whom the symptoms of this disease can be unbearable. As the data from Mavoric matures we are beginning to see a change in the behaviour of the disease following Mogamulzumab leading to a more indolent character compared with pre Mogamulizumab. Many of us with first-hand experience of this drug have witnessed this but we recognise that with such a rare condition, it will take considerable time for this to be proven in a clinical trial. What is quite clear however, is the overall survival of the cohort of patients who have been fortunate to have received Mogamulzumab is considerably longer than the 36 months quoted in the literature. In summary, we have not had a drug to significantly change the course of this terrible disease for over 30 years. Mogamulizumab is such a drug . [redacted]	

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			On behalf of the Manchester Cutaneous Lymphoma Group"	
33	Web comment	Web commentator 5	Has all of the relevant evidence been taken into account? “No. Anecdotal evidence from the sufferers, in my opinion is of equal importance, to scientific evidence. Perhaps even more important, sufferers know what's making them feel better. Improving blood stats is quantifiable but improving life quality is immeasurable.” Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? “No. I feel that the rarity of these conditions means that numbers coming forward for treatment must be small. In comparison to some other forms of cancers. Therefore, these illnesses should be classed as a special case. Both in clinical and cost effective terms.” Are the recommendations sound and a suitable basis for guidance to the NHS? “No, because the overall human costs have not been taken into account. Using this drug would ultimately save costs, by slowing the progress of the disease and the subsequent incurred costs of other treatments such as frequent antibiotics, other medications, radiotherapy, etc. Also it would reduce the costs of caring and potentially allow some sufferers to continue working” Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Comment noted. During both committee meetings, the committee heard from patient experts on the impact of mycosis fungoides and Sézary syndrome. In addition, during the second meeting, the company discussed comments received from people with mycosis fungoides and Sézary syndrome during the consultation process. The committee recognised the impact on the quality of life of these conditions on patients. The rarity of the disease was also recognised by the committee. As stated in the NICE methods guide, the committee is aware that the evidence base may be weaker for some technologies, including those for rare diseases. In relation to costs, the health economic model submitted by the company took an NHS

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			“Yes, on the grounds of disability. The impact of these diseases can be very severe atheistically. Appearance is the first thing we register, when we meet an individual. I have seen individuals with terrible skin lesions, shedding large quantities of skin and some with actual tissue loss. Trying to live with this is hard. I myself lost a large amount of skin with underlying tissue off my legs. It took three months to heal. Thus any drug that can slow things from getting to this level is vital. We are disabled by virtue of having the illness.” "Dear committee members, I have Cutaneous T Cell Lymphoma at the Sensory Stage and Mogamulizumab is quite simply keeping me alive by keeping the disease stable and non-progressive at present. More so, I not only feel well and can function fully, but at times I also feel ‘normal’ and can almost kid myself into thinking I do not have a terminal illness. The impact of receiving my diagnosis was seismic and the effects were catastrophic. I became very ill, very quickly and deteriorated rapidly. My husband and family were in shock. I was prepared for death and then miraculously I was rescued by my medical team and I started to feel a little better. I moved through various treatments to try and control the disease from progressing, but 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. Mogamulizumab gives me a good quality of life and I am deeply grateful for being allowed to receive it. I would like to continue on this drug for a long as it is working, but more importantly I would like it to be available to the patients that come after me. The rarity of my disease means that the number of those needing Mogamulizumab will be low. Therefore, I feel that the benefits will probably outweigh the costs in financial terms. However, in life changing terms, the benefits are immeasurable. When I was diagnosed in 2016, I didn’t think I would still be alive in 2020. Now I	and personal social services (PSS) perspective. Overall, based on the evidence available, the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.

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			plan for a future; I hope to celebrate my 50th Wedding Anniversary next year in Nov 2021. I plan to live for several years more with the help of Mogamulizumab, which I know receive on compassionate grounds. Please give people after me the chance to feel better and live longer by making Mogamulizumab unconditionally available. Thank you for your deliberations. Yours respectfully, [redacted]	
34	Web comment	Web commentator 6	"The following bullet points demonstrate the difficulties and effects of caring for a loved one with Sezary syndrome. 1. The most difficult aspect is without doubt watching someone you love suffer with the debilitating symptoms that Sezary syndrome causes, muscle pain, constant itch, cuts and infection in skin. The feeling of being completely helpless to aid their suffering. 2. Family life is organised around medical appointments and treatment. Restrictions to family life is unavoidable as family holidays and outings may have to be cancelled due to a severe flair up of symptoms. 3. Explaining the condition and the life limiting implications to children is extremely upsetting. 4. Trying to hold down a full- time job whilst providing support for your partner is difficult. The need to keep employers happy and the desire to attend appointments is a constant emotional drain. 5. As it is often necessary to apply emollients during the night it is necessary to sleep separately so that I can continue to work. 6. The constant fear that is caused by having your partner diagnosed with cancer and the uncertainty for the future of your family. [redacted]	Comment noted. The committee recognised the impact of mycosis fungoides and Sézary syndrome on carers and discussed this at both meetings. The company submitted carer utility data, however the committee did not consider the company's approach appropriate for use in decision-making. Overall, based on the clinical and cost-effectiveness evidence available, the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.

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35	Web comment	Cutaneous Lymphoma Foundation	"The Cutaneous Lymphoma Foundation, the leading international patient organization supporting individuals living with cutaneous lymphoma, concurs with our colleagues from Lymphoma Action with regard to the critical importance of mogamulizumab for patients suffering from Sezary syndrome, a debilitating and often life-threatening form of cutaneous lymphoma. The Foundation has been serving this patient population for 22 years and has seen the positive impact of this new treatment on the lives of patients. We urge the NHS to take into consideration the impact on patient's quality of life this new treatment can provide."	Comment noted. The committee discussed the impact of mycosis fungoides and Sézary syndrome on the quality of life of patients both meetings. In addition, quality of utility values for patients were included within the company's health economic model. However, based on the available clinical and cost-effectiveness evidence the committee concluded that mogamulizumab was not cost-effective and therefore could not be recommended.
36	Web comment	Web commentator 7	"Patients with advanced stage MF and SS have shortened survival and poor life quality. Current treatments have low response rates and the responses are very short-lived. With advancement of science, mogamulizumab has been developed that can target key molecules and cells in this rare cancer, and in well-controlled clinical trials, has been shown to be effective with great safety profile. The MAVORIC study, a randomized clinical trial with rigorous response evaluation criteria, has shown mogamulizumab to be a valuable added therapy that shows promising durable responses and improved progression-free survival and life quality, especially in those with Sezary syndrome. Mogamulizumab has shown rapid and durable clearance of blood disease in Sezary syndrome, rarely obtained safely and reliably with other therapies. Given that standard therapies have short-lived responses, more treatment options are essential for the survival and life quality of patients with previously treated MF and SS. In those patients with high-burden Sezary disease, the rapid reduction of Sezary burden has supported mogamulizumab as a preferred initial treatment option by the NCCN	Comment noted. The committee considered results of the MAVORIC study. However, it was concerned about the clinical effectiveness data because vorinostat is not licensed for use in the UK and does not represent NHS standard care. Overall, the committee considered the evidence for mogamulizumab to be limited and concluded that the size of the relative benefits was uncertain (see sections 3.4 and 3.5 in the FAD). The committee concluded that mogamulizumab was not

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			(clinical experts) and not restricted to those who are previously treated. Lastly, mogamulizumab is a rigorously evaluated immunotherapy that has great safety profile, and such immune therapy option is needed in these patients with refractory CTCL who are already immune-suppressed and at risk for infections where sepsis is a major cause of death.”	cost-effective and therefore could not be recommended.

NICE National Institute for Health and Care Excellence

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 19 August 2020 via the NICE Docs link.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kyowa Kirin Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Kyowa Kirin is committed to the NICE process and bringing mogamulizumab to eligible patients living with mycosis fungoides and Sézary syndrome. We welcome the opportunity to provide additional information to NICE and other relevant stakeholders and are optimistic we can find a positive way forward to ensure that patients in England and Wales can access this innovative medicine as quickly as possible. There is a high unmet need among people living with both mycosis fungoides and Sézary syndrome and they need better therapeutic options. Kyowa Kirin thanks NICE and the Committee for sharing their views on the evidence submitted to date in the Appraisal Consultation Document. Whilst we do not agree with the current conclusions the Committee has reached, we welcome the opportunity to address the areas of uncertainty highlighted. We will respond to all three questions posed by NICE and, more specifically, focus on the nature of these rare sub-types of Cutaneous T-Cell Lymphoma and the robustness of the clinical trial evidence. We will spell out the rationale for using vorinostat as a comparator, the choice of the trial population and the generalisability of the evidence to NHS clinical practice. We hope the Appraisal Committee reviews the requested evidence fairly and reconsiders its current evaluation of mogamulizumab for the treatment of people living with advanced mycosis fungoides and Sézary syndrome, two subtypes of Cutaneous T-Cell Lymphoma, who have had at least one prior systemic treatment and who are either clinically ineligible or refractory to brentuximab vedotin.
1	Kyowa Kirin does not agree with the Committee's review of the clinical trial evidence taken from **MAVORIC, the largest phase III randomised control trial in Cutaneous T-Cell Lymphoma (n=372), which for the first time includes Sézary syndrome patients** We feel the rarity of Cutaneous T-Cell Lymphoma and the limited systemic treatment options for mycosis fungoides and Sézary syndrome have not been considered appropriately with regards to the design of this trial. To ensure heavily pre-treated patients were ethically recruited for this study, a new medicine not previously used was agreed to by the European Medicines Agency to be the chosen comparator. Generalisability of the trial evidence to the NHS population was supported by Cutaneous T-Cell Lymphoma clinical expert opinion and further analyses, which are referred to in the section below. Based on the evidence from the MAVORIC trial, mogamulizumab demonstrates significant benefits versus a licensed comparator in a patient population with very limited treatment options left.
2	Kyowa Kirin recognises the Committee's **concerns about the uncertainty surrounding mogamulizumab as a result of treatment crossover/switching from comparator to active treatment and the use of vorinostat as a comparator** in the MAVORIC trial. Crossover was allowed for ethical reasons due to the poor prognosis for non-responding patients. Vorinostat was chosen as a comparator because it was licensed and widely used in several countries. To recruit ethically in a rare disease trial, a new medicine option was needed for this heavily pre-treated mixed mycosis fungoides and Sézary syndrome population and it was felt preferable to have a defined comparator rather than 'physician's choice'. The European Medicines Agency approved the MAVORIC study design. In order to address these uncertainties in the original submission, a number of analyses were conducted. These included a naïve indirect comparison between vorinostat and the physician's choice arm of the ALCANZA trial (which included methotrexate and bexarotene), bexarotene pivotal trials (phase II study with similar Cutaneous T-Cell Lymphoma population as done for vorinostat) and analyses that adjusted for treatment switching in the vorinostat arm of the MAVORIC trial. The results of the switching analysis were validated against data from the UK Hospital Episode Statistics and three published observational studies (one from the UK and two from the US).

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	As an additional analysis, at the recommendation of the Committee, Kyowa Kirin has now conducted an unanchored indirect comparison of mogamulizumab directly with data from patients (n=198) from the UK Hospital Episode Statistics database that matches well the mogamulizumab arm of the MAVORIC study. This analysis benefits from the following: • Does not require any adjustment for treatment switching with its attendant uncertainties as no patients in the Hospital Episode Statistics database received mogamulizumab • Provides a direct comparison against current UK clinical practice rather than vorinostat as the Hospital Episode Statistics data is an administrative dataset including all patients treated in England • Reflects the current UK mycosis fungoides and Sézary syndrome population as the Hospital Episode Statistics data is an administrative dataset including all patients treated in England (NHS secondary care setting) The revised analyses, using the Evidence Review Group's base case for all other additional relevant aspects and [redacted], resulted in incremental cost-effectiveness ratios of £28,887 and £29,848 per quality-adjusted life-years depending on the carer utilities included for the delay in disease progression. Details of the analyses and the results are presented in the additional analyses document.
3	Kyowa Kirin is concerned, that the **wording of the summaries of clinical and cost effectiveness does not provide an accurate summary view of the evidence regarding the efficacy of mogamulizumab.** The MAVORIC trial provides strong evidence of a benefit compared to vorinostat with respect to progression-free survival and response. The analysis of overall survival adjusting for switching from vorinostat to mogamulizumab provides evidence of a benefit in overall survival. Alongside this, there is evidence that the effectiveness of UK current treatment is not markedly superior to that of vorinostat. Based on these points we feel that the following comments in the Appraisal Consultation Document are potentially misleading: • Page 3: "*This means it is unclear how well mogamulizumab works*" • Page 8: "*concluded that its relative treatment effect compared with NHS standard care was unknown*" • Page 15: "*The relative treatment effect of mogamulizumab compared with NHS standard care was unknown*" • Page 9: "*But the company's analysis was unreliable because […] did not compare mogamulizumab with a relevant comparator*" The Appraisal Consultation Document also states on page 12: "*The Committee was not convinced that mogamulizumab provided an overall survival benefit compared with standard care*". However, even in the worst-case estimate using the 2-stage estimation for crossover adjustment, mogamulizumab resulted in 19 months survival benefit. The uncertainty described in the Evidence Review Group's report was not if mogamulizumab provided overall survival benefit, but rather how much this benefit was. Additionally, Kyowa Kirin has identified some instances of inaccurate description in the Appraisal Consultation Document including in the description of comparative effectiveness, and crossover adjustment. For detailed descriptions, please see accompanying Appendix with this response document.
4	Kyowa Kirin is concerned about the **lack of justification provided for the Committee's preferred choice of crossover adjustment method**. This choice is the single most influential input and Kyowa Kirin has submitted 10-year data from the UK Hospital Episode Statistics database, one published UK observational study and two published

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

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	US observational studies, which support the use of inverse probability of censoring weighting adjustment. This affects the following statements: • Page 10: "*The results from the crossover adjustment methods represent the upper and lower range of plausible overall survival in the standard care arm*" • Page 10: "*The Committee was not convinced that the IPCW-adjusted curve was clinically plausible for the average patient in the modelled population with severe disease*" • Page 12: "*The ERG preferred to use the 2-stage estimation crossover adjustment* • Page 17: "*But it recognised that the lower ICERs reflected the IPCW adjustment method, which it considered to be clinically implausible*" Kyowa Kirin does understand the uncertainty in the cross over adjusted overall survival analyses. Therefore, the additional analyses requested by the Committee, are based on the Hospital Episode Statistics data submitted together with this document. These analyses avoids this issue, as using the Hospital Episode Statistics database for comparison does not require any adjustment for treatment switching with its attendant uncertainties as no patients in the Hospital Episode Statistics database received mogamulizumab. Importantly, the Hospital Episode Statistics data represents current UK NHS clinical practice in advanced mycosis fungoides and Sézary syndrome patients. Additionally, the survival curve for the current standard of treatment in the NHS from the Hospital Episode Statistics analyses is in line with the survival curve from the MAVORIC trial using the inverse probability of censoring weighting adjustment method.
5	Kyowa Kirin is concerned about the **inconsistent requirements in modelling mycosis fungoides and Sézary syndrome between this appraisal compared to the technology appraisal (TA 577) for brentuximab vedotin and the exclusion of allogeneic stem cell transplant after current treatment.** • Regarding the inclusion of allogeneic stem cell transplant: ▪ The Appraisal Consultation Document states on page 4: "it is acceptable to remove allogenic stem cell transplant after current treatment from the company's economic model because this was not allowed in the trial and reduces the risk of bias ".However, in TA577 a higher rate of allogeneic stem cell transplant than that than seen in the pivotal ALCANZA trial was accepted by the Committee. This was a key input in TA577. The additional allogeneic stem cell transplant not seen in the pivotal trial was kept in the model, and as a result influenced the treatment's cost-effectiveness and contributing significantly to the positive recommendation. ▪ Additionally, the UK's Hospital Episode Statistics database demonstrated a 5.2% allogeneic stem cell transplant use after 2nd line treatment. Thus, the current UK clinical practice includes allogeneic stem cell transplant and the survival curves from the Hospital Episode Statistics database takes these into account and corroborates the UK specialist opinion on likely allogeneic stem cell transplant expected rates in this population. ▪ In the MAVORIC trial patients were treated to progression. Responding patients did not interrupt treatment in order to receive an allogeneic stem cell transplant. Upon progression they then switched to further treatments during which some patients received allogeneic stem cell transplant. In real life practice, a proportion of patients receiving mogamulizumab would interrupt treatment in order to receive allogeneic stem cell transplant. This was captured in the model as allogeneic stem cell transplant during current treatment and we believe this reduces the bias in the estimates of cost-effectiveness as it represents anticipated clinical practice. Similar adjustments were made in the modelling of brentuximab vedotin in TA577 in order to reflect differences between actual clinical practice and practice during the trial. ▪ We have concerns that by excluding aSCT after current treatment both is not representative of UK NHS clinical practice and does not consider the clinical governance advice given in the Summary of Product Characteristics for mogamulizumab, which is a regulatory document that is approved by the European Medicines Agency . ▪ While previously there were concerns about including the outcomes of patients who

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	could have received aSCT after current treatment, but the MAVORIC trial did not allow, In the additional HES data based analyses, we have double counted the health benefit of aSCT for patients who have received aSCT in the standard of care arm, thus biasing the results towards standard of care. • Regarding the analyses: ▪ On page 9 the Appraisal Consultation Document states: "the company's analysis was unreliable because it included a mixed population which grouped several lines of treatment together, did not differentiate between disease type and did not compare mogamulizumab with a relevant comparator". Mixed population analyses are very common in non-first line oncology diseases, especially in rare conditions including in mycosis fungoides and Sézary syndrome in the TA577 and are usually considered reliable if they reflect the potential clinical practice in the UK. Single line analyses would not reflect the potential place of mogamulizumab in the treatment pathway, which depending on the CD30 status, and the line of treatment brentuximab vedotin was given, can be second, or third or further line.
6	Kyowa Kirin would like to highlight that the **summary sentence on page 18 stating that "Mogamulizumab is not innovative and all benefits are captured in the model" is not an accurate summary of the evidence.** With regards to innovation: mogamulizumab was granted Promising Innovative Medicine (PIM) designation from UK's The Medicines and Healthcare Products Regulatory Agency (MHRA) in March 2018 for the treatment of advanced refractory mycosis fungoides and Sézary syndrome. With regards to all benefits being captured in the model: this summary is inaccurate in light of the Evidence Review Group's preferred base case as described in the Appraisal Consultation Document. The model, on which the decision is based does not capture important and relevant benefits. For example, carer burden is excluded, as stated in the Appraisal Consultation Document: "carer utility values had not been included in the model". (Please see more information and additional analyses in the additional document submitted with this form.)
7	**While there are uncertainties, given the evidence, the assumption of equal efficacy for the physician's choice arm of the ALCANZA trial and the vorinostat arm of the MAVORIC trial is likely to be conservative.** Kyowa Kirin agrees with the Evidence Review Group on page 8, that "if vorinostat and the physician's choice were similar, patients in the physician's choice arm in ALCANZA would have longer progression-free survival and overall survival because patients had less severe disease. However, overall survival for the physician's choice arm was shorter than with vorinostat." ▪ Regarding the progression-free survival results, the MAVORIC vorinostat arm produced the same progression-free survival Kaplan-Meier curve as the ALCANZA physician choice arm, despite the ALCANZA trial including a better prognostic patient population (e.g., no Sézary syndrome, less advanced patients and less prior pre-treatments). This means, that vorinostat is likely be a more efficacious treatment than methotrexate/bexarotene, which were used in the ALCANZA physician choice arm. This therefore, makes the assumption of similar efficacy conservative. Hence the incremental health benefit included in the cost-effectiveness model is conservative. ▪ Regarding the overall survival results, it is not possible to assess what the ALCANZA trial results would have looked like, since 46% of the patients on the physician's choice arm crossed over to brentuximab vedotin, while 73% of the patients on the vorinostat arm crossed over to mogamulizumab. The very different crossover rates and the lack of reliable crossover adjusted physician's choice arm makes predictions unreliable.

Insert extra rows as needed

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Appendix: Descriptions requiring amendment

Kyowa Kirin accepts that the additional analyses required due to the MAVORIC trial design (naïve indirect comparison, crossover adjustment), and the importance of carer burden in this patient population, can impact uncertainty around the outcomes. However, in the description of these uncertainties and analyses in the Appraisal Consultation Document , Kyowa Kirin identified the following instances, where the descriptions do not completely represent the submitted analyses or evidence base. We very much welcome NICE's stance that all evidence reviews need to be robust, justifiable and fair.

Topic	Descriptions requiring amendment
Indirect comparison and comparators	• The Appraisal Consultation Document states on page 7 that "*an indirect treatment comparison using ALCANZA was not possible*". While we agree, that an anchored indirect comparison using ALCANZA was not possible due to the lack of common comparator and crossover design, an unanchored indirect comparison was conducted by Kyowa Kirin using the ALCANZA trial and was submitted in the original submission for progression-free survival and during the clarification process for overall survival. • The Appraisal Consultation Document states on page 8: "*The company assumed that vorinostat was a suitable proxy for standard care in the NHS because it showed similar progression-free survival to the physician's choice arm in ALCANZA*". The assumption that vorinostat was a suitable proxy for standard of care in the NHS was also based on similar response rates as in the bexarotene pivotal trials and clinical expert opinion in this rare disease. • The Appraisal Consultation Document mentions on pages 3, 5, 7 interferon as part of standard of care, however "interferon alfa-2a has been withdrawn from the market and the stores are being used up, it is substituted with pegylated derivatives of interferon alfa (peginterferon)" (Evidence Review Group report Table 5.5). This should be clarified to represent current NHS clinical practice. • The Appraisal Consultation Document mentions on page 10: "*the model did not include treatment costs that reflected clinical practice*". The model included the treatment costs most relevant in the UK based on NHS England and UK Hospital Episode Statistics data and UK clinical expert survey for this rare disease. While the MAVORIC trial comparator, vorinostat, is not available in the UK, the cost-effectiveness model comparator (bexarotene and a basket of other treatment options) and its treatment costs are representative of UK clinical practice.
Crossover adjustment and overall survival	• The Appraisal Consultation Document states on page 10 "*The company preferred the inverse probability of censoring weights (IPCW) method to adjust for crossover because it produced estimates in line with the company's clinical expert advice and accounted for a potential post-progression benefit of mogamulizumab*". Kyowa Kirin preferred the inverse probability of censoring weights adjustment mainly because it was in line with UK Hospital Episode Statistics data with 10-year follow-up, and three large observational studies. The statement should therefore, read as "*The company preferred the inverse probability of censoring weights (IPCW) method to adjust for crossover because it produced estimates consistent with UK Hospital Episode Statistics data and observational studies, in line with the company's clinical expert advice and accounted for a potential post-progression benefit of mogamulizumab*". • The Appraisal Consultation Document discusses the representativeness of the Kaplan-Meier curve with the inverse probability of censoring weights crossover adjustment and the results with it on page 11. However, this curve is not used in the cost-effectiveness model. Only the parametric survival model fitted to the adjusted patient level data is used, the representativeness of which is supported by the UK NHS Hospital Episode Statistics data and three observational studies. The Kaplan-Meier curve is only an interim result, not the final input. • The Appraisal Consultation Document states in the discussion about the 2-stage crossover

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Topic	Descriptions requiring amendment
	adjustment on page 11: "*The company suggested that the long-term predictions using the 2-stage estimation adjusted curve did not account for the potential disease-modifying effect of mogamulizumab*". However Kyowa Kirin discounted this method mainly as it predicted more than double median survival than UK NHS Hospital Episode Statistics data, higher survival estimates at 1, 3 and 5 years and similar survival at 10 and 20 years from second-line as the observational data for a better patient population from diagnosis. • The Appraisal Consultation Document states on page 14: "*It recalled that mogamulizumab could also be used after 2 previous treatments, but the HES database did not include these [survival values]*". However, the Hospital Episode Statistics data included these and Kyowa Kirin had submitted this in the Technical engagement) stakeholder response form (for third line, the median survival was 1.1 years for mycosis fungoides and 1.0 year for Sézary syndrome). • The Appraisal Consultation Document states on page 14: "*The Committee noted that median overall survival was around 1.3 years using the HES data for people who have had 1 treatment, but only a small number had Sézary syndrome*". The 1.3 years is the result of survival from Hospital Episode Statistics data weighted for mycosis fungoides and Sézary Syndrome distribution in the MAVORIC trial, i.e., based on 45% of Sézary syndrome patients.
Carer utility values	• On page 13 the Appraisal Consultation Document states that "*The Committee questioned if it was appropriate to include carer utility values for disease control (0.56) and subsequent treatment (0.37*)". However, these utilities were not applied in the model. Only the utility advantage of the patient having controlled disease (0.19) was applied in the model. We welcome NICE's review of this as absolute values derived from the care giver burden study were NOT used in the cost-effectiveness model. • On the same page, the Appraisal Consultation Document states *"However, the patient experts indicated that they mostly self-managed the condition"* However, this only applied to the patient's current health state, controlled disease. The other patient indicated, that prior to achieving disease control with mogamulizumab, he was limited in everyday activities.

Company response to the appraisal consultation document: Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

Single Technology Appraisal (STA)

Additional Manufacturer Evidence and Analyses Requested by the Committee (accepted by NICE to submit)

Submitted by Kyowa Kirin

National Institute for Health and Care Excellence

Submitted 19 August 2020

Contents

Executive summary

Kyowa Kirin supports the opportunity to present additional analyses recommended by the NICE's Appraisal Committee in the Appraisal Consultation Document (ACD) to reduce the uncertainty around the comparative efficacy of mogamulizumab and continues to be committed to provide support for the decision-making processes.

Kyowa Kirin trusts in a thorough and fair review of the submitted evidence. We do want to make it clear that this is a rare haematological malignancy which is debilitating and often fatal due to very limited systemic treatment options as the disease progresses. The trial evidence from MAVORIC, the largest phase III randomised clinical trial (n=372) in Cutaneous T-Cell Lymphoma (CTCL), with the first ever inclusion of Sézary syndrome patients, is the most robust clinical evidence to date in this rare disease. Evidence based on assessments across four compartments (skin, blood, viscera and lymph nodes) are extremely rare, with ALCANZA for brentuximab vedotin being the only other study to date to have done so. Additionally, inclusion of real word data from the UK's Hospital Episodes Statistics (HES) database, which represents NHS clinical practice in all hospitals in England over a 10-year period (2009-19) and comprises all current UK NHS patients with this very rare disease.

Mycosis fungoides (MF) and Sézary syndrome (SS) are orphan indications with very limited treatment options for heavily pre-treated patients. Despite these limitations, the MAVORIC trial is the largest randomised study in MF/SS. Due to ethical concerns for the poor prognosis for non-responding patients, crossover was allowed and due to their pre-treatment history, vorinostat was chosen as a comparator. The European Medicines Agency (EMA) approved the MAVORIC study design, population, vorinostat as the comparator based on the reported clinical data for vorinostat in MF and SS.

The resulting, unavoidable uncertainties regarding the choice of comparator were addressed using naïve indirect comparisons between vorinostat and the physician's choice arm of the ALCANZA trial and vorinostat and the bexarotene "clinical trials of 193 patients with CTCL of whom 93 had advanced stage disease refractory to prior systemic therapy,"[1] and analyses that adjusted for treatment switching/crossover in

the vorinostat arm of the MAVORIC trial. The results of the crossover analysis were validated against data from the UK HES database and three published observational studies (one from the UK and two from US).

As an additional analysis, at the recommendation of the Committee, Kyowa Kirin has conducted an unanchored indirect comparison of mogamulizumab directly with data from patients from the UK HES database, including a reweighting of the mogamulizumab arm of the MAVORIC trial to match the current UK clinical practice in the HES dataset. This approach avoids the uncertainties flagged by the Committee. The new analysis provides a direct comparison against current UK clinical practice and the analysed target population reflects the current UK MF/SS population, as the HES data is an administrative dataset that includes all MF/SS patients treated in secondary care in England. Additionally, the new analysis is not confounded by crossover, as no patients in the HES database received mogamulizumab.[1]

The results of the new analyses were included in the economic evaluation. The changes requested by the Evidence Review Group (ERG), and the settings of the preferred base case of the ERG not affected by the HES database, were also implemented. Crossover adjustment was not relevant anymore and the use of allogeneic stem cell transplant (aSCT) after current treatment is now based on the HES data, i.e. current UK clinical practice. The only exception was carer utilities, where an alternative base case was implemented addressing the ERG's concerns. Only the difference in carer burden between the Disease control and Subsequent treatments health state (0.19 or 0.09), i.e. the advantage of having disease control, was included in the model. Additionally, this was only implemented for the additional/incremental time patients spend with disease control with mogamulizumab compared to standard of care. As we have heard at the Committee meeting, and

[1] Kyowa Kirin would also like to point out an update to the previously submitted patient numbers from the HES database. The correct number of advanced patients receiving second line treatment in the HES database is 198 for MF/SS. The previous number submitted (82 and 14 for MF and SS respectively) was the number of patients at risk at the end of the first year, and therefore, an underestimate of actual patients receiving second line treatment.

seen in the study conducted by Kyowa Kirin, the carer burden is significantly less, when the disease is controlled. This provides a conservative implementation of these carer utilities, as absolute carer health state utilities were not included in the model, nor were any effect of the longer life expectancy taken into account for carers. This potentially underestimates the documented disproportionate effect of MF/SS on the carers, that is due to the extensive mutilating impact caused by extensive skin breakdown and the associated extensive skin manifestations.

The analysis based on the HES data resulted in 2.84 discounted incremental quality-adjusted life-years (QALYs) and due to the very high disease management costs for MF/SS and the mostly cheaper generic or short-term comparator treatments, [redacted], £81,955 incremental costs. The incremental cost-effectiveness ratio (ICER) was £28,887 and £29,848 per QALY depending on the carer utilities. These estimates were robust in the sensitivity analyses with mogamulizumab having approximately 60% and almost 100% probability of being cost-effective at the thresholds of £30,000 and £50,000 per QALY respectively.

For the end of life criteria, mogamulizumab results in an extension of life substantially higher than 3 months (5.16 years), while the median life expectancy in the current clinical practice in England is lower than 24 months (17.83 months in the HES data).

While Kyowa Kirin have tried to address all data gaps in MF/SS with new studies, due to the limitations of EQ-5D in assessing quality of life in MF/SS, and the conservative approach used in the implementation of the carer burden, there are potentially additional benefits not taken into account.

Additionally, for NICE we would like to re-emphasise that mogamulizumab was granted Promising Innovative Medicine (PIM) designation from the UK's MHRA in March 2018 for the treatment of advanced refractory MF and SS based on its innovative mode of action compared to established therapies.

Introduction

In the NICE ACD 'Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome' (ID1405) the committee has requested "scenario analyses using HES data to model overall survival in the standard care arm" (page 11, section 3.8). In response to this request Kyowa Kirin has conducted an unanchored matching adjusted indirect comparison of the mogamulizumab arm of the MAVORIC trial with the 10-year survival information for MF and SS available from HES and incorporated the results into the economic evaluation.

This additional analysis addresses the Committee's concerns around

i. Comparator: Provides a direct comparison against current UK clinical practice rather than vorinostat as the HES data is an administrative dataset including all patients treated in England (n=198).
ii. Representativeness: Reflects the current UK MF/SS population as the HES data is an administrative dataset including all patients treated in England
iii. Cross-over adjustment: Does not require any adjustment for treatment switching with its attendant uncertainties as no patients in the HES database received mogamulizumab.

Methods

The analyses included the following steps:

1. Reweighting the MAVORIC trial data to match the UK patient population for second-line, advanced MF/SS
2. Survival analyses of the time-to-event (TTE) outcomes for the reweighted MAVORIC trial and the HES data-based comparator arm (Established Clinical Management ([ECM])
3. Additional changes were implemented in other model inputs based on the HES data and according to ERG recommendations
4. Inclusion of the results in the economic evaluation

The HES data represents patients' experience on treatments currently used in routine clinical practice in the UK, as it includes all patients treated with MF/SS in secondary care in the last 10 years (198 second-line patients).

For detailed description of the dataset please see the extended HES Report[2]. For the description of additional analyses, please see Section 8.4.1, page 44. For the data used in the analyses, please see the following tabs in the Excel document (titled 'CTCL Analysis Cohort A -final version including additional OS analyses from 2nd progression_17Aug2020'): Table 8.4d NEW AUG2020 KM_OS MF, Table 8.4e NEW AUG2020 KM_OS_SD, Figure 8.4a KM curve_2nd prog, Table 8.4f-8.4g.

To match the target population in the UK for mogamulizumab, second-line, advanced MF/SS patients were selected. Although the HES data does not contain information on disease stage, the fact that by definition these patients were treated in hospitals, and the types of systemic treatments they have received (described in Table 4.10 and Appendix 2 of the HES Report[2]) indicate that the MF patients included in the analyses were advanced patients. All SS patients are by definition advanced. For MF patients, of the therapy codes used to identify significant treatment changes during the analysis, only one of the radiotherapy options (external beam radiotherapy) could potentially be used for patients with earlier stage disease. However, only a very small proportion (2%) on patients received any type of radiotherapy, therefore, patients in the HES data can be considered to be advanced in their disease. This was the same cohort of patients, for whom the health state costs were estimated in the original analyses.

Table 1 presents a comparison of the patient characteristics between the MAVORIC trial and the HES data available in both data sets. Mean age and gender distribution were very similar between the two data sources, therefore the matching was performed only on the proportion of MF and SS patients. The MAVORIC trial was reweighted to represent the distribution of MF and SS patients as observed in the HES data, therefore in UK clinical practice.

Table 1: Comparison of the MAVORIC population and HES population

	MAVORIC trial	HES data
% MF	53%	85%
% SS	47%	15%
Age (mean)	63	65
Males	58%	62%
Females	42%	38%

Key: HES: Hospital Episode Statistics, MF: mycosis fungoides, SS: Sezary syndrome

In the revised analyses, the overall survival (OS) parameters and the proportion of aSCT after current treatment for the comparator arm were estimated from the HES data, while OS for the mogamulizumab arm, next-treatment-free survival (NTFS), and time on (randomised) treatment (ToT), for the scenario analyses progression-free survival (PFS) were estimated from the reweighted MAVORIC trial.

Table 2 provides a comparison between the data sources of the originally submitted analyses and the current additional analyses based on the HES data for the above-listed outcomes.

Table 2. Summary of clinical parameters applied in the economic model in the base case

Variable	Treatment	Data source in original submission	Data source in current additional analysis
Overall survival (OS)	Mogamulizumab	MAVORIC trial post-hoc analyses excluding patients with aSCT	Re-weighted MAVORIC trial post-hoc analyses
	ECM	MAVORIC trial post-hoc analyses for vorinostat adjusted for crossover, excluding patients with aSCT	HES data
	aSCT	NICE TA577 using real-world data from the London supra-regional centre	No change
Next-treatment-free survival (NTFS)	Mogamulizumab	MAVORIC trial post-hoc analyses	Re-weighted MAVORIC trial post-hoc analyses
	ECM	MAVORIC trial post-hoc analyses for vorinostat	Re-weighted MAVORIC trial post-hoc analyses for vorinostat

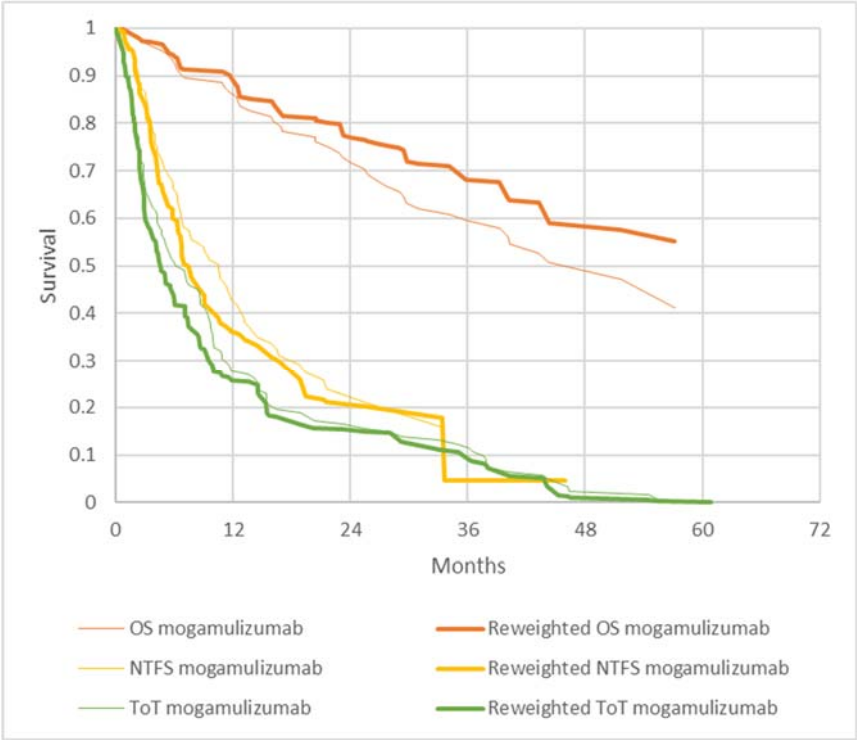
Variable	Treatment	Data source in original submission	Data source in current additional analysis
Time on treatment (ToT)	Mogamulizumab	MAVORIC trial post-hoc analyses	Re-weighted MAVORIC trial post-hoc analyses
	ECM	MAVORIC trial post-hoc analyses for vorinostat	Re-weighted MAVORIC trial post-hoc analyses for vorinostat
Disease-free survival (DFS)	aSCT	NICE TA577 using real-world data from the London supra-regional centre	No change
Dose intensity	Mogamulizumab	MAVORIC trial CSR	No change
	ECM	Assumed same as for mogamulizumab	No change
Adverse events (AEs)	Mogamulizumab	MAVORIC trial CSR	No change
	ECM	MAVORIC trial CSR, assumed same as for vorinostat	No change
Proportion receiving aSCT after current treatment	Mogamulizumab	Clinician survey	No change
	ECM	Clinician survey	HES data

Revised inputs

Reweighting of the MAVORIC trial data

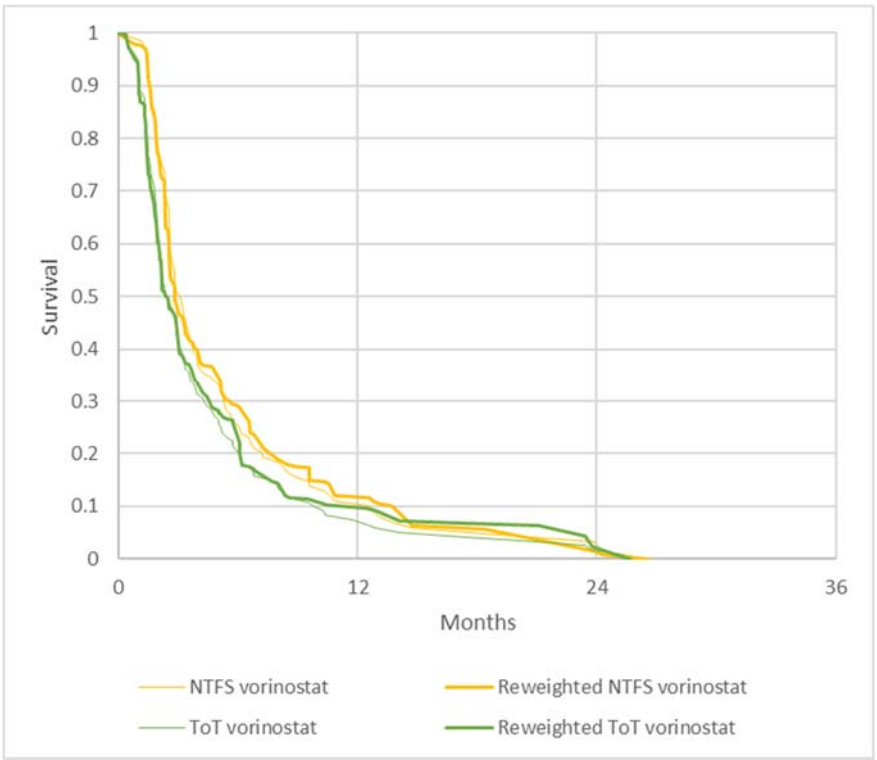
As expected based on the original analyses results of the MAVORIC trial, increasing the weight of MF patients slightly lowered ToT and NTFS, and slightly increased OS in the mogamulizumab arm, while the re-weighting had a very limited impact on the ToT and NTFS outcomes of the vorinostat arm (Figure 1, Figure 2).

Figure 1 Impact of reweighting according to HES MF/SS proportions on MAVORIC trial mogamulizumab arm



Please note, that the drop at the end of reweighted NTFS mogamulizumab curve is based on very few patients and events

Figure 2 Impact of reweighting according to HES MF/SS proportions on MAVORIC trial vorinostat arm



Survival analyses

In line with the original submission as well as guidance from NICE DSU 14[3], six alternative parametric model structures were used to capture and extrapolate data for each TTE outcome of interest: exponential, generalised gamma, Gompertz, Weibull, log-logistic, log-normal. TTE analyses were conducted in R: Kaplan-Meier (KM) plots were produced using 'survminer' package. The package "flexsurv" was used for parametric survival analysis. Based on the original analyses separate models were fitted to all TTE outcomes.

Selection of the base case parametric model for each TTE outcome was based on standard criteria, following Technical Support Document (TSD) 14:

- Objective statistical measures of goodness of fit to observed KM data: Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics
- Visual inspection of goodness of fit to observed KM data
- Visual inspection of diagnostic plots, including log cumulative hazard plots, Schoenfeld residuals plot and quantile- quantile plot

Additionally, the clinical plausibility of extrapolations beyond observed KM data was explored.

Overall survival for mogamulizumab

Figure 3 presents the re-weighted unadjusted KM curves by randomised treatment arm. The median survival was not reached in the mogamulizumab arm. Note that the vorinostat information was not used for this analysis.

Figure 3: Re-weighted MAVORIC OS Kaplan-Meier data, advanced population

Key: KW-0761, mogamulizumab; OS, overall survival;
Note: Patients were censored upon receiving aSCT.

Diagnostic plots for these data are included in Appendix A. When considering the statistical fits (Table 3), the exponential provides the best fit to the re-weighted mogamulizumab OS.

Table 3: AIC and BIC statistics - Advanced disease OS

Model	AIC M	BIC M
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Key: AIC: Akaike Information Criterion, BICE: Bayesian Information Criterion

Parametric survival models shown alongside observed data are provided in Figure 4. The statistically best fitting exponential curve provided a good fit visually and also the middle-ground in terms of proportions of patients predicted to be alive in the long-term also among all the tested extrapolations. Therefore, it was chosen to be the base case.

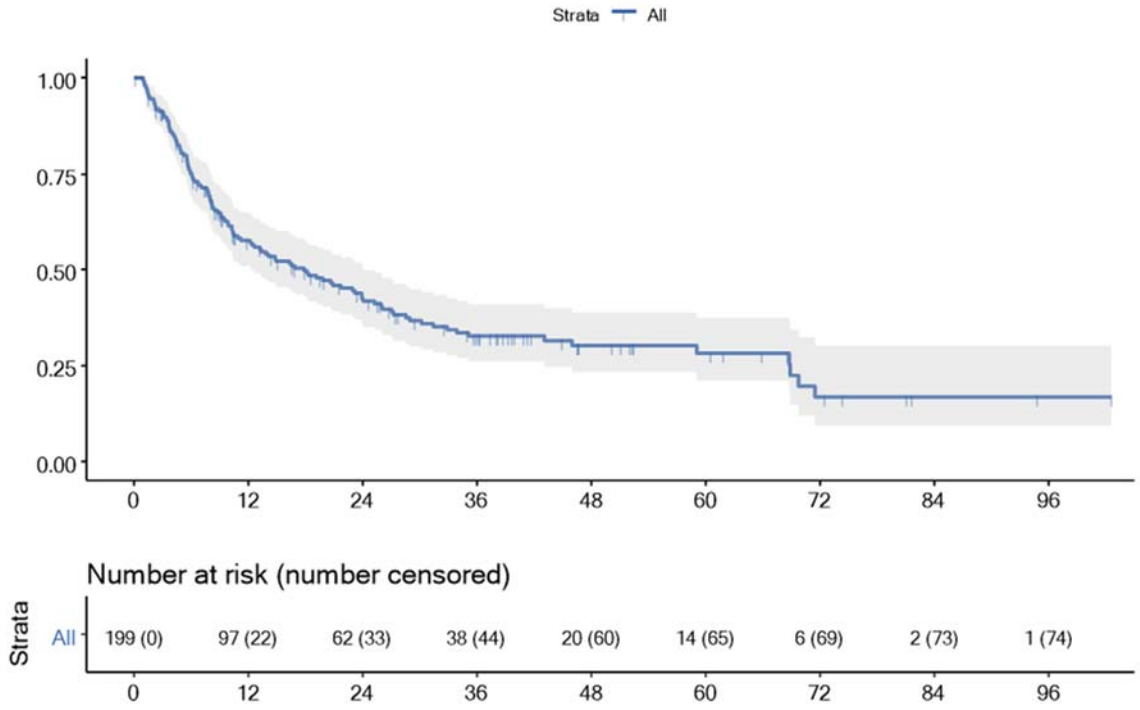
Figure 4: Re-weighted MAVORIC OS, advanced population

Key: OS, overall survival.

Overall survival for ECM arm based on HES data

The OS from the HES data is shown in Figure 5. Patient numbers halve by end of the first year and fall below 40 by the end of year 3. Median survival was 17.83 months.

Figure 5 HES data on OS of UK patients



Diagnostic plots for this data are included in Appendix A. Based on statistical fits (Table 4), the generalised gamma provides the best fit to the HES OS data.

Table 4: AIC and BIC statistics – HES OS

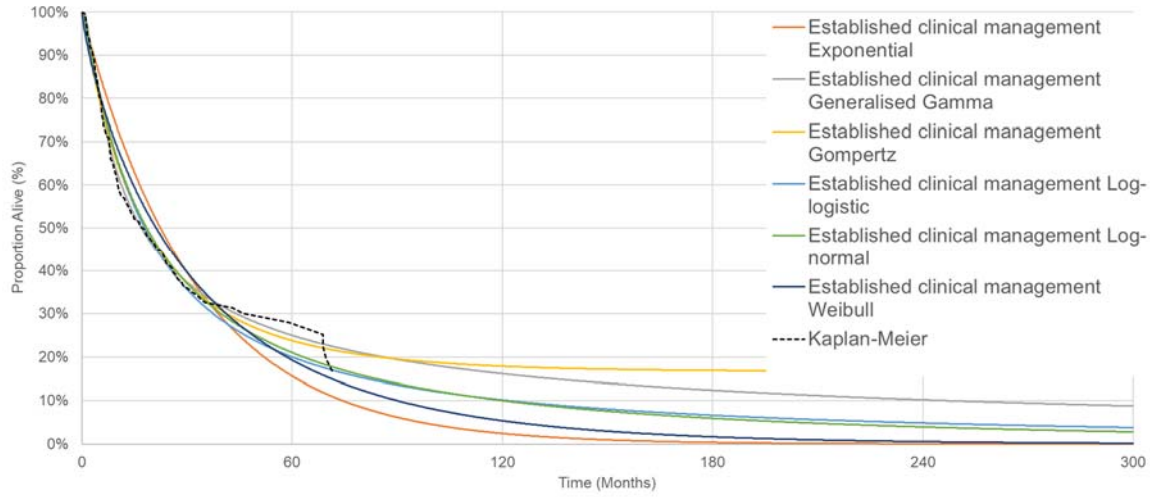
Model	AIC M	BIC M
Exponential	1112.00	1115.30
Generalised Gamma	1079.00	1088.90
Gompertz	1093.30	1099.90
Log-logistic	1090.30	1096.90
Log-normal	1084.00	1090.60
Weibull	1106.70	1113.30

Key: AIC: Akaike Information Criterion, BICE: Bayesian Information Criterion

Parametric survival models shown alongside observed data are provided in Figure 6. Although the generalised gamma curve provided the best statistical fit to the data, it predicts a plateau in survival, with 25%, 16% and 10% of patients predicted to be alive at 5, 10, and 20 years, respectively. As was seen in the original Manufacturer submission (section B.3.3.1) it is not clinically reasonable to expect such high proportion of long-term survivors given the nature of the disease and the lack of

long-term response seen with the treatments currently available. Furthermore, when comparing with extrapolations of the re-weighted mogamulizumab data from the MAVORIC trial (see Figure 7), OS curves cross and many of the HES data extrapolations predict better survival than for those who received mogamulizumab in the long-term. This is also clinically not reasonable or credible. Therefore, in line with the previously submitted analyses as well as the ERG's recommended base case and the survival curve form selected for the mogamulizumab arm, the exponential curve was selected as the base case to model OS in the ECM arm.

Figure 6: HES OS extrapolations



Key: OS, overall survival.

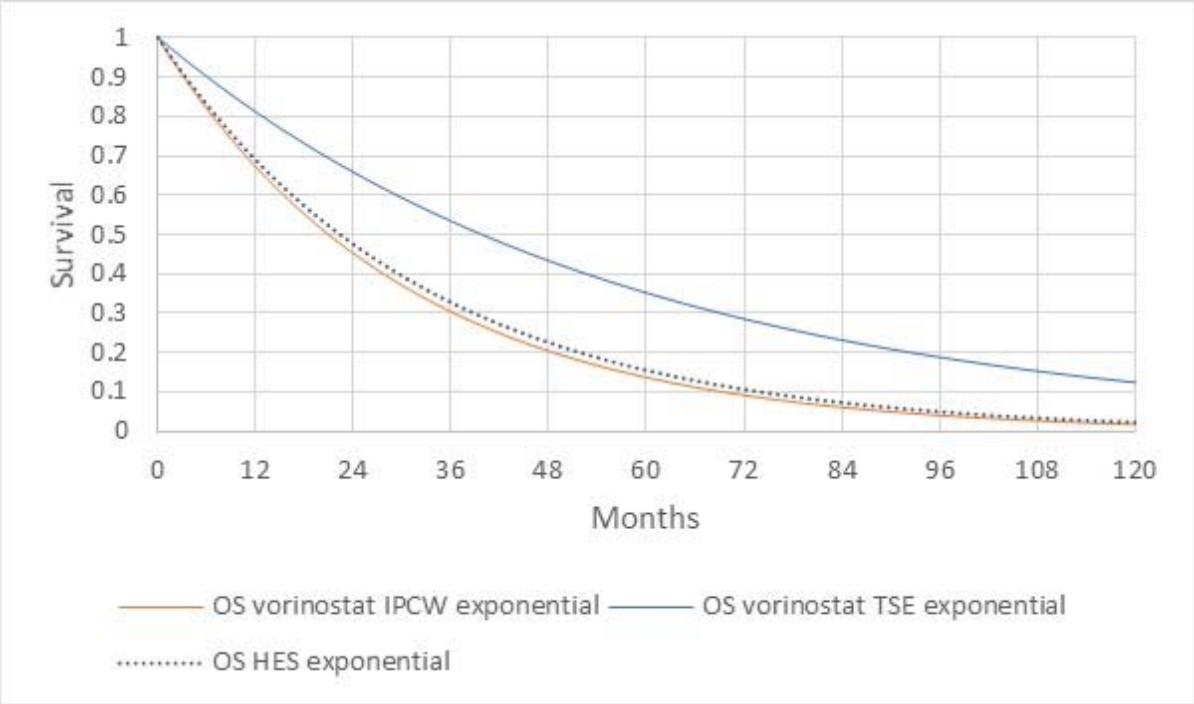
Figure 7 Comparison of OS extrapolations between re-weighted MAVORIC mogamulizumab arm and HES data

[redacted]

Key: ECM, established clinical management; OS, overall survival.

In the originally submitted analyses, the raw HES data was used to aid the selection between crossover adjustment methods for the vorinostat arm. As shown in Figure 8, the new, more detailed analysis of the HES data provides further support for the originally submitted analyses which reasoned that the inverse probability of censoring weighting (IPCW) crossover adjustment method is a better reflection of what OS would look like for patients not receiving mogamulizumab in the UK.

Figure 8 Comparison of HES data exponential extrapolation with the OS predictions of the previous analyses' two crossover adjustment methods



Key: HES, Hospital Episode Statistics; IPCW, inverse probability of censoring weights; OS, overall survival; TSE, two-stage estimation.

Next-treatment-free survival

Figure 9 presents the KM curve of NTFS by randomised treatment arm.

Figure 9: Re-weighted MAVORIC NTFS KM data, advanced population

Diagnostic plots for these data are included in Appendix A. Table 5 shows AIC and BIC statistics for the model fits. NTFS data is almost complete; therefore, all fits were close to one another. For the vorinostat arm generalised gamma models provide the best statistical fit according to AIC/BIC statistics, while for the mogamulizumab arm, the log-normal model provides the best fit. There is no clinical reason for choosing a different type of model between the treatment arms, therefore for consistency between the treatment arms as well as consistency with PFS extrapolations in the scenario analyses (where the generalised gamma was the best statistical fit for both mogamulizumab and vorinostat, see Appendix A), the generalised gamma function was selected as the base case.

Table 5: AIC and BIC statistics for PSM fits to advanced disease NTFS KM data

Model	AIC V	AIC M	cAIC	BIC V	BIC M	cBIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval, HR, hazard ratio; NTFS, next-treatment-free survival.

Parametric survival models shown alongside KM data are provided in Figure 10.

Figure 10: Reweighted MAVORIC NTFS, advanced population

Please note, that the drop at the end of reweighted NTFS mogamulizumab Kaplan-Meier curve is based on very few patients and events

Changes in other model inputs based on the HES data and according to ERG recommendations

Patient access scheme (PAS)

[redacted].

Time on treatment

Time on treatment was estimated from the MAVORIC trial for both treatment arms, thus this was also revised based on the reweighted data. Since time on treatment curves are complete, similarly to the originally submitted analyses, these were used directly in the economic model. Figure 11 presents the resulting KM curves from the re-weighted analysis.

Figure 11 Re-weighted MAVORIC ToT data, advanced population.

Proportion of patients receiving aSCT

The HES data also provided information on the proportion of patients receiving aSCT after different lines of treatment (data originally submitted during the Stakeholder Consultation phase). In the UK clinical practice 5.2% of patients went on to receive aSCT after second line treatment in the HES data, therefore to represent current UK clinical practice this proportion was used in the updated analysis as opposed to the 4.6% which was used in the original submission based on the clinician survey.

While there is the possibility of double counting the survival benefit of patients receiving aSCT in both treatment arm, by not excluding or censoring them, this benefits the ECM arm to a larger extent, as patients in the mogamulizumab arm were only allowed to receive aSCT after subsequent treatment and these patients with the exception of one were all censored for survival. Thus, the analyses are representative of the current UK clinical practice. The use of aSCT after current treatment is also supported by the clinicians' survey for current clinical practice (mean: 4.6%).

While there were concerns around the use of aSCT after mogamulizumab based on an aggressive adult T-cell leukemia/lymphoma study in Japan, these were mitigated by using the washout period[4]. The Summary of Product Characteristics (SmPC) states: "Complications, including severe graft versus host disease (GVHD), have been reported in patients with T-cell lymphomas **other than MF or SS who received allogeneic HSCT after mogamulizumab. A higher risk of transplant**

complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT."[4].

All three UK clinicians interviewed, with experience with mogamulizumab in MF/SS, agreed that aSCT will be used after the washout period as per the European Medicines Agency's SmPC[4] for a limited number of eligible patients (mean: 8.0%, range 4%-10%).

In the MAVORIC trial patients were treated to progression. Responding patients did not interrupt treatment in order to receive an aSCT. Upon progression they switched to further treatments during which some patients received aSCT. In real life practice, a proportion of patients receiving mogamulizumab would interrupt treatment in order to receive aSCT. This was captured in the model as aSCT during current treatment and we believe this reduces the bias in the estimates of cost-effectiveness as it represents anticipated clinical practice. Similar adjustments were made in the modelling of brentuximab vedotin in TA577 in order to reflect differences between actual clinical practice and practice during the trial[5].

Additionally, aSCT use was also seen among patients who switched from vorinostat to mogamulizumab (6.6%), and around the same time from randomization as for those randomised to mogamulizumab (80 weeks vs. 81 weeks from randomisation for those who switched and those who started on mogamulizumab respectively). This suggests, that once not bound by the trial protocol to have to wait for progression, patient receive aSCT after mogamulizumab earlier.

In summary, **including aSCT after current treatment is both representative of UK NHS clinical practice and considers the clinical governance advice given in the Summary of Product Characteristics for mogamulizumab**, which is a regulatory document that is approved by the European Medicines Agency.

Composition of treatments in ECM

The original submission included a basket of treatments in the ECM arm, based on information received during the clinician surveys. This assumption was later revised based on NHS England recommendations to include only bexarotene as a comparator and to use a longer treatment length as opposed to the ToT observed for

vorinostat. The Committee questioned this revised approach, therefore this additional analysis reverted back to the ERG preferred original submission assumption of using the ToT observed for vorinostat and the basket of treatments.

As described by the ACD, during the first committee meeting “a clinical expert explained that triple therapy with bexarotene, ECP and interferon is used in clinical practice”. Thus, a scenario analysis was performed using this triple therapy assumption.

Patient utilities

The Committee has requested “if it was possible to map utility for patients from more sensitive instruments to EQ-5D”. Kyowa Kirin has explored two options:

- Developing a new mapping algorithm: Kyowa Kirin does not have access to any alternative trial’s patient level data, that would include both EQ-5D and one of the range of other quality of life assessments included in the MAVORIC trial (Skindex-29, Functional Assessment of Cancer Therapy-General [FACT-G], pruritus evaluation (Likert scale), and ItchyQoL) to develop a mapping algorithm, which can then be used for the MAVORIC trial. Thus, this option was not feasible. Performing the mapping on the MAVORIC trial would results in the same EQ-5D utilities already submitted.
- Using a published algorithm: Longworth et al. have developed a mapping algorithm for estimating EQ-5D values from the FACT-G questionnaire[6]. This algorithm would provide alternative utility values; however, these mapped values would not provide more reliable information compared to those that have been directly elicited with EQ-5D. The additional instruments used in the MAVORIC trial also stopped collecting quality of life information at treatment discontinuation, similarly to the EQ-5D questionnaire. Additionally, the mapping algorithm was not developed for MF/SS patients, thus would add additional uncertainty.

As a result, no additional mapping was conducted.

Carer utilities

The NICE Reference case states that ""all direct health effects, whether for patients, or when relevant, carers" should be considered[7]. While this is not common, a recent review found 12 technology appraisals (TAs) and four Highly Specialised Technologies in eight indications where carer QALYs have been included in the cost-effectiveness analyses[8]. While the approaches varied, in most appraisals where the carer utilities were quantitatively included, the Committee felt that they should be included in the decision making. In the previous NICE TA in MF/SS (TA577)[5], the Committee and the ERG agreed, that in addition to the impact on patients, the disease has an important impact on carers also, however there was no quantitative analyses provided. Kyowa Kirin aimed to address this data gap by conducting a vignette study and estimating EQ-5D carer utilities.

Care giver burden is extremely important to capture in this disease. The patient advocacy and clinical community do support this[2]. Advanced MF/SS, whilst a fatal and debilitating rare haematological malignancy, does also include extensive mutilating impact caused by widespread skin breakdown and the associated extensive skin manifestations of the disease that do severely impact quality life. This visual nature of devastating breakages of the skin and associated unbearable pain and discomfort in the largest organ of the body, from head to toe, does significantly impact the family and carer context for CTCL patients as their diseases progresses. These profound skin manifestations of a blood cancer is very much a unique perspective in oncology that Kyowa Kirin and the clinical and patient advocacy community in this rare disease supported further research on[9].

While there are discussions about the correct implementation of carer utilities, Kyowa Kirin has used a conservative approach that avoided the pitfalls listed by ERG. The model did not include the health state carer utilities, it only accounted for the carer benefit of the longer disease control. Thus, only the difference between the utilities for the Disease control and the Subsequent treatment health state utilities

[2] https://lymphoma-action.org.uk/nice-consultation-mogamulizumab-skin-lymphoma

(0.193) was applied in the model for the additional stay in the Disease control health state, thereby potentially underestimating the effect of carer burden.

However, given the fact that there are no clear guidelines on how caregiver utilities should be implemented, a number of additional analyses have also been undertaken:

- The Committee considered that the utility gain for carers between the 'Disease control' and the 'Subsequent treatments' health state was "implausibly large compared with the expected utility gain for patients". The Committee also requested "more details of the difference in health-related quality of life of patients [and carers] in the disease control health state and the subsequent treatment health state", and the use of alternative utility values in the model. While a utility study eliciting values directly from the carers would be the gold standard, given the rarity of the disease this was not feasible. However, the vignettes were developed from qualitative research with patients and caregivers and were fully validated by CTCL clinical specialists. In qualitative studies, carer burden for people supporting patients with MF or SS has been shown to be substantial[4–6]. There is a possibility of some responders valuing both the burden of caring and the burden of the disease. This means the carer carries their own burden and possibly further burden of the patient they care for. However, we do want to address the Committee concerns and explore the consequences of this concern an alternative base case is presented that assumes that the difference between carers' utilities for the 'Disease control' and 'Subsequent treatments' health state is the same as the difference observed for the patients in the trial (i.e., the incremental utility gain of keeping patients in the 'Disease control' health state longer was reduced to 0.091);
- The Committee also asked, "if more plausible carer utility values were available from the literature". To explore this, a systematic literature review has been conducted in Embase, Econlit, Medline, NHS EED and the Health Technology Assessment Database (HTAD) for both patient and carer utilities in adult patients with any-stage R/R CTCL. Due to the orphan nature of the disease and the limited evidence available for the comparators, only three

studies were identified, none of which included utility values for carers. (Please see Appendix H of the Manufacturer submission for more details.) This echoes the finding of the NICE TA577[5] previously.

- The Committee also questioned if it was "appropriate to include carer utility values for disease control (0.56) and subsequent treatment (0.37) that were lower than for patients having mogamulizumab". As described above, carer utilities were not implemented this way neither in the original submission, nor in this current analysis, as only the incremental gain between the two health states was used, therefore only captured the incremental gain of keeping patients in the 'Disease control' health state longer. However, to demonstrate that the original implementation is a conservative assumption, a scenario analysis is presented here which directly applies the above quoted carer utilities for both of the health states.
- A scenario is also presented which excludes carer utilities

Other changes compared to the original submission based on the ERG's recommendations

The ERG has identified a number of issues and made recommendations for the base case. In the current analyses, Kyowa Kirin has implemented all recommendations relevant for the current analyses in the base case, or revised them according to the new evidence and implemented additional scenarios for the carer utilities.

Table 6 Issues and recommendations by the ERG and subsequent changes in the current analyses

Issue	ERG recommendation	Implemented?	Change in current analyses
Linking mistake in monitoring and subsequent treatments after aSCT	Fix mistake	Yes	Mistake fixed
Washout period extended to all costs	Correct implementation of washout period	Yes	Corrected: patients now accrue all additional costs except for treatment and administration costs
PFS utility scenario analyses	Fix mistake	Not relevant	Not used in current analyses
24-month stopping rule	There should be no stopping rule	Yes	No stopping rule implemented

Issue	ERG recommendation	Implemented?	Change in current analyses
Time horizon	Extend time horizon to 45 years	Yes	Time horizon extended to 45 years
aSCT after current treatment	No aSCT after current treatment	No	The HES data shows that aSCT is routinely performed in each line of treatment, therefore, to represent current clinical practice, the ECM arm was modelled according to the HES data
OS crossover adjustment	Preferred TSE over IPCW	Not relevant	No crossover adjustment required in current analyses
OS extrapolation	Preferred exponential / exponential for mogamulizumab / ECM arm	Yes	Exponential / exponential for mogamulizumab / ECM used as base case for new analyses
NTFS extrapolation	Preferred log-normal	Yes / Not relevant	Generalised gamma / generalised gamma for mogamulizumab / ECM used as base case for new analyses (see justification above), but log-normal is presented as a scenario
DFS for aSCT extrapolation	Preferred log-normal	Yes	Log-normal used as base case in current analyses
Carer utilities	Preferred to exclude caregiver utilities	Yes/No	Base case includes caregiver utilities, but an alternative base care is also presented which reduces caregiver utilities
Increase in utilities while on treatment	Preferred overall mean utilities for entire health state over cycle-specific utilities	Yes	Overall mean utilities used for health state

Cost-effectiveness results Base-case incremental cost-effectiveness analysis results

In the base case (including carer utilities), mogamulizumab results in a discounted incremental LYs of 3.71, with the highest proportion of gain in the Subsequent treatment health state (Table 7). This led to a discounted QALY gain of 2.84 (Key:

aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.

Table 8).

Table 7: Discounted disaggregated life -years (LYs) including carer utilities

	Mogamulizumab	Established clinical management	Increment	% increment
Disease control - Current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
Total	**6.59**	**2.87**	**3.71**	**100%**

Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.

Table 8. Discounted disaggregated quality-adjusted life-years (QALYs) including carer utilities

	Mogamulizumab	Established clinical management	Increment	% increment
Disease control - Current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
Total	**4.75**	**1.92**	**2.84**	**100%**

Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.

Including the [redacted], the discounted incremental costs were £81,955 driven by the drug costs [redacted] and the disease monitoring costs [redacted] (Table 9). The high incremental disease management costs are due to the high cost of MF/SS in the community setting due to the intense schedule of dressings and other wound care, while the incremental drug costs are driven by the mostly cheaper generic treatments or short-term interventions.

Table 9. Discounted disaggregated costs [redacted] and carer utilities

	Mogamulizumab	Established clinical management	Increment	% increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - Subsequent treatments	[redacted]	[redacted]	[redacted]	[redacted]
ESC costs – Progressed	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs - non aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]
aSCT costs and monitoring DF	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs - aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring aSCT – Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
ESC costs – aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	**£81,955**	**100%**

Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.

This, with the [redacted], resulted in an incremental cost-effectiveness ratio (ICER) of £28,887/QALY (Table 10).

Table 10: Base-case results (discounted) [redacted] and carer utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Established clinical management	[redacted]	2.87	1.92				
Mogamulizumab	[redacted]	6.59	4.75	£81,955	3.71	2.84	£28,887

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Alternative base-case incremental cost-effectiveness analysis results

In the alternative base case, where difference between the carer utilities for the 'Disease control' and 'Subsequent treatments' health state is assumed to be the same as the difference between patient utilities, LY results are unaffected, therefore mogamulizumab still results in a discounted incremental LYs of 3.71. The reduction in the difference between carer utilities across health states led to a discounted QALY gain of 2.75 (Table 11).

Table 11. Discounted disaggregated quality-adjusted life-years (QALYs) excluding carer utilities

	Mogamulizumab	Established clinical management	Increment	% increment
Disease control - Current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
Total	**4.66**	**1.92**	**2.75**	**100%**

Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.

Incremental costs were also unaffected by the reduction in the difference between carer utilities across health states. This scenario resulted in an incremental cost-effectiveness ratio (ICER) of £29,848/QALY [redacted] (Table 12).

Table 12: Base-case results (discounted) [redacted], excluding carer utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Established clinical management	[redacted]	2.87	1.92				
Mogamulizumab	[redacted]	6.59	4.66	£81,955	3.71	2.75	£29,848

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Sensitivity analyses

Similarly, to the original Manufacturer submission, parameter uncertainty was assessed in the univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis (PSA). Structural uncertainty was explored in a series of scenario analyses, including assumptions around the structural form of OS and NTFS, the sources used to inform parameters and assumptions regarding the underlying calculations.

Probabilistic sensitivity analysis

The probabilistic results for the base case are presented in Table 13 and are similar to the deterministic results. The results are presented on the cost-effectiveness plane in Figure 12. The probability of mogamulizumab being cost-effective at the £30,000/QALY threshold is 58.6%, while at the £50,000/QALY threshold 98.8%.

Table 13: Comparison of the probabilistic and deterministic results

[redacted]

	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALYs)	ICER (£/LYs)
Deterministic results	81,955	2.84	3.71	28,887	22,068
Probabilistic results	81,298	2.84	3.72	28,603	21,874

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 12: Cost-effectiveness plane [redacted]

Figure 13: Cost-effectiveness acceptability curves (CEACs) [redacted]

Deterministic sensitivity analysis

The tornado diagram showed that the results are most sensitive to survival extrapolations, the utility for the 'Subsequent treatment' health state, and the disease management / monitoring costs for the 'End-stage care' health state (Figure 14).

Figure 14: Tornado diagram [redacted]

Scenario analysis

Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties. These included assumptions around:

- Discount rate;
- Extrapolations;
- Rates of aSCT;
- Utilities and
- Composition of the comparator arm

The results are presented in Table 14. The results were stable. Twenty-five scenarios resulted in ICER below £30,000/QALY. Only two scenarios resulted in ICERs above £35,000:

- Extrapolating OS in both arms with Gompertz distribution with both base case scenarios, which suggested very optimistic survival predictions for ECM, that lacked clinical validity and suggested a potential plateau that is not seen in clinical practice or the literature for ECM.

End of life criteria using the HES database

- Treatment is indicated for patients with a short life expectancy, normally less than 24 months:
    - The median life expectancy of the UK current clinical practice in the HES database is 17.83 months
    - The mean extrapolated discounted and undiscounted life-years in the ECM arm of the cost-effectiveness model is 2.87 and 3.31 years respectively
- There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment
    - The mean additional discounted and undiscounted months from the cost-effectiveness model compared to current NHS treatments are 44.6 and 61.9 months.

Table 14: Deterministic scenario analysis

Parameter	Base case	Scenario analysis	Justification	Technology	Total costs	Total QALYs	ICER	Total costs	Total QALYs	ICER
					Including carer utilities			Carer utility difference = patient utility difference		
Base case				**ECM**	[redacted]	**1.92**		[redacted]	**1.92**	
				Mogam	[redacted]	**4.75**	**£28,887**	[redacted]	**4.66**	**£29,848**
Annual discount rate (costs and health outputs)	3.5%	6%	Testing model result sensitivity to time-preference discount rate assumptions	ECM	[redacted]	1.76		[redacted]	1.76	
				Mogam	[redacted]	4.13	£30,905	[redacted]	4.03	£32,258
Discount rate (costs and health outputs)	3.5%	0%		ECM	[redacted]	2.22		[redacted]	2.22	
				Mogam	[redacted]	6.06	£26,072	[redacted]	5.99	£26,583
Per mg costing (vial sharing) for mogamulizumab	Dose banding: £2,002 per administration	£1,902 per administration	Centres seeing more patients may be able to share vials	ECM	[redacted]	1.92		[redacted]	1.92	
				Mogam	[redacted]	4.75	£28,067	[redacted]	4.66	£29,000
No aSCT after current treatment	HES data 3rd line for ECM: 5.2% Clinician survey for Moga 8.0%	0% for both arms	Corresponds to MAVORIC trial protocol	ECM	[redacted]	1.69		[redacted]	1.69	
				Mogam	[redacted]	4.63	£31,353	[redacted]	4.53	£32,447
Use of exponential for NTFS	Generalised gamma	Exponential	Testing alternative functional forms for extrapolation	ECM	[redacted]	1.91		[redacted]	1.91	
				Mogam	[redacted]	4.66	£29,615	[redacted]	4.60	£30,276
Use of Weibull for NTFS		Weibull		ECM	[redacted]	1.91		[redacted]	1.91	
				Mogam	[redacted]	4.65	£29,445	[redacted]	4.60	£30,086
Use of lognormal for NTFS		Lognormal		ECM	[redacted]	1.91		[redacted]	1.91	
				Mogam	[redacted]	4.69	£29,536	[redacted]	4.62	£30,319
Use of loglogistic for NTFS		Loglogistic		ECM	[redacted]	1.91		[redacted]	1.91	
				Mogam	[redacted]	4.71	£29,221	[redacted]	4.63	£30,069
Use of Gompertz for NTFS		Gompertz		ECM	[redacted]	1.91		[redacted]	1.91	
				Mogam	[redacted]	4.72	£29,253	[redacted]	4.64	£30,120

Parameter	Base case	Scenario analysis	Justification	Technology	Total costs	Total QALYs	ICER	Total costs	Total QALYs	ICER
					Including carer utilities			Carer utility difference = patient utility difference		
Use of Weibull for OS for both arms	Exponential	Weibull		ECM	[redacted]	2.06		[redacted]	2.06	
				Mogam	[redacted]	4.53	£31,615	[redacted]	4.44	£32,822
Use of lognormal for OS for both arms		Lognormal		ECM	[redacted]	2.35		[redacted]	2.35	
				Mogam	[redacted]	5.50	£27,765	[redacted]	5.41	£28,589
Use of loglogistic for OS for both arms		Loglogistic		ECM	[redacted]	2.35		[redacted]	2.35	
				Mogam	[redacted]	5.23	£29,104	[redacted]	5.14	£30,052
Use of generalised gamma for OS for both arms		Generalised gamma		ECM	[redacted]	2.84		[redacted]	2.84	
				Mogam	[redacted]	5.45	£30,607	[redacted]	5.36	£31,708
Use of Gompertz for OS for both arms		Gompertz	Clinically not justifiable, results in plateau for ECM	ECM	[redacted]	2.99		[redacted]	2.99	
				Mogam	[redacted]	4.70	£39,519	[redacted]	4.61	£41,747
Use of Gompertz for DFS after aSCT	Lognormal	Gompertz	Gompertz was used for the same data in TA577	ECM	[redacted]	1.91		[redacted]	1.91	
				Mogam	[redacted]	4.75	£28,321	[redacted]	4.66	£29,264
Use of cycle-specific utilities for first 12 cycles	Average utility throughout disease control health state	Cycle-specific utilities for first 12 cycles	Shows variability of treatment impact over time	ECM	[redacted]	1.90		[redacted]	1.90	
				Mogam	[redacted]	4.74	£28,874	[redacted]	4.64	£29,834
Exclude carer utilities	Include carer utilities	Exclude carer utilities	Magnitude of carer utilities is uncertain	ECM	[redacted]	1.92		Same as main base case		
				Mogam	[redacted]	4.66	£29,848			
Carer utilities applied to health states	Only additional gain of 'Disease control' over	Carer utilities applied to both health states	Best practice for implementation of carer utilities in unclear	ECM	[redacted]	2.87		[redacted]	3.06	
				Mogam	[redacted]	6.84	£20,680	[redacted]	7.24	£19,581

Parameter	Base case	Scenario analysis	Justification	Technology	Total costs	Total QALYs	ICER	Total costs	Total QALYs	ICER
					Including carer utilities			Carer utility difference = patient utility difference		
	'Subsequent treatments'									
Comparator costs: triple therapy	Cost of mixed basket of comparators (see **Error! Reference source not found.**); ToT re-weighted vorinostat arms from MAVORIC	Cost of triple therapy of bexarotene, ECP, interferon; ToT re-weighted MAVORIC	NICE committee request	ECM	[redacted]	1.92		[redacted]	1.92	
				Mogam	[redacted]	4.75	£24,144	[redacted]	4.66	£24,947
Comparator costs: ALCANZA physicians choice		Bexarotene: 59.4% Methotrexate: 40.6% ToT: median 3.25 months	ALCANZA trial comparator	ECM	[redacted]	1.92		[redacted]	1.92	
				Mogam	[redacted]	4.75	£28,278	[redacted]	4.66	£29,221

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3. Latimer NR. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials—Extrapolation with Patient-Level Data: Inconsistencies, Limitations, and a Practical Guide. *Medical Decision Making*. 2013;33(6):743-754. doi:10.1177/0272989X12472398

4. European Medicines Agency (EMA). Poteligeo (mogamulizumab): EPAR - Product Information. Published online January 10, 2020. Accessed August 18, 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/poteligeo

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9. Williams K, Gibson A, McNamara L, Jones T, Lloyd A. Health state utilities associated with caring for an individual with cutaneous T-cell lymphoma (CTCL). Published online July 9, 2020.

Appendix: Time to event data extrapolation - Additional information

Figure 15 Diagnostic plots for re-weighted MAVORIC trial OS

[redacted]

Figure 16 Diagnostic plots for HES data OS

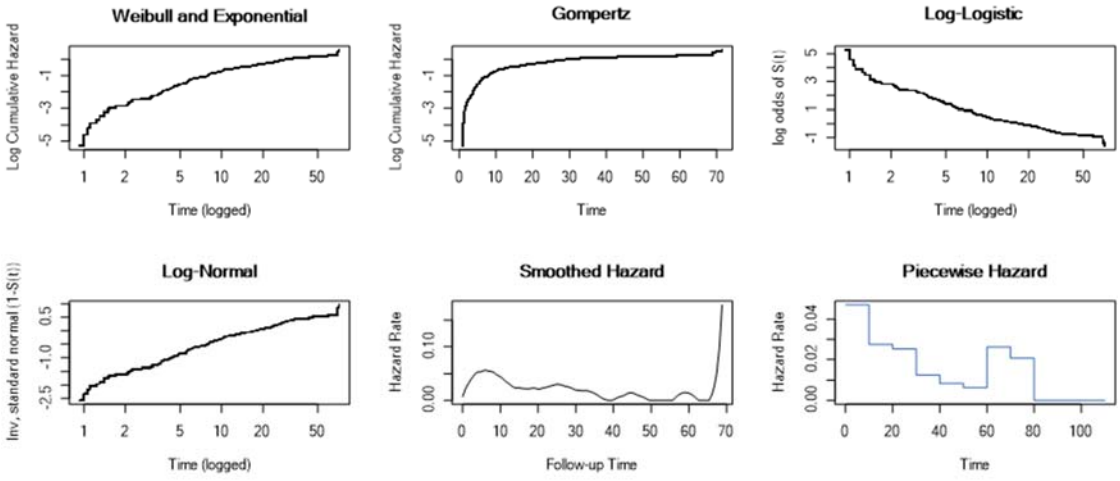

Figure 17 Diagnostic plots for re-weighted MAVORIC trial NTFS

Figure 18 Re-weighted MAVORIC KM plot for PFS

Figure 19 Diagnostic plots for re-weighted MAVORIC trial PFS

Table 15 AIC/BIC values for re-weighted MAVORIC PFS

Model	AIC			BIC		
	Vorinostat	KW-0761	Joint	Vorinostat	KW-0761	Joint
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 20 Re-weighted MAVORIC PFS extrapolations

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Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lymphoma Action
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the rarity of mycosis fungoides (MF) and Sezary syndrome (SS) has not been given sufficient consideration. It is unreasonable to demand the same standards of trial evidence in rare subtypes of cancers as in more common cancers. In the MAVORIC trial, mogamulizumab was not directly compared with the committee's defined UK options for MF/SS because it would have been unethical to use a comparator agent that many of the trial participants had already been treated with unsuccessfully. Patients recruited into the trial had already received a median of 3 previous treatments and most had already had bexarotene and/or interferon. Excluding patients who had already received these treatments would have significantly affected trial recruitment which, for such a rare condition, would have led to an inadequately powered trial. Instead, an alternative comparator was selected that has been proven in clinical trials to be effective and well tolerated in CTCL and has been widely used in other countries for several years.
2	We feel the clinical evidence supporting mogamulizumab has been unreasonably dismissed. Many treatments currently used for people with MF/SS have only been studied in single-arm trials or are not specifically licensed for the condition and are prescribed off-label. However, mogamulizumab is supported by robust data from a randomised phase 3 trial involving 370 patients – the largest trial ever conducted in cutaneous T-cell lymphoma (CTCL). It is unreasonable to dismiss the positive data from this large trial because it does not directly compare mogamulizumab with treatments currently used as NHS standard – especially since most patients recruited into the trial had already been treated with many of these standard options but had failed to respond or had experienced relapse. Despite this, mogamulizumab provided significant, measurable benefits against an active comparator in this difficult-to-treat, heavily pretreated population.
3	We are concerned that this recommendation does not acknowledge the impact of advanced stage MF and SS on patients. These are long-term conditions that cause significant symptoms and can be aggressive. Existing treatments do not, in general, produce durable responses and patients are keen for treatment options that give them longer disease control. In the MAVORIC trial, the primary outcome measure of progression-free survival (PFS) supports a longer duration of response with mogamulizumab treatment. Patients treated with mogamulizumab reported improvements in disease-related symptoms and functioning. Delaying disease progression is important for these chronic conditions and there is a clear unmet need for an effective, durable treatment.
4	We believe the recommendations do not give sufficient consideration to the impact of MF and SS on quality of life. This can be difficult to capture adequately using clinical scoring systems but has a considerable impact on the day-to-day lives of patients. Even small improvements can be beneficial and can make a disproportionate difference to patients' lives. The benefit of mogamulizumab on quality of life is supported by clinical data and by the testimony of clinical experts and patients alike.
5	We consider the recommendation underestimates the potential impact of MF/SS on carers. It can have a significant psychological, emotional and financial impact beyond the patient themselves and can negatively affect work, leisure activities, relationships and emotional wellbeing due to caring responsibilities, frequent appointments, anxiety and stress. An effective treatment such as mogamulizumab therefore has the potential to benefit not just the patient but also the carer – psychologically, emotionally and financially.
6	

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted] On behalf of Royal College of Pathologists, British Society Haematology, British Association Dermatologists.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**PI on MAVORIC Trial, Consultancy Kyowa (educational), Educational Grant 2019, Kyowa**]

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Name of commentator person completing form:	[redacted] **Royal Marsden Hospital.** **&** [redacted] **University Hospital Birmingham**

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The comment that the clinical trial (MAVORIC) evidence is 'very uncertain' is an unfair comment. This was the largest randomised controlled trial in CTCL which include 372 patients. The comparator was vorinostat an FDA approved oral therapy for CTCL. Whilst vorinostat is not available in UK it is a proven anti-CTCL therapy and reasonable comparator. The patients included in MAVORIC had a median of 3 previous systemic treatments (interquartile range 2-5) so many would have exhausted all the available anti CTCL therapies in UK. The trial met its primary endpoint of improving progression free survival compared with vorinostat therapy (median 7·7 months [95% Confidence Interval 5·7–10·3] in the mogamulizumab group versus 3·1 months [2·9–4·1] in the vorinostat group; hazard ratio 0·53, 95% CI 0·41–0·69; stratified log-rank p<0·0001).
2	The rarity of CTCL variants mycosis fungoides and Sézary syndrome has not been considered at around 6 per million for mycosis fungoides and <1 per million for Sezary syndrome so very few patients per year would need treatment in England (refractory to one systemic). Limiting the overall cost to the NHS. The health related quality of life in mycosis fungoides and notable Sézary syndrome is severely reduced and adds a huge burden to patients . [redacted]
3	There is no clearly defined treatment pathway for patients with CTCL due to the rarity of the disease, and so the fact that there are differences in the trial population is just reflective of this fact and typical of any series of patients with CTCL.
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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more

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than 1 set of comments from each organisation.

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- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	United Kingdom Cutaneous Lymphoma Group
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.

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Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

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Name of commentator person completing form:	*Prepared by* [redacted] *Approved by members of the UK-Cutaneous Lymphoma Group, including* [redacted], *Nottingham* [redacted], *The Christie Hospital* [redacted], *Leeds* [redacted] [redacted], *Guys and St Thomas* [redacted], *Liverpool* [redacted], *Glasgow* [redacted], *Newcastle* [redacted], *Southampton* [redacted], *Leicester* [redacted], *Cardiff* [redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The UK Cutaneous Lymphoma Group is an organisation that represents clinicians across the UK who are involved in the diagnosis, treatment and support of patients with skin lymphomas. We were highly disappointed as a group of Cutaneous Lymphoma Specialists with the decision by NICE to not recommend mogamulizumab CTCL patients refractory to at least one previous systemic treatment. On behalf of the UK Cutaneous Lymphoma Group (UKCLG), we would like to respond to this recent NICE recommendation, and make particular reference to the following comment made by NICE regarding the largest randomised controlled trial in CTCL (MAVORIC). As the specialist UK Cutaneous Lymphoma Group we felt that it was most appropriate to prepare one unanimous response from our Group in response to the NICE recommendations. NICE recommendations: “The clinical trial evidence is very uncertain because mogamulizumab is compared with

	vorinostat, a treatment that is not used or licensed in the UK. Also, many people switch treatments and there are a lot of differences among the trial population. This means it is unclear how well mogamulizumab works" UKCLG response: This response reflects the UKCLG responsibility to advise on the management of CTCL patients and to publish multi-disciplinary treatment guidelines for UK CTCL patients (see BJD, Gilson et al 2018). The historical evidence base for much CTCL treatment is weak, not due to failures in the approach of researchers, or due to lack of engagement in the treating community, but reflecting the rarity of CTCL, and the difficulty of researching an unusual condition, the principle difficulties of which NICE will be well versed in. The recent publication of two large randomised controlled trials (RCTs) ALCANZA and MAVORIC, has provided impressive efficacy data for Brentuximab and Mogamulizumab in advanced stages of disease, and has offered a unifying platform for international approaches to a debilitating, life-changing and dangerous disease. The MAVORIC trial is the largest RCT study completed in CTCL to date (n=372) and is the first to address progression free survival (PFS) as a primary endpoint. This is a highly relevant endpoint in CTCL, which has a huge symptom burden which detrimentally affects quality of life, and increases burden on healthcare systems. In addition, the patient population recruited is entirely representative of the UK CTCL patient cohort, namely stage IB-IV MF/SS patients refractory to at least 1 systemic treatment, consisting of methotrexate, bexarotene, alpha interferon or chemotherapy, all of which are in current use and/or approved for CTCL in the UK, and are recommended in the published joint UKCLG/BAD guidelines already referenced. Furthermore, the 3 main supra-regional centres for CTCL all contributed patients to MAVORIC, and have, since EMA approval, treated patients with mogamulizumab on the Compassionate Use Scheme. The trial design with vorinostat as a comparator was approved by the EMA even though Vorinostat is not EMA approved for CTCL, and the significant UK patient numbers recruited to the study is testament to the clinical need for patient access to novel treatments in CTCL in view of the poor prognosis for advanced disease and lack of effective standard therapies. This RCT is the largest study of sezary syndrome (SS) patients (n=168) to date, and provides invaluable evidence of treatment responses for this rare aggressive leukaemic CTCL variant. The trial recruited patients resistant or refractory to current UK standard SS treatments. Specifically, the trial stratified patients according to stage and CTCL subtype (MF vs SS). This is especially important as SS has a poor OS (median 32 months from diagnosis) and controlled trial data on current standard first line treatment options such as combination therapy consisting of photopheresis, pegylated alpha interferon and bexarotene, is lacking despite the high cost of such therapies. Furthermore, the trial results for Mogamulizumab show an improved PFS compared to Vorinostat as the primary endpoint, and this was most striking in the SS patient cohort which is also reflected in the improved PFS for stage III-IV. In addition ORR for SS was excellent at 37% with a median duration of response of 17.3 months. The efficacy data is supported by the ORR (31%) of patients on Vorinostat who crossed over to Mogamulizumab after progression (136/186).

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

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	Serious adverse reaction were rare and the safety profile is wholly acceptable. The UK recruitment into MAVORIC coupled with the high usage on compassionate basis since August 2019 (n=23 across 5 centres) provides further evidence that mogamulizumab is a much needed addition to our anti CTCL therapies. In conclusion the efficacy of Mogamulizumab in terms of PFS and ORR/duration of response is clear and especially impressive for the SS cohort which is a rare and difficult to treat CTCL subtype with no published controlled trial data. As such Mogamulizumab represents an important treatment option for CTCL patients which is reflected in both FDA and EMA approval. As a group of clinicians representing all nations of the UK, we cannot tolerate another drift further from our European and worldwide counterparts in our ability to access appropriate and effective treatment for patients with a disease as damaging as CTCL including sezary syndrome.
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Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Association of Dermatologists (BAD)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	[redacted], on behalf of the BAD's Therapy & Guidelines sub-committee

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The British Association of Dermatologists would like to support the submission made by the UKCLG
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Insert extra rows as needed

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Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 19 August 2020 via the NICE Docs link.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	George Fletcher

Please return to: **NICE Docs**

NICE National Institute for Health and Care Excellence

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 19 August 2020 via the NICE Docs link.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	As a Sezary Syndrome patient I have been privileged to be set on a course of Mogamulizumab which has completely changed my life after suffering some fifteen years with the condition. I have been through all the usual treatments of drugs, light ECP, and progressed through three different chemotherapies treatments all of which made my condition worse. Having been set on a course of Mogamulizumab my whole skin condition miraculously improved to where I have no skin flaking, no itchiness and have a better feeling of well being. I have not had any adverse or side effects from the treatment. For me it has changed my whole social and home life and above all my expectations are beyond belief. I would thoroughly recommend and commend the use of the treatment to the low numbers of Sezary Syndrome patients to offer such relief of symptoms as I have experienced.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

Please return to: **NICE Docs**

NICE National Institute for Health and Care Excellence

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 19 August 2020 via the NICE Docs link.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

"No, mogamulizumab is compared to a drug not used in the UK (Vorinostat).Mycosis Fungoides and Sezary Syndrome are both very rare diseases.
We have very little in our treatment armoury (NICE approved), in order to be able to treat patients with this awfully debilitating condition(s).

Refusing NICE approval of Mogamulizumab on the basis of the recommendations given is unreasonable due to the following reasons.
-Trial evidence available in more common cancers will be much more readily obtainable, and due to the rarity of the disease it is unfair to expect the same volume of available data."

"Mycosis Fungoides and Sezary Syndrome are both very rare diseases.
We have very little in our treatment armoury (NICE approved), in order to be able to treat patients with this awfully debilitating condition(s).

Refusing NICE approval of Mogamulizumab on the basis of the recommendations given is unreasonable due to the following reasons.
-Trial evidence available in more common cancers will be much more readily obtainable, and due to the rarity of the disease it is unfair to expect the same volume of available data.
- In your review of trial data Mogamulizumab is compared to a drug not used in the UK (Vorinostat).

- The benefit of Mogamulizumab on quality of life is supported by clinical data, patients and clinical experts and It feels that the impact this condition has on patients and their carers has not been acknowledged in this decision making process.
The debilitating symptoms of this disease (a few as an example… constant itching, unable to sleep, unable to maintain/ control own body temperature, pain, regular dressing changes, bleeding skin, unable to work/ hold a job down) that our patients suffer with means many of them do not wish to continue living if they do not have access to adequate treatment in order to help with their ongoing suffering. It makes life for most unbearable. These patients need treatment to improve comfort and quality of life as symptoms in turn severely have an effect on psychological and emotional well-being.
Improving quality of life must be paramount in this decision making process, to make sure the time the patient has, has some quality.

- It seems the impact on carers has not been fully appreciated in the decision making process. Carers and family often have to take lots of time off work to assist and even may not be able to work themselves due to the negative impact this condition has on their loved one. All of this in turn will have an impact on their relationships and increases anxiety and stress beyond the patient."

Name	[redacted]
Role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

"There are very few randomised studies in CTCL, and the evidence base for then majority of treatments used are from anecdotal series and single-arm studies. The evidence for MAVORIC is from a large scale multicentre trial, which is a real rarity in this context."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"Highlighting the use of vorinostat as a comparator, in the context of very limited UK experience in this setting, is fully valid. However it must also be acknowledged that many patients in the study had already been exposed to most of the agents that are routinely used in UK practice. Furthermore, quality of life considerations are crucial in CTCL, as many patients can live for years but with very considerable and life-affecting symptoms."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"Advanced stage CTCL is a significant area of unmet need for the reasons stated above. The data for mogamulizumab are derived from a robust large-scale international trial with significant crossover. I would be grateful if this could be considered"

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"Not that I'm aware of."

Name	[redacted]
Role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

"The committee have discounted the use of Vorinostat in the Mavoric trial largely because it is not available in the UK. Studies show that it's effectiveness is similar to that of Bexarotene and interferon. Most of the UK patients had already received multiple therapies (median 3) including methotrexate, bexarotene and interferon, so these would not have been a suitable comparator. In such a rare disease this trial is the largest RCT for MF/SS and in particular the largest cohort of SS published to date. It shows marked improvement in PFS, ORR and duration of response, particularly of blood burden. No other drug has shown similar improvements in a RCT in SS. As clinicians looking after patients with this condition we have seen dramatic and lasting control of distressing symptoms for the first time, when our usual 'standard' therapies have not worked. Very few therapies are available for this disease and our patients should not be denied the option of Mogamulizumab which has shown significant effectiveness in this difficult to treat group."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"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. There has never been a trial which has documented this sort of response in the SS cohort; the largest to date in CTCL history. There is also data on improved quality of life and carer burden for the first time. It will be a tragedy for individual patients and the clinical teams who have to look after them if this drug is not approved; in particular for SS"

Name	[redacted]
Role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

"As a team of Cutaneous Lymphoma Clinical Nurse Specialists at St John's Institute of Dermatology, we were incredibly saddened and disappointed with NICE's recommendation not to consider mogamulizumab for CTCL patients.

We are in full agreement with the comments made by the UKCLG with regards to the success of mogamulizumab in our patient group, which is reflected in the

MAVORIC and ALCANZA trials. We feel it is difficult to fully portray the importance of mogamulizumab due to the rarity of the disease, and it is unreasonable to demand the same standards of trial evidence in rare subtypes of cancers as in more common cancers.

Our first-hand experience in nursing patients with CTCL has shown us how invaluable mogamulizumab is. Patients with severe disease are overwhelmingly debilitated and have limited treatment options. We feel that it goes against humanity to deny patients of this option when their quality of life is so low. We feel that is it our duty as nurses to advocate for our patients and implore you to reconsider your decision.

We look forward to hearing your response.

Prepared by,
[redacted]
"

Name	[redacted]
Role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

"I feel these recommendations are not taking into account that MF and SS are long term conditions having a strong impact on patients' quality of life. the MAVORIC trial https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30379-6/fulltext shows that Mogamulizumab significantly prolonged progression-free survival and could provide a new, effective treatment for patients with MF and SS, a subtype that represents a major therapeutic challenge in cutaneous T-cell lymphoma. These patients' clinical conditions can deteriorate rapidely and Mogamolizumab can improve disease related symptoms in cases where conventional treatment has not been successful. Also, these patients often die for complications related to the skin disease (like sepsis) and controlling disease related symptoms/skin deterioration may delay the occurence of fatal events."

Name	[redacted]
Role	Not specified
Organisation	Lymphoma specialist nursing team, The Christie NHS Foundation Trust
Location	Not specified
Conflict	N/A
Comments on the ACD:	

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"As a lymphoma specialist nursing team working within a UK NHS supra-network cutaneous lymphoma service in the North West of England we have extensive experience caring for patients with all types of cutaneous lymphoma including MF and SS, including patients who are receiving Mogamulizumab. We currently provide support to patients who are receiving Mogamulizumab and 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. Mogamulizumab, although not without its potential but overall manageable side effects, has been well tolerated and integrated into lymphoma treatment service delivery within our haematology/oncology day services without any challenges.

We feel it was unreasonable to dismiss the results of the MAVORIC phase 3 randomised controlled trial on the basis that the comparator arm is not licenced for use in the UK for patients with MF or SS. MF and SS are rare types of cancer and systemic treatments currently used in the UK to treat these cancers have not been subject to such a large robust randomised controlled trial as the MAVORIC study demonstrated, or patients are prescribed treatments off label. The data from the patients treated on the Mogamulizumab arm demonstrated superior results compared to the comparator arm. In addition, many of the patients in this study had already received and relapsed following standard UK treatments."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"MF and SS are rare and aggressive diseases that have a significant negative impact on all aspects of a patients' quality of life. This recommendation does not adequately reflect the impact that advanced stage MF and SS has on patients with these rare and aggressive diseases, and that other existing treatments do not produce meaningful or durable responses. Although the comparator arm treatment in the MAVORIC trial is not used in the UK, the treatments accessed by trial patients previously (and failed) are treatments currently used in the UK. In the MAVORIC study Mogamulizumab demonstrated longer duration of responses and these results have been reflected in our real-world experience of patients receiving this treatment.
We do not feel that the recommendation adequately reflects the significant impact MF and SS has on patients' quality of life. Where a patient is not transplant eligible (either due to performance status, age, comorbidities or progressive disease), all treatment options are considered palliative and aim to improve the patient's quality of life. Quality of life is of paramount importance in this patient group and this concept is being supported by NHS England who are carrying out quality of life questionnaires in the hope to show the importance of quality of life alongside survival (https://www.england.nhs.uk/cancer/living/). We see first-hand in our clinical practice the poor quality of life this patient group experience prior to access to Mogamulizumab.

The impact on carers, including carer burden modelling, does not adequately reflect 'real world' observations during day to day clinical practice in supporting both patients and carers with MF and SS. We have witnessed the positive impact Mogamulizumab has had on the lives of both patients and carers receiving this treatment at our centre.
The burden on carers often starts from the presentation of the disease, including the often many years of uncertainty before a diagnosis of this rare condition is confirmed. Carers witness patients suffering due to intractable symptoms such as

pain, pruritus, loss of temperature control as well as the disfiguring skin appearances with patches, plaques and tumours that require dressing changes. Carers often express helplessness and hopelessness in their attempts to alleviate their loved ones' suffering. Carers are often the primary source of psychological support for patients, and indeed the only source of support before a cutaneous lymphoma diagnosis is made. Healthcare professionals, such as ourselves, provide professional holistic support to patients and carers, in reality we only have a limited period of time with patients and carers and the burden of care falls to the carer who is with the patient the majority of the time. Practically, carers assist patients with their often complex, frequent and time-consuming topical skin management regimens including application of whole body topical applications. This can include areas patients cannot reach, including intimate areas, often both during the day and the night. Patients requiring systemic treatments are required to attend hospital appointments on frequent basis, spending many hours in a hospital setting for assessment and treatment. Patients and carers often travel a long distance to a specialist cutaneous lymphoma treatment centre.. This can make it difficult for carers to maintain their employment, often relying on the goodwill of their employers to work flexible hours to be able to support their loved one. Carers can often be the single source of income due to the nature of MF/SS and treatment side effects of treatment resulting in patients with advance stage disease often being unable to continue to work. This can have significant financial impact on the whole family, including costs of transport, increased utility bills due to frequent requirements to wash bedding and clothing and heating for temperature control comfort. Carers' own physical and mental health and well-being can be neglected as they focus on their loved ones at the expense of their own needs. Carer can experience a high degree of stress, exacerbated by sleep interruptions, in an attempt to alleviate their loved ones suffering e.g. topical application of creams during the night, pain control, temperature control, itch control. Relationships, including sexual relationships can be affected due to the condition and treatment side effects.

The financial cost of resources required to treat skin tumours or erythroderma for patients with MF or SS has not been reasonably considered. These include time and expertise of specialist tissue viability nurses and district nursing teams to assess and manage complex wound care, often requiring frequent and complex dressings. With the high risk of infection and sepsis due to the break in skin integrity there is also the additional financial cost of anti-microbial antibiotics, hospital inpatient stays and associated costs. Unlike standard goals of wound care management, caring for patients with MF or SS presents major challenges. Wound care can only provide partial relief to this group of patients as it is the effective treatment of the underlying cutaneous lymphoma that allows the tumours to heal. Mogamulizumab can provide such effective treatment, not only providing physical and emotional relief to patients but also reducing the financial burden on NHS services as described above."

Name	[redacted]
Role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	
Has all of the relevant evidence been taken into account?	

"On behalf of:

[redacted], Consultant Dermatologist & Lead Cutaneous Lymphoma Service
[redacted], Consultant Dermatologist
[redacted], Consultant Dermatologist
[redacted], Consultant Haematologist
[redacted] Consultant Oncologist,
[redacted], SpR Dermatology/Clinical Fellow in Cutaneous Lymphoma
[redacted], Skin Oncology Nurse Practitioner,
[redacted], Skin Oncology Nurse Practitioner,

Cutaneous Lymphoma Multidisciplinary Team,
Queen Elizabeth Hospital Birmingham,
University Hospitals Birmingham NHS Foundation Trust,
Mindelsohn Way,
Birmingham,
B15 2TH

The aforementioned respondents write this comment in response to NICE consultation response in relation to "Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome". As key stakeholders in the management of patients with this disease, we wish to raise concerns in relation to the following items raised in the consultation process:

1. Section 1 Recommendations, Subsection (Why the committee made these recommendations), Paragraph 2: "The clinical trial evidence is very uncertain because mogamulizumab is compared with vorinostat, a treatment that is not used or licensed in the UK. Also, many people switch treatments and there are a lot of differences among the trial population. This means it is unclear how well mogamulizumab works."

2. Section 3 Committee Discussion, Subsection 3.3 "It concluded that standard care was the most appropriate comparator, which includes treatments such as methotrexate, bexarotene, interferon and chemotherapy."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"We disagree that there is uncertainty regarding the clinical trial evidence regarding the effectiveness of mogamulizumab. In the MAVORIC trial, mogamulizumab was not directly compared with standard of care treatments (e.g., methotrexate, bexarotene, interferon and chemotherapy) as many of the trial participants had already been treated with unsuccessfully with these agents.

We have treated 8 patients (3 males, 5 females) with a mean (+/- SEM) age of 61.38 (+/- 4.07) years with mogamulizumab on a compassionate basis since July 2019. These included 4 patients with advanced mycosis fungoides (IIIB – IVA2 disease), two patients with Sezary syndrome (IVA2) and two patients with HTLV-1 lymphoma (one mycosis fungoides and the other Sezary syndrome like). These patients were all heavily pre-treated and included 6.625 (+/- 0.98) previous treatments of which 1.125 (+/- 0.39) were skin directed therapies and 5.5 (+/- 0.65) systemic therapies. Previous systemic therapies in these patients included methotrexate (n=4), bexarotene (n=4), interferon (n=4), gemcitabine (n=4), CHOP (n=3), interferon (n=4), ECP (n=3), resminostat (n=3) and brentuximab (n=2). In

this cohort, 6/8 achieved an overall response rate (OR) in skin of 50% (complete response, CR, n=1; partial response, PR, n=2; stable disease, SD, n=2; and progressive disease PD, n=1). In these same six patients, nodal disease remained stable. It was not possible to assess skin/lymph node follow-up status in 2/8 patients as they only received mogamulizumab for one month at the time of our review. Blood response assessment was possible in 7/8 patients and demonstrated an OR of 71.4% (CR, n=3; PR, n=2 and SD, n=2) with a reduction in peripheral blood absolute Sezary cell counts of 77.40 (+/- 8.95)% with a mean time to response of 0.76 (+/- 0.24) months. None of our patients had visceral disease and therefore no visceral response assessment following mogamulizumab was possible. Mogamulizumab was well tolerated and the most common treatment-emergent adverse events (TEAEs) were grade 1-2 (97.5% of all TEAEs) and only one episode (2.5%) of grade 3 TEAE was observed. The most common TEAEs included skin infection (n=4), rash (n=2), fever (n=2), nausea (n=3), lethargy (n=3) and diarrhoea (n=2).
In our real-world observations of treating patients with mogamulizumab, we found similar response rates to those observed in the MAVORIC trial. These included similar response rates of 71.4% in blood (MAVORIC = 68%) and 50% in skin (MAVORIC = 42%)."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"Given our experience in treating these patients we argue strongly that mogamulizumab, a drug which has shown significant and measurable benefits in clinical trials has been unfairly dismissed and denies patients with this rare disease an effective durable treatment."

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"No"

Name	[redacted]
Role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

"Having been diagnosed with MF (CTCL) back in 1999 and endured every treatment available resulting in going through two Allogeneic Stem Cell Transplants ANY new drug that can delay or even stop the need for enduring Stem Cell Transplant can only be positive and in the long run much more cost effective as Stem Cell Transplant is in its self expensive but the long term post treatment support and medical complications just adds to the costs. I full support the adoption of this new drug"

Name	[redacted]
Role	Not specified

Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"Rare skin disease"

"I read this paper with interest as I believe it is very relevant to the patients I care for in the South West Skin Lymphoma clinic. This is a rare condition that patients and their carers find bewildering and utterly miserable. Current treatment options are limited and development of new medicines should be a priority. This trial has involved an astonishing number of patients and produced clearly significant results in support of Mogamulizumab as an option for patients with refractory disease. The cost of the treatment reflects the in depth research that has gone into this breakthrough which is reminiscent of the immune targeting treatments in Melanoma which have developed over the past 10 years. It is essential to allow these new treatments to be used and ultimately refined in clinical practice. I would ask NICE to carefully reconsider its decision to allow this progress to take place for Cutaneous Lymphoma."

Name	[redacted]
Role	Not specified
Organisation	Manchester Cutaneous Lymphoma Group
Location	Not specified
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

"The Results of the Mavoric trial have been considered but the committee have expressed concerns regarding the validity of comparator arm. This concern is misplaced (as detailed below).
The committee did not have access to the real world data demonstrating efficacy outside a clinical trial. Our experience has been outlined below.
The Committee did not compare the survival of the Sezary Syndrome patients who have received Mogamulizumab (in and outside clinical trials) with the consistent historical evidence showing a median survival of 36 months"

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"We recognise the cost effectiveness of any intervention is very difficult to measure due to so many complexities. The situation of aggressive CTCL and Sezary Syndrome is a good example.
This is a rare disease and the published evidence regarding the efficacy of any treatment is sparse.
We recognise that Overall Survival (OS) is a key element to be considered by NICE. The Mavoric trial design was cross over, which offers the patients the

advantage of always having access to Mogamulizumab irrespective of the initial treatment arm. The company should be commended for supporting this trial design in the knowledge that it makes OS comparisons very difficult. As the longer term follow up from Mavoric emerges and in combination with the increasing real world experience, clinicians looking after these patients are becoming ever more confident that Mogamulzimab changes the course of the disease not only in terms of an improvement in PFS but in the stiking observation that it leads to a more indolent behaviour post Mogamulzimab. In time, this will translate into patients living longer as a result of Mogamulizumab.
A very important issue to take into account in terms of cost effectiveness is the impact any intervention has on a patient's quality of life. Nowhere is this more evident than in this very distressing disease where patients can live for several years with relentless symptoms including progressive weeping wounds, unbearable itch and disfigurement. The Movoric trial and our real world experience with Mogamulizumab shows a dramatic reduction in the suffering of our patients and a transformative improvement in they way in which they can live their lives including returning to work and caring for their families.
In this disease, the impact on quality of life should have equal importance to the possibility of prolongation of lifespan as a consequence of Mogamulizumab therapy."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"We strongly reject the recommendations of NICE in this case and the current guidance to the NHS will increase suffering of our patients and will deny them the opportunity for a longer lifespan."

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"We are not aware of any such considerations in this case"

"Response to NICE re the recent decision regarding Mogamulizumab in CTCL and Sezary Syndrome

On behalf of the Manchester supra regional cutaneous lymphoma service we wish to register our challenge to the recent decision by NICE.
The Manchester supra regional cutaneous lymphoma service comprises a multidisciplinary team of dermatologists, oncologists, haematologists, histopathologists and specialist nurses responsible for the care of this rare group of patients drawn from a population of over 5 million.
We have one of the largest number of patients with advanced Cutaneous Lymphoma in the UK and have extensive experience with the use of Mogamulizumab.
We participated in the international Mavoric trial and we have 5 patients currently receiving this therapy in the patient access programme. All 5 patients have experienced a dramatic improvement in their skin and associated Quality of Life. In addition, we have a further 2 patients due to commence in the near future.
The data from the Mavoric trial shows a clear benefit in terms of PFS and quality of life. We however note the concern expressed by the NICE committee regarding the comparator arm of Vorinostat which is not licenced in the UK.

The current literature is very clear that Vorinostat has equivalent activity in phase II studies to Bexarotene which was one of the comparator arms in the Alcanza trial, the results of which led to NICE approving Brentuxmab in advanced CTCL. (The other comparator arm in this study was methotrexate which has been used as first line systemic therapy for over 50 years and for which there is little recently published evidence for efficacy).
In contrast to the Alcanza trial, the Mavoric study included many more patients with advanced disease, particularly with blood involvement, diagnosed as Sezary syndrome. The literature for Sezary syndrome has been very consistent over many years showing an obstinate median survival of 36 months. Up to now, there has been no treatment available which has had an impression on this dismal prognosis.
Mogamulizumab in contrast, in the Mavoric study has shown the highest response rate and the longest PFS ever recorded.
In addition we now have clear evidence from the Mavoric study that Mogamulizumab therapy led to a sustained improvement in the quality of life for these patients for whom the symptoms of this disease can be unbearable.
As the data from Mavoric matures we are beginning to see a change in the behaviour of the disease following Mogamulzumab leading to a more indolent character compared with pre Mogamulizumab. Many of us with first-hand experience of this drug have witnessed this but we recognise that with such a rare condition, it will take considerable time for this to be proven in a clinical trial. What is quite clear however, is the overall survival of the cohort of patients who have been fortunate to have received Mogamulzumab is considerably longer than the 36 months quoted in the literature.
In summary, we have not had a drug to significantly change the course of this terrible disease for over 30 years. Mogamulizumab is such a drug .

[redacted] *Consultant in Clinical Oncology*
Consultant Dermatologist
Consultant Dermatologist
Cutaneous Lymphoma Clinical Fellow
Cutaneous Lymphoma Nurse Clinician
Consultant in Clinical Oncology

On behalf of the Manchester Cutaneous Lymphoma Group"

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

"No. Anecdotal evidence from the sufferers, in my opinion is of equal importance, to scientific evidence. Perhaps even more important, sufferers know what's making them feel better. Improving blood stats is quantifiable but improving life quality is immeasurable."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"No. I feel that the rarity of these conditions means that numbers coming forward for treatment must be small. In comparison to some other forms of cancers. Therefore, these illnesses should be classed as a special case. Both in clinical and cost effective terms."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"No, because the overall human costs have not been taken into account. Using this drug would ultimately save costs, by slowing the progress of the disease and the subsequent incurred costs of other treatments such as frequent antibiotics, other medications, radiotherapy, etc. Also it would reduce the costs of caring and potentially allow some sufferers to continue working"

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"Yes, on the grounds of disability. The impact of these diseases can be very severe atheistically. Appearance is the first thing we register, when we meet an individual. I have seen individuals with terrible skin lesions, shedding large quantities of skin and some with actual tissue loss. Trying to live with this is hard. I myself lost a large amount of skin with underlying tissue off my legs. It took three months to heal. Thus any drug that can slow things from getting to this level is vital. We are disabled by virtue of having the illness."

"Dear committee members,
I have Cutaneous T Cell Lymphoma at the Sensory Stage and Mogamulizumab is quite simply keeping me alive by keeping the disease stable and non-progressive at present. More so, I not only feel well and can function fully, but at times I also feel 'normal' and can almost kid myself into thinking I do not have a terminal illness.
The impact of receiving my diagnosis was seismic and the effects were catastrophic. I became very ill, very quickly and deteriorated rapidly. My husband and family were in shock. I was prepared for death and then miraculously I was rescued by my medical team and I started to feel a little better. I moved through various treatments to try and control the disease from progressing, but 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. Mogamulizumab gives me a good quality of life and I am deeply grateful for being allowed to receive it.
I would like to continue on this drug for a long as it is working, but more importantly I would like it to be available to the patients that come after me.
The rarity of my disease means that the number of those needing Mogamulizumab will be low. Therefore, I feel that the benefits will probably outweigh the costs in financial terms. However, in life changing terms, the benefits are immeasurable. When I was diagnosed in 2016, I didn't think I would still be alive in 2020. Now I plan for a future; I hope to celebrate my 50th Wedding Anniversary next year in Nov 2021. I plan to live for several years more with the help of Mogamulizumab, which I know receive on compassionate grounds.
Please give people after me the chance to feel better and live longer by making Mogamulizumab unconditionally available.

Thank you for your deliberations.
Yours respectfully,
[redacted]

Name	[redacted]
Role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

"The following bullet points demonstrate the difficulties and effects of caring for a loved one with Sezary syndrome.
1. The most difficult aspect is without doubt watching someone you love suffer with the debilitating symptoms that Sezary syndrome causes, muscle pain, constant itch, cuts and infection in skin. The feeling of being completely helpless to aid their suffering.
2. Family life is organised around medical appointments and treatment. Restrictions to family life is unavoidable as family holidays and outings may have to be cancelled due to a severe flair up of symptoms.
3. Explaining the condition and the life limiting implications to children is extremely upsetting.
4. Trying to hold down a full- time job whilst providing support for your partner is difficult. The need to keep employers happy and the desire to attend appointments is a constant emotional drain.
5. As it is often necessary to apply emollients during the night it is necessary to sleep separately so that I can continue to work.
6. The constant fear that is caused by having your partner diagnosed with cancer and the uncertainty for the future of your family.

[redacted]

Name	[redacted]
Role	Not specified
Organisation	Cutaneous Lymphoma Foundation
Location	Not specified
Conflict	N/A
Comments on the ACD:	

"The Cutaneous Lymphoma Foundation, the leading international patient organization supporting individuals living with cutaneous lymphoma, concurs with our colleagues from Lymphoma Action with regard to the critical importance of mogamulizumab for patients suffering from Sezary syndrome, a debilitating and often life-threatening form of cutaneous lymphoma. The Foundation has been serving this patient population for 22 years and has seen the positive impact of this new treatment on the lives of patients. We urge the NHS to take into consideration the impact on patient's quality of life this new treatment can provide."

Name	[redacted]
Role	Not specified

Organisation	Not specified
Location	Not specified
Conflict	N/A
Comments on the ACD:	

"Patients with advanced stage MF and SS have shortened survival and poor life quality. Current treatments have low response rates and the responses are very short-lived. With advancement of science, mogamulizumab has been developed that can target key molecules and cells in this rare cancer, and in well-controlled clinical trials, has been shown to be effective with great safety profile. The MAVORIC study, a randomized clinical trial with rigorous response evaluation criteria, has shown mogamulizumab to be a valuable added therapy that shows promising durable responses and improved progression-free survival and life quality, especially in those with Sezary syndrome. Mogamulizumab has shown rapid and durable clearance of blood disease in Sezary syndrome, rarely obtained safely and reliably with other therapies. Given that standard therapies have short-lived responses, more treatment options are essential for the survival and life quality of patients with previously treated MF and SS. In those patients with high-burden Sezary disease, the rapid reduction of Sezary burden has supported mogamulizumab as a preferred initial treatment option by the NCCN (clinical experts) and not restricted to those who are previously treated. Lastly, mogamulizumab is a rigorously evaluated immunotherapy that has great safety profile, and such immune therapy option is needed in these patients with refractory CTCL who are already immune-suppressed and at risk for infections where sepsis is a major cause of death."

Name	[redacted] (Consultant Haematologist), [redacted] (Consultant Oncologist), [redacted] (Consultant Dermatologist), [redacted] (Consultant Dermatologist), [redacted] (Nurse Specialist), [redacted] (Nurse Specialist), [redacted] (Lymphoma Fellow)
Role	Various – see name field
Organisation	University Hospital Birmingham
Location	Not specified
Conflict	Not specified
Comments on the ACD:	

We write this comment in response to NICE consultation response in relation to "Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome". As key stakeholders in the management of patients with this disease, we wish to raise concerns in relation to the following items raised in the consultation process:

1. *Section 1 Recommendations, Subsection (Why the committee made these recommendations), Paragraph 2: "The clinical trial evidence is very uncertain because mogamulizumab is compared with vorinostat, a treatment that is not used or licensed in the UK. Also, many people switch treatments and there are a lot of differences among the trial population. This means it is unclear how well mogamulizumab works."*

2. *Section 3 Committee Discussion, Subsection 3.3 "It concluded that standard care was the most appropriate comparator, which includes*

treatments such as methotrexate, bexarotene, interferon and chemotherapy."

We disagree with these recommendations and conclusions and present our experience at our Specialist Skin Lymphoma Service of treating this complex patient group with cutaneous T-cell lymphoma on a compassionate basis with mogamulizumab over the past 1 year.

We have treated 8 patients (3 males, 5 females) with a mean (+/- SEM) age of 61.38 (+/- 4.07) years with mogamulizumab on a compassionate basis since July 2019. These included 4 patients with advanced mycosis fungoides (IIIB – IVA2 disease), two patients with Sezary syndrome (IVA2) and two patient with HTVL1 lymphoma (one MF-like and the other Sezary syndrome-like). These patients were all heavily pre-treated and had received a median of 6.625 (+/- 0.98) previous treatments of which 1.125 (+/- 0.39) were skin directed therapies and 5.5 (+/- 0.65) systemic therapies. Previous systemic therapies in these patients included methotrexate (n=4), bexarotene (n=4), interferon (n=4), gemcitabine (n=4), CHOP (n=3), interferon (n=4), ECP (n=3), resminostat (n=3) and brentuximab (n=2). In this cohort, 6/8 achieved an overall response rate (OR) in skin of 50% (complete response, CR, n=1; partial response, PR, n=2; stable disease, SD, n=2; and progressive disease PD, n=1). In these same six patients nodal disease remained stable and it was not possible to assess skin/lymph node follow-up status in 2/8 patients as they only received mogamulizumab for one month at the time of our review. Blood response assessment was possible in 7/8 patients and demonstrated an OR of 71.4% (CR, n=3; PR, n=2 and SD, n=2) with a reduction in peripheral blood absolute Sezary cell counts of 77.40 (+/- 8.95)% with a mean time to response of 0.76 (+/- 0.24) months. None of our patients had visceral disease and therefore no visceral response assessment following mogamulizumab was possible. Mogamulizumab was well tolerated with similar safety profile to the MAVORIC Trial and the most common treatment-emergent adverse events were grade 1-2 (97.5% of all TEAEs) and only one episode of grade 3 TEAEs was observed (2.5%). The most common TEAEs included skin infection (n=4), rash (n=2), fever (n=2), nausea (n=3), lethargy (n=3) and diarrhoea (n=2).

In our real world experience of treating patients in a Specialist Lymphoma Centre we observed similar response rates with mogamulizumab those observed in the MAVORIC trial, in our heavily pre-treated group of cutaneous T-cell lymphoma patients. These included similar response rates of 71.4% in blood (MAVORIC = 68%) and 50% in skin (MAVORIC = 42%). Given our experience in treating these patients we argue strongly that mogamulizumab, a drug which has shown significant and measurable benefits in clinical trials has been unfairly dismissed and denies patients with this rare disease an effective durable treatment.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma – Addendum (post-ACD)

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Rider on responsibility for report

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Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Mickaël Hiligsmann, Ben Wijnen, Charlotte Ahmadu, Steve Ryder and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker, Regina Leadley and Vanesa Huertas Carrera acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Isabel Syndikus provided clinical expertise. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

The company's ACD response and new evidence

In response to the appraisal consultation document (ACD), the company provided new evidence and analyses. The company implemented most, but not all, of the Evidence Review Group's (ERG) preferences. The updated company's model furthermore contains a new comparison: the comparator overall survival (OS) is now informed by Hospital Episode Statistics (HES) data instead of the comparator arm of the MAVORIC trial. Unfortunately, the company have not provided in their updated model file the possibility to switch back to the original comparison, hence hampering the ERG's ability to verify the updated model. The ERG attempted to replicate the company's new analysis by updating its own base-case: for this, the company's new survival curves for progression-free survival (PFS), next treatment-free survival (NTFS), time on treatment (ToT) and OS were used in the ERG base-case file; the Allogenic stem cell transplant (aSCT) proportion in the comparator arm was updated and the new PAS was used. For this replication, the ERG used all settings of the previous ERG base-case, with the notable exceptions of caregiver utilities (which were used in this replication exercise), using the generalised gamma for modelling NTFS in the mogamulizumab arm and enabling aSCT after current treatment. The company's incremental cost effectiveness ratio (ICER) could not be replicated, and instead the ERG obtained an ICER of £30,642 per quality-adjusted life year (QALY) gained. The ERG could not explain the difference between this and the company's ICER and therefore used its own model for all analyses.

Comparator data based on MAIC using HES data

Most noteworthy, the company provided a new comparison of mogamulizumab with United Kingdom (UK) standard care by analysing HES data. This analysis avoided two serious problems with MAVORIC: 1) vorinostat being an inappropriate comparator as it is not available in the UK, and 2) patients in the comparator arm were allowed to cross over to the mogamulizumab arm.

Whilst the company's new analysis is therefore of value, there are serious problems associated with it. The company stated that they "*conducted an unanchored matching adjusted indirect comparison"* (MAIC), which involved "*reweighting the MAVORIC trial data to match the UK patient population for second-line, advanced MF/SS"* (p.6). However, the company did not provide a description of the methods which should have included at least the process of selection of variables for which adjustment is required. As recommended in Technical Support Document (TSD) 18:

1. *"Evidence must be presented that there are grounds for considering one or more variables as effect modifiers on the appropriate transformed scale. This can be empirical evidence, or an argument based on biological plausibility"* (p.61).
2. *"Quantitative evidence must be presented that population adjustment would have a material impact on relative effect estimates due to the removal of substantial bias"* (p.61)
3. *"Submissions using population-adjusted analyses in an unconnected network need to provide evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects, and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison"* (p.62)

Based on the available information, it appears that only three variables were considered and only one chosen for adjustment, given the statement that "*mean age and gender distribution were very similar between the two data sources, therefore the matching was performed only on the proportion of MF* [mycosis fungoides] *and SS* [Sézary syndrome] *patients"* (p.7). Most problematically, as stated in TSD 18, *"an unanchored MAIC or STC* [simulated treatment comparison] *effectively assumes that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered*

impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate" (p.80).

Therefore, the ERG would conclude that the results of the company's HES MAIC analysis need to be regarded with a considerable degree of caution. The ERG has a preference for the company's original analysis based on MAVORIC data.

Survival analysis

For the HES analysis, the ERG is concerned that the methods for reweighting MAVORIC were not well explained and considers that the estimated increase in OS in the mogamulizumab arm is uncertain. The ERG is also concerned that using the exponential distribution to model OS in the established clinical management (ECM) arm is not based on the statistical fit. Whilst the ERG accepts the company's argument that the generalised gamma may place undue emphasis on the plateau that is only informed by a very small number of patients at risk, the ERG prefers the use of the lognormal distribution, which provides the second-best statistical fit. For NTFS, the company chose the generalised gamma for both treatment arms (which provided the best fit for the ECM arm) and only provided a visual fit for the mogamulizumab arm. The ERG still considers the better-fitting lognormal distribution to be more appropriate.

With regards to the company's claim that its HES analysis validated results from the inverse probability of censoring weighting (IPCW) method for cross-over adjustment, the ERG considers the HES analysis using reweighting of MAVORIC results based on one variable not to be methodologically sound enough to reach this conclusion. Given the substantial uncertainty about the appropriate choice of crossover method, the ERG presents the original analysis based on MAVORIC with both cross-over adjustment methods (with the company's new price).

Inclusion of aSCT after current treatment

The company, in contrast to the ERG base-case, included aSCT after current treatment in the mogamulizumab arm. The ERG continues to exclude aSCT after current treatment from the modelling to avoid the double-counting of survival benefit of patients in MAVORIC who would have been eligible to receive aSCT but did not receive it due to the study protocol, who are modelled in both populations: the "no aSCT" and the "aSCT after current treatment" pathways of the model. The impact of this on model outcomes is minimal.

Caregiver utilities

The company maintains its inclusion of caregiver utilities in the base-case. The ERG excludes these from their base-case, but provides scenarios with caregiver utilities included.

ERG analyses

The ERG maintained its original base-case settings but updated it with the company's new price. Based on this ERG base-case, the ERG explored the following scenarios:

- IPCW method
- Inclusion of caregiver utilities
- Both together

The ERG also explored a scenario using the company's HES data base-case (as reproduced by the ERG), but with the following preferences / changes:

- Lognormal for OS in ECM arm
- Lognormal for NTFS in ECM arm
- No aSCT after current treatment
- No caregiver utilities

Lastly, the ERG explored the impact of how much the inclusion of caregiver utilities impact the company's HES data base-case (as reproduced by the ERG and using the ERG's preferences).

Table 1: Deterministic (unless indicated) ERG analyses

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case (MAVORIC data) with company's new price					
Mogamulizumab	[redacted]	3.63	£68,555	0.85	£80,564
ECM	[redacted]	2.78			
ERG base-case (MAVORIC data) with company's new price and IPCW method					
Mogamulizumab	[redacted]	3.63	£87,226	2.04	£42,816
ECM	[redacted]	1.60			
ERG base-case (MAVORIC data) with company's new price and caregiver utilities (TSE method)					
Mogamulizumab	[redacted]	3.81	£68,555	1.03	£66,715
ECM	[redacted]	2.78			
ERG base-case (MAVORIC data) with company's new price and IPCW method and caregiver utilities					
Mogamulizumab	[redacted]	3.81	£87,226	2.83	£39,386
ECM	[redacted]	1.60			
ERG base-case (probabilistic)					
Mogamulizumab	[redacted]	3.65	£67,648	0.84	£80,438
ECM	[redacted]	2.81			
Company's new base-case (HES data) as reproduced by the ERG					
Mogamulizumab	[redacted]	4.75	£86,706	2.83	£30,642
ECM	[redacted]	1.92			
Company's new base-case (HES data) with all ERG preferences					
Mogamulizumab	[redacted]	4.42	£85,879	2.27	£37,840
ECM	[redacted]	2.15			
Company's new base-case (HES data) with all ERG preferences, including caregiver utilities					
Mogamulizumab	[redacted]	4.55	£85,879	2.40	£35,823
ECM	[redacted]	2.15			

ECM = established clinical management; ERG = Evidence Review Group; HES = Hospital Episode Statistics; ICER = incremental cost effectiveness ratio; IPCW = inverse probability of censoring weighting; QALY = quality-adjusted life year; TSE = two-stage estimation

Conclusions

The company presented additional analysis based on Hospital Episode Statistics data, which could be helpful in supporting decision-making as this provides survival data in the relevant population from the UK. Unfortunately, the methods used to analyse these data have not been clearly described and the resulting survival estimates are uncertain.

Additional information request

Single Technology Appraisal (STA)

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

Company response

27th November 2020

In the NICE ACD 'Mogamulizumab for previously treated mycosis fungoides [MF] and Sézary syndrome [SS]' (ID1405) the Committee requested "scenario analyses using HES data to model overall survival in the standard care arm", compared to mogamulizumab. Kyowa Kirin has submitted the requested additional analyses on 19 August 2020.

The HES data is to date the only available real-world data on NHS clinical practice using secondary care-based therapies for MF and SS patients over a ten-year period. The data from HES is used for payment of secondary care treatments and therefore:

- represents standard of practice in the NHS in England
- represents the current treated patient population.

For this analysis, the ERG has now requested the following:

- A new version of the cost-utility model which includes:
    - The matching-adjusted indirect comparison (MAIC) with the real-world evidence from the Hospital Episode Statistics (HES) database, and
    - The trial-based analysis based on the naïve indirect comparison with the physician's choice arm of the ALCANZA trial, leading to the conservative[1] assumption of equal efficacy for the physician's choice and the vorinostat arms.
- Further clarification on the methods of the MAIC, focusing on the process of selection of variables requiring adjustment according to the NICE Decision Support Unit guidance(2).

The cost-utility model including both requested options with all flexibility is submitted with this document named 'Mogamulizumab CE model_Combined version 1.0 for NICE 26Nov2020 AIC-CIC'. The two analyses are not comparable, as they apply to different populations with regard to the distribution of MF and SS, which is a known important prognostic factor(3–5) (Table 1). There are also differences in the inputs. The HES-based analysis uses the overall survival and the aSCT rates for the current NHS clinical practice after second line treatment from the database. Additionally, the HES analyses reweights the mogamulizumab overall survival and for both treatment arms, the next-treatment-free survival and time on treatment survival curves to represent the distribution of MF/SS (85:15) seen in clinical practice described by the HES data. In contrast, the MAVORIC trial-based comparison uses the survival curves directly from the trial with the distribution of MF/SS (55:45) seen in the trial.

[1] The physician's choice arm in a population with better prognosis led to the same progression-free survival as the vorinostat arm in a population with worse prognosis, suggesting, according to the clinical experts(1), a better efficacy for vorinostat; thereby potentially underestimating the relative efficacy of mogamulizumab.

Table 1: Differences in the analyses included in the combined model

	MAVORIC-based analysis	**HES based analysis**
Model characteristics		
Population	Based on the MAVORIC trial with 55% MF and 45% SS	Based on current clinical practice 85% MF and 15% SS
Source of efficacy data	MAVORIC trial Indirect comparison with ALCANZA trial	HES database MAVORIC trial
Inputs		
Overall survival: Mogamulizumab arm	MAVORIC trial post-hoc analyses excluding patients with aSCT	Re-weighted MAVORIC trial post-hoc analyses
Overall survival: ECM arm	MAVORIC trial post-hoc analyses for vorinostat adjusted for crossover, excluding patients with aSCT	HES data
Next-treatment-free survival (both arms)	MAVORIC trial post-hoc analyses	Re-weighted MAVORIC trial post-hoc analyses
Time on treatment (both arms)	MAVORIC trial post-hoc analyses for vorinostat	Re-weighted MAVORIC trial post-hoc analyses for vorinostat
Proportion receiving aSCT after current treatment: ECM arm	Clinician survey	HES data

Key: ECM, established clinical management

The model includes the correction of issues identified by the Evidence Review Group (ERG) (Table 2). These corrections have been already implemented in the HES-based model submitted on 19th August 2020.

Please note, that the model has been marked up for confidentiality, however, has not been redacted. The health state costs estimated from the HES database have now been released from the academic in confidence marking, due to their publication at Virtual ISPOR Europe 2020.

Table 2: Changes requested by ERG compared to previous models

Difference compared to MAVORIC-based submission model	**Difference compared to HES-based model submitted on 19th August 2020**
Changes requested by ERG: • Linking mistake in monitoring and subsequent treatments after aSCT corrected • Washout period extended so patients now accrue all additional costs except for treatment and administration costs • Extended time horizon to 45 years	None All requested changes were already implemented in 19th August 2020 version

Clarification on the MAIC

The HES database, while comprehensive (including all MF/SS patients treated in NHS England secondary care within the last 10 years), has limited reporting of all detailed patient characteristics. Table 3 describes the list of relevant patient/disease characteristics from the MAVORIC trial(6) and their availability in the HES database. Age, gender, race and disease type (MF vs. SS) potentially available for the matching. The number and type of previous

treatments are available as determined by the codes used for this database. The level of detail recorded in the MAVORIC trial is not recorded in this administrative database. Additionally, only treatments provided in secondary care setting are available.

Table 3: Data availability in the HES database vs. MAVORIC trial

Patient characteristics available in the MAVORIC trial	Availability in the HES database
Age	Yes
Gender	Yes
ECOG performance status	No
Body weight	No
Time from initial diagnosis	Limited to secondary care setting
Disease type	Yes
Clinical Stage	No
Sites of Disease	No
Number of previous systemic regimens received	Yes, treatments provided in secondary care setting
Previous cutaneous T-cell lymphoma therapies	Yes, treatments provided in secondary care setting and described by HRG/OPCS codes*

Key: HES, Hospital Episode Statistics; ECOG, Eastern Cooperative Oncology Group; OPCS, Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures; HRG, Healthcare Resource Groups

*Codes used are available in the report: Analysis of Hospital Episode Statistics data to demonstrate the detailed secondary care treatment pathway for patients with Cutaneous T-Cell Lymphoma in England submitted 19th November 2020(7)

The matching of the MAVORIC trial population to the current NHS patient population represented by the HES data, was done in two steps:

- Determining inclusion criteria to select the target population for mogamulizumab from the HES database
- Matching remaining prognostic factors that differ between the MAVORIC trial and the HES population

Inclusion/exclusion criteria for the HES database

To match the target population for mogamulizumab all patients included in the study were required to have at least one ICD-10 diagnosis of MF (C84.0) or SS (C84.1) in the HES database between 1st October 2010 to 31st March 2019 (study observation period), with secondary care activity tracked from first diagnosis in secondary care to the end of the study or death (Table 4). Patients selected has one prior systemic therapy recorded in secondary care. (For further details, please see report on the analyses of the HES data submitted 19th August 2020. (7)) While staging, performance status and haematological, hepatic, and renal function is not available in an administrative dataset, this can be inferred by the type of treatment received. This inference is drawn from the HES data being used for payment of secondary care treatments and as such patients receiving such treatment would have to have the accepted clinical fitness to do so.

Table 4: Main inclusion criteria in MAVORIC trial

MAVORIC trial	HES population
Histologically confirmed mycosis fungoides or Sézary syndrome	At least one ICD-10 diagnosis of MF (C84.0) or SS (C84.1)

MAVORIC trial	HES population
Stage IB–IVB (mostly advanced)	• Staging not recorded in HES database • Patients treated in secondary care with systemic treatments can be assumed to be mostly advanced according to clinical experts(1)
Failed at least one 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	• Performance score and haematological, hepatic, and renal function not recorded in HES database • Patients selected were eligible for systemic therapy suggesting performance score of 1 or less and adequate haematological, hepatic, and renal function

Key: HES, Hospital Episode Statistics; ECOG, Eastern Cooperative Oncology Group

Matching prognostic factors

As this is an unanchored MAIC, the characteristic should be included in the matching if it is believed that there are material differences between the characteristics in the studies at baseline, and if the characteristic is considered a prognostic factor or treatment effect modifier, as outlined in the NICE DSU guide. The available HES data included limited additional detailed information on patient characteristics. Table 5 presents a comparison of the patient characteristics between the MAVORIC trial and the HES data available in both data sets. Information on disease stage and time from diagnosis was not available from the HES data. While the HES population had lower median number of prior treatments than the MAVORIC population, this would lead to the HES population having a better prognosis, and therefore would overestimate the health outcomes with a HES based comparator arm, leading to an underestimation of the comparative efficacy of mogamulizumab and, as a result, to conservative results.

Table 5. Baseline demographic and disease characteristics of patients in MAVORIC trial and the HES database

Target population	MAVORIC trial	HES data	Matching
Mean age	63	65	Similar, no matching needed
Male, n (%)	58%	62%	Similar, no matching needed
Race	Not directly comparable		
Disease type			
MF (%)	55%	85%	Matching required
SS (%)	45%	15%	
ECOG performance status, n (%)			
0	210 (56.0)	Not available	Matching not possible
1	160 (43.0)		
Time from initial diagnosis (months), median (min, max)	Mogamulizumab: 41.0 (17.4–78.8) Vorinostat: 35.4 (16.2–68.2)	Not available, only start of secondary care treatment	Matching not possible
Current clinical stage	Mostly advanced (85%)	Secondary care patients receiving systemic treatment	Breakdown not available in HES, but representative according to clinical experts

Target population	MAVORIC trial	HES data	Matching
Number of prior systemic therapies	≥1	1 systemic therapy prescribed in secondary care	Selected to be conservative
Median number of prior systemic therapies received	3.0	1 systemic therapy prescribed in secondary care	
Prior systemic therapies	Chemotherapies Radiotherapy Phototherapy Biologic therapies	Chemotherapies Radiotherapy Phototherapy Biologic therapies (immunomodulating drugs, immunoglobulins)	Chemotherapies, phototherapies, radiotherapy, biologic drugs matching

Key: ECOG, Eastern Cooperative Oncology Group
Source: Kim et al 2018 (6)

As there were differences in the proportion of patients with MF vs. SS disease type between the trial and the HES datasets (see Table 5) and this is a known prognostic factor(3–5), the trial data were reweighted to match the proportion of MF and SS data in the HES data set, conducting an unanchored MAIC.

While age is also a known prognostic factor and potentially gender distribution can affect survival (3,4), they were very similar between the two data sources, therefore it was decided to only perform the matching on the proportion of MF and SS patients in order to not further reduce the sample size post-matching unnecessarily. The MAVORIC trial was reweighted to represent the distribution of MF and SS patients as observed in the HES data, therefore in UK clinical practice. Post-matching patient characteristics are provided in Table 6.

Table 6 Post-matching patient characteristics

	MAVORIC trial	HES data
N	**261**	**171**
% MF	87%	85%
% SS	13%	15%
Age (mean)	60.48	65
Males	61.4%	62%
Females	38.6%	38%

The effective sample size (ESS) post-match is 261. This is a reduction of 30%.

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in collaboration with:

Erasmus School of Health Policy & Management

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Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma – ERG comments on additional evidence

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

Additional evidence provided

Following on from reviewing the ERGs critique of the additional data submitted by the company post-ACM1 for ID1405, the NICE team went back to the company with some additional questions for clarification:

- Request to submit a model which enabled switching between the old and new analyses (issue 1)
- Request for an explanation for the methods of matching in the unanchored MAIC (issue 2)

In an email to the ERG on 30 November, two additional questions were asked:

- To provide further details on/ critique on the new carer utilities evidence provided (issue 3)
- To comment on the company response to ACD claims that end-of-life criteria is met with the use of new HES data (issue 4)

Issue 1: Model validation

The company submitted a version of their model file that allows for switching between the use of HES data and the originally used MAVORIC data. The ERG undertook some further validation exercises and identified an error in the company's updated model. The company had basically taken into account the cost of only one aSCT procedure (instead of two), by introducing an error in column BZ on the PF mogamulizumab sheet. Fixing that in the company's model, the new company's base-case ICER increased to £31,030.21 per QALY gained. The ERG noticed another change the company had undertaken. PFS distributions are changed from lognormal in the original model file to the generalized gamma (presumably to be in line with the NTFS distributions): the company had not informed the ERG of this change, and the cells for this change are hidden on the Controls sheet. Furthermore, this should not have an impact on model outcomes as PFS is only used in a scenario and NTFS is used instead. However, due to the company's approach to calculating proportion of patients in health states (Disease control surveillance and Disease control surveillance continued states), this change also has a small impact on the ICER. When changed in the ERG's replication of the company's base-case, the ICER (company's base-case as reproduced by the ERG) becomes £31,021.01 (instead of £30,642 in the previous ERG critique), which is very close to the company's ICER. The ERG considers that the company should be requested to correct their model file and provide analyses, including the ones using MAVORIC data (both with TSE and IPCW) and with and without carer disutilities, and the updated price.

Issue 2: MAIC

The company has provided a justification for the choice of variables included in an unanchored MAIC which used data from the MAVORIC trial and the HES database. As this is an unanchored MAIC, NICE DSU TSD 18 recommends that all known prognostic variables and treatment-effect modifiers are included in the matching model. This is not usually possible as the analysis can only adjust for those variables measured in both studies, i.e. an important prognostic variable might be in one data source but not the other. The company selected patients from the HES database with a recorded diagnosis of MF or SS to match with the inclusion criteria of the MAVORIC trial. The decision on which variables to include in the matching model was made based on the comparability and availability of baseline variable between the two studies. Matching was used for disease type (MF, SS) but no other variables. However the ERG considers that the model should have also included age and gender as even though they were stated to be similar, the difference in mean age in the post-matched population was larger than before matching.

The original company submission did not contain a MAIC comparing MAVORIC to HES data so the ERG has not been able to review the analysis methods or results. The additional information also did not contain any details of the methods used for the matching, to obtain outcome data from both of the studies, or the statistical models used to compare them. Therefore, it is not possible for the ERG to comment on the reliability of the MAIC methods or results.

Issue 3: Carer utilities

As stated in the original ERG report, *"a carer utility gain was included in the model using the utility value of the incremental difference between caring for a patient in second line of treatment versus caring for a patient in third line of treatment (utility values of 0.559-0.366=0.193) for the time spent in the 'Disease control'-state by using the incremental time spent by patients in the mogamulizumab arm versus the ECM arm"*. In response to the ACD, the company have provided additional scenarios exploring the impact of the inclusion of carer utilities:

1. Instead of using the carer utilities based on the vignette study, assuming that the difference between carers' utilities for the 'Disease control' and 'Subsequent treatments' health state is the same as the difference observed for the patients in the trial
2. Directly including carer utility values for disease control (0.56) and subsequent treatment (0.37) for the respective health states in the model

The ERG considers that the company's base-case implementation is preferred, as it used carer utilities as opposed to patients' utilities (Scenario 1) and it is conservative compared to using the small utility values of carers directly (Scenario 2).

The caveat around inclusion of carer disutilities, lack of methodological guidance and when they should be included, remains. For this reason, the ERG's base-case excludes them, but the ERG considers that if they should be considered the company's base-case implementation is probably most appropriate (and hence presented as an ERG scenario).

Issue 4: End-of-life criteria

It should be noted that *"in the CS, the company did not include any statement regarding mogamulizumab meeting the end of life criteria defined by NICE"* (see section 8 of the ERG report).

NICE defines two end-of-life criteria:

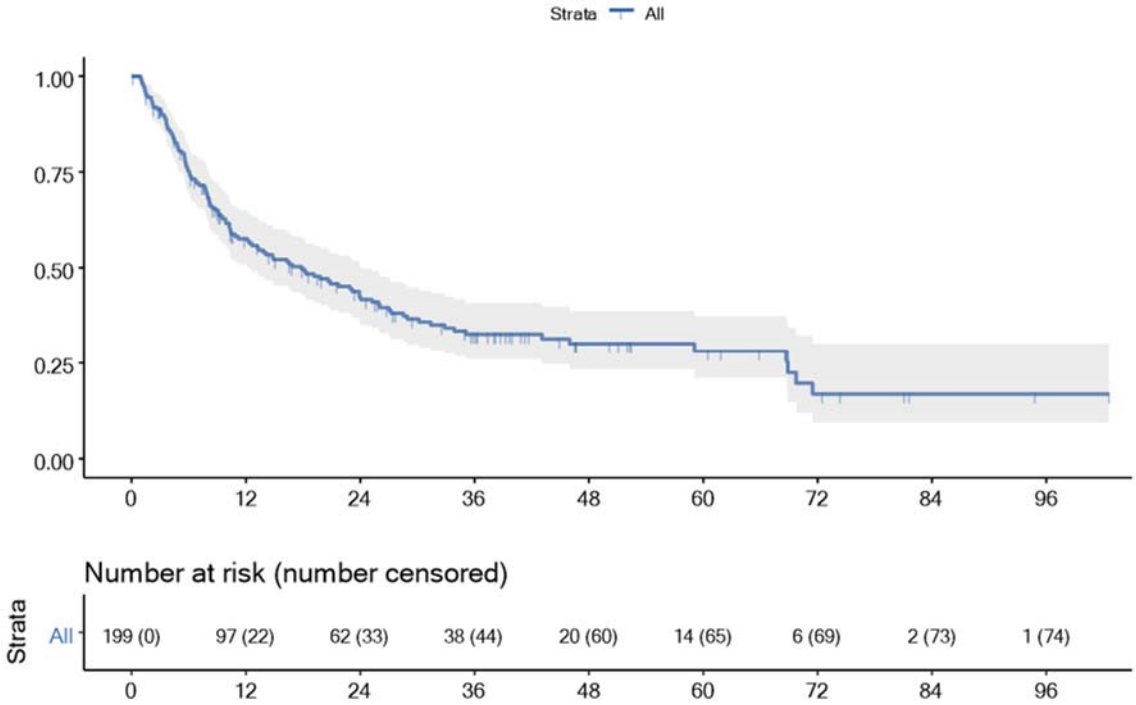
1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months
2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

As detailed below, the additional evidence indicate that these criteria have been met.

Criterion 1: Life expectancy of less than 24 months

In response to the ACD, the company provided new evidence including HES data on overall survival (see Figure 1). Patient numbers halve by end of the first year and fall below 40 by the end of year 3. Median survival was 17.83 months.

Figure 1: HES data on OS of UK patients



In addition to the *"median life expectancy of the UK current clinical practice in the HES database"* (17.83 months), the company reported the *"mean extrapolated discounted and undiscounted life-years in the ECM arm of the cost-effectiveness model"* (2.87 and 3.31 years, respectively).

As detailed in section 4.2.5.3 of the ERG report, *"overall survival (OS) was an exploratory outcome of the MAVORIC trial. Updated OS results using a data cut-off of 2 March 2019 were provided in the appendices of the CS and the clarification letter response. MAVORIC was not powered to estimate OS and maturity was not achieved. Therefore, there is some uncertainty associated with the OS results (…) The median OS was 51.7 months for mogamulizumab and 58.4 months for vorinostat with a corresponding HR of 1.13 (95% CI 0.80 to 1.60) showing no statistically significant difference in OS"*.

As summarised in section 5.2.6 of the ERG report, *"the main sources of evidence on treatment effectiveness used for intervention and comparators are: the MAVORIC trial, which informs OS, NTFS, PFS, ToT, proportion of patients undergoing aSCT after subsequent treatments and dose intensity; data used in TA577 from the London supra-regional centre to inform estimates of disease-free survival (DFS) and OS for patients undergoing aSCT; and expert opinion to inform proportions of patients undergoing aSCT after current treatment (mogamulizumab or ECM)"*. Results on overall survival are discussed in section 5.2.6.1 of the ERG report.

The data obtained from the HES database can be considered the best source of evidence and criterion 1 of the end-of-life criteria appears to have been met.

Criterion 2: Extension to life of at least an additional 3 months

According to the company, *"the mean additional discounted and undiscounted months from the cost-effectiveness model compared to current NHS treatments are 44.6 and 61.9 months"*.

As stated above, "*the median OS was 51.7 months for mogamulizumab and 58.4 months for vorinostat*", i.e. an extension to life of at least an additional 3 months is supported by the available trial data.

Comments on Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma – ERG's critique and ERG comments (post-ACD)

Kyowa Kirin (KK) has received from NICE the ERG's post-ACD critique (27th November 2020) and ERG comments on the additional clarification (10th December 2020) on the additional analyses (submitted by KK on 19th August 2020) and the additional clarifications (submitted 27th November 2020).

KK is grateful for NICE for encouraging the continuous engagement in this debilitating and fatal rare end of life condition and would like to make the following observations.

The evidence

Mycosis fungoides (MF) and Sézary syndrome (SS) are orphan indications (approximately 125 patients/year in advanced stage)[1] with limited and often off-label or recycled treatment options for already heavily pre-treated patients. The clinical trial evidence (MAVORIC) provided for mogamulizumab is based on the largest phase III randomised clinical trial (n=372) in Cutaneous T-Cell Lymphoma (CTCL), with the first ever inclusion of Sézary syndrome patients. It is the most robust clinical evidence to date in this rare disease.

At the recommendation of the Committee, Kyowa Kirin has also conducted an unanchored indirect comparison of mogamulizumab directly with data from patients from the UK's Hospital Episodes Statistics (HES) database. This analysis avoids the uncertainties flagged by the Committee as it provides a direct comparison against current UK clinical practice, includes no crossover and the analysed target population reflects the current UK MF/SS population. The HES data is an administrative dataset that includes all MF/SS patients treated in secondary care in the NHS in England within the last 10-year period (2009-19) with this very, debilitating and fatal rare haematological malignancy resulting in a sample size of 198. The patients of the HES analysis have been selected to match the target population in the MAVORIC trial and the remaining difference (MF/SS distribution) was adjusted for.

The HES data for the relevant patient population was not available at the time of the original submission. The additional evidence provided by KK based on the HES data represents UK clinical practice, and KK welcomes the ERG decision that based on this information both end-of-life criteria have been met. However, as the ERG mentions, there are some discrepancies between the Company and the ERG base cases.

Discrepancy between Company and ERG base cases

HES-based vs. vorinostat-based analyses

The ERG base-case, by returning to MAVORIC based analyses, contradicts the NICE committee discussions and concerns about the use of vorinostat as a comparator and the

high levels of cross-over. As the ERG itself mentions in their comments on the additional evidence (10th December 2020) "*The data obtained from the HES database can be considered the best source of evidence*".

Kyowa Kirin has provided all information and has responded to all clarification questions in detail. Therefore, the ERG's conclusion in the critique, that "*the methods used to analyse these data have not been clearly described and the resulting survival estimates are uncertain*" does not reflect the fact that all information requested was provided, and the results are based on the one hand, the largest clinical trial in CTCL, and on the other hand, survival information on all patients treated in the NHS in England over a 10-year period, an exceptional amount of data in such a rare condition with results validated by highly experienced clinical experts.

ERG also mentioned that age and gender should have been included in the matching despite them being similar between the MAVORIC trial and the HES data, due to the mean age difference increasing after matching. While the age difference increased, it was only by 2.5 years, and the gender difference decreased by 3.4%, neither of which is a magnitude that could be expected to influence results. Altogether nine variables were considered (see Table 5 in the 27 November response to ERG questions), three used in defining the inclusion/exclusion criteria (stage, number and type of prior therapies), three considered for matching (age, gender, disease type), and three were not available from the HES database (ECOG performance status, race, time from diagnosis). KK is happy to provide any further details required around the methods used for matching.

Carer utilities

KK agrees with the ERG's conclusion that "that the company's base-case implementation is preferred, as it used carer utilities as opposed to patients' utilities (Scenario 1) and it is conservative compared to using the small utility values of carers directly (Scenario 2)". Caregiver burden is extremely important to capture in this disease. The visual nature of the disease and associated pain and discomfort and intensive care required in the largest organ of the body, from head to toe, does significantly impact the family and carer context for CTCL patients as their diseases progresses. This have been supported by:

- the literature review (provided in the Manufacturer submission Appendix H and summarised in sections B.1.3 and B.3.4.3),
- the vignette study by Williams et al. (2020) which showed significant reduction in carer utility after loss of disease control on second line treatment,
- the patient and clinical expert submissions and
- the description of patient representatives at the Committee meeting in describing the difference between their current disease control health state with mogamulizumab and uncontrolled disease without mogamulizumab.

While there are discussions about the correct implementation of carer utilities, Kyowa Kirin, as described by the ERG, has used a conservative approach that avoided the potential pitfalls listed by ERG.

Overall survival: Crossover adjustment for the MAVORIC-based analyses

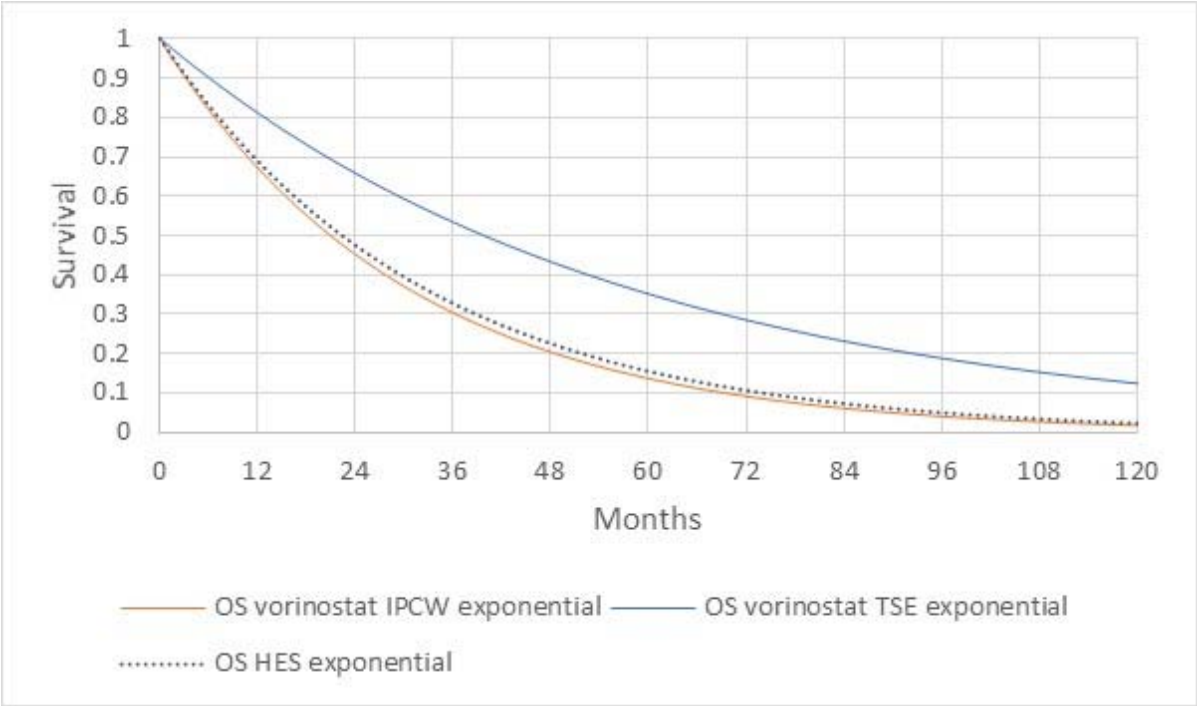
ERG disregards the validation the HES analyses (representing NHS clinical practice) provides for the IPCW crossover adjustment method and the use of the two-stage estimation (TSE) method is not in line with the evidence. KK has provided evidence which all supports the use of IPCW including 3 observational studies, the UK HES database analyses based on all MF/SS patients treated in NHS England, clinical expert opinion (ID1405_mogamuliumab for treating MF or SS CTCL_Document B_FINAL.doc January 2020 Pages 105-107; ID1405 mogamulizumab Clarification letter to PM_MASTER_updated marking 24022020.doc page 59; ID 1405 Mogamulizumab Technical engagement response_5th June 2020_ACIC Final.doc pages 2-6.). While all analyses have inherent uncertainty, this is an exceptional amount of evidence submitted for this orphan drug.

The ERG has held, that TSE would be the best approach, however, have not yet provided any evidence for this decision (the clinical implausibility of an interim result was contested by clinical experts at the Committee meeting). TSE is not considered gold standard methodology, where only deviation from it requires justification. Both TSE and IPCW are approaches that make assumptions and the choice between them should be based on which is more appropriate given the evidence. The ERG has not justified the use of the TSE method as base case.

While Kyowa Kirin recognises that both analyses have limitations, the IPCW MAVORIC and the HES-based analyses support each other as described and depicted in ID1405 Mogamulizumab additional ACD requested analysis report_Kyowa Kirin_v1.0 Final 19th August 2020.doc; page 15-16 and Figure 8 reproduced below as Figure 1. We would like to understand what evidence the ERG has used to support use of the TSE method.

The choice of TSE not only contradicts the evidence, but also the ACD itself, which stated that “the results from the cross-over adjustment methods represent the upper and lower range of plausible overall survival in the standard care arm”, therefore the results should be presented for the two cases set out by the ACD: results with crossover adjustment with TSE and IPCW, both of these should be presented as base cases.

Figure 1 Comparison of HES data exponential extrapolation with the OS predictions of the previous analyses' two crossover adjustment methods (Figure 8 in the ID1405 Mogamulizumab additional ACD requested analysis report_Kyowa Kirin_v1.0 Final 19th August 2020.doc)

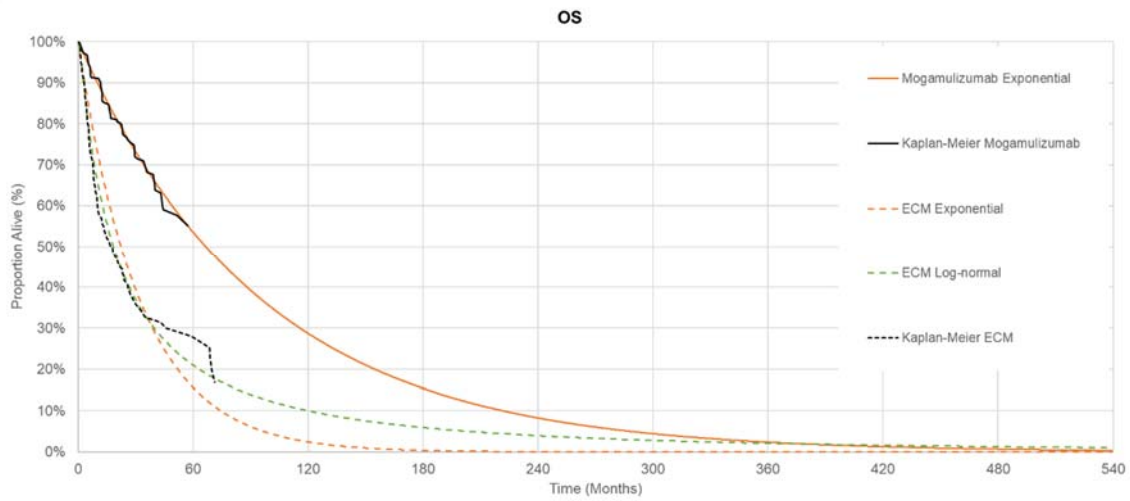


Overall survival: Extrapolation of comparator arm

For the comparator OS based on the HES data "ERG prefers the use of the lognormal distribution, which provides the second-best statistical fit", while keeping exponential for the mogamulizumab arm. This choice means that the OS curves cross, and slightly higher proportions patients on current treatments are predicted to survive than patients receiving mogamulizumab after 30 years (as described in *ID1405 Mogamulizumab additional ACD requested analysis report_Kyowa Kirin_v1.0 Final 19th August 2020.doc; page 14)*. But more importantly, the lognormal distribution predicts 21% of patients to be alive at 5 years (see Figure 2). As shown in the slides (slide 22) presented during the first committee meeting, the ERG's own clinical advisor estimated the proportion of patients expected to be alive after 5 years to be around 10%. This estimate is lower even than the proportion predicted to be alive by the exponential distribution used by Kyowa Kirin.

While the ERG is entitled to change their mind compared to the ERG Report, this change requires justification. ERG's argument was that different distributions should not be used for the two arms since there are insufficient data to support it. The ACD stated that "The committee agreed that the company would need to make a strong case to justify using different parametric curves in each treatment 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.

Figure 2 Overall survival extrapolations in model



aSCT after current treatment

The ERG continues to exclude aSCT after current treatment from the modelling "to avoid double-counting of survival benefit of patients in MAVORIC who would have been eligible to receive aSCT but did not receive it due to the study protocol". There is an inconsistency with the original ERG report which acknowledged that there was only a potential for bias and concluded that it was "difficult to assess the impact on the ICER". Kyowa Kirin continues to question the "double-counting" argument. However, if the hypothetical argument is accepted, then the ERG's model biases results towards the comparator arm. The HES survival data used to inform the treatment pathway of patients not receiving aSCT includes the impact of aSCT after current treatment for 5.2% of patients as the data was available for the whole cohort only (i.e., it was not possible to exclude patients who have received an aSCT from the HES data). Therefore, there is an inconsistency in the ERG's base case:

- survival information for those who received an aSCT in the MAVORIC trial is excluded for the estimation of the mogamulizumab arm's patient pathway for those not receiving an aSCT, but
- survival advantage for patients receiving aSCT is included for the comparator arm's estimate.

Having aSCT for the select few patients with MF and SS is standard of care in the NHS and therefore, to exclude this curative intent treatment option after receiving current treatment is not in line with clinical practice in the NHS.

Additional considerations

Kyowa Kirin would also like to highlight the additional considerations regarding the inaccuracies and issues in the consideration of the evidence highlighted below.

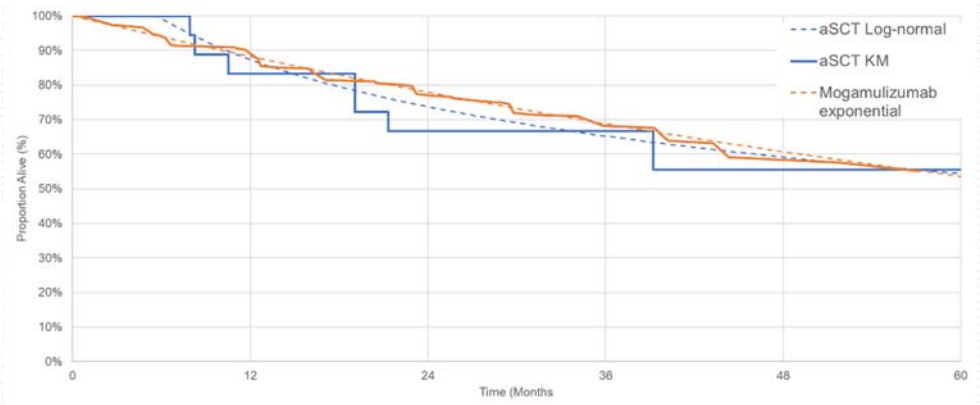
The ERG base case is not in line with the evidence

- "The ERG continues to exclude aSCT after current treatment from the modelling to avoid the double-counting of survival benefit of patients in MAVORIC"

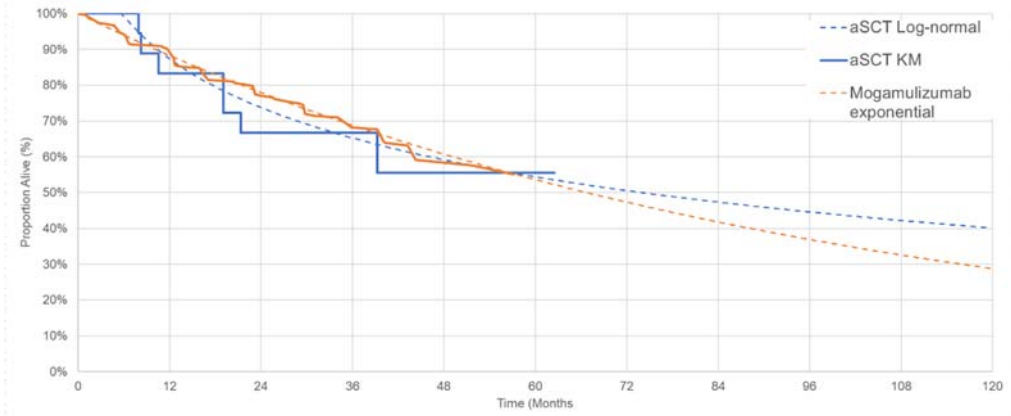
- Patients in MAVORIC were not allowed to receive aSCT after current treatment. To avoid the double counting three separate patient flows were included in the model.
- aSCT in itself is associated with high mortality shortly after the procedure, therefore with its inclusion, the short-term risk would manifest itself during the trial period, while the long-term survival benefits would not be captured in the MAVORIC trial data. Therefore, it is not clear which way the immediate bias goes for mortality. As shown in Figure 3, short-term mortality is higher for patients receiving aSCT compared to patients who were on mogamulizumab and did not receive aSCT in the MAVORIC trial. Since aSCT is only considered for responders, leaving the patients in the analysis who theoretically could have received aSCT after mogamulizumab in clinical practice, but did not receive aSCT in the MAVORIC trial due to protocol restrictions could bias results in favour of mogamulizumab. However, adding in the patient flow of those who did receive aSCT after current treatment based on outside data sources, biases the results against mogamulizumab in the initial 5 years, as these patients have worse survival compared to those who did not have aSCT. Therefore, the overall impact of this assumption is uncertain.

Figure 3 Naïve comparison of survival after aSCT (including time-lag since randomisation) and the mogamulizumab arm in MAVORIC

a) During the trial observation period



b) Long-term extrapolation



- A scenario analyses based on all patients and based on only on patients who have never received an aSCT was presented, showing the impact of this assumption to be minimal *(a difference of less than £300/QALY in the ICER) (ID1405 mogamulizumab Clarification letter to PM_MASTER_updated marking 24022020.doc; page 69-70).*
- The ERG has requested to implement a scenario "by excluding a proportion of the best responders, and therefore increasing the proportions of patients with partial response" to account for this perceived double counting of effect. A scenario analysis was presented down-weighting the patients who demonstrated a complete/partial response according to the proportion of patients who were modelled as receiving aSCT (in excess of those observed in the trial), and again, the impact on the estimated survival curve for those who did not receive aSCT in the model was minimal (*ID 1405 Mogamulizumab Technical engagement response_5th June 2020_ACIC Final.doc pages 14-15).*
- As mentioned above, the HES comparator arm overall survival estimate used for the patient pathway without aSCT includes the survival impact of the 5.2% of patients who had an aSCT in HES, therefore if one accepts the "double-counting" argument, the ERG's base case biased in favour of the comparator arm.

Inaccuracies

- "For NTFS, the company chose the generalised gamma for both treatment arms […] and only provided a visual fit for the mogamulizumab arm"
  - This is incorrect: Table 6 (page 17) in the submission provides the fit for both treatment arms (*ID1405_mogamuliumab for treating MF or SS CTCL_Document B_FINAL.doc January 2020)*
- The ERG stated that the company did not provide evidence for the "grounds for considering one or more variables as effect modifiers on the appropriate transformed scale"
  - This was submitted in the Original Manufacturer submission, and extended in the Additional analysis document, then reiterated in the response for additional clarifications
  - The ACD itself already considered this evidence and criticized the imbalance of MF/SS between MAVORIC trial and HES data
- The ERG stated that "Quantitative evidence must be presented that population adjustment would have a material impact on relative effect estimates due to the removal of substantial bias" which the company did not provide
  - This was submitted in the Original Manufacturer submission, discussed when comparing with HES by the Committee itself, then reiterated in the response for additional clarifications

Confidentiality

- CiC marking is incorrect in Table 1 of the ERG critique leaving CiC information unmarked
    - All Total costs should be marked CiC (both mogamulizumab and ECM arms)
    - Incremental costs and ICERs should not be marked CiC

Model validation

The ERG requested an updated company model, that matches exactly their results, and includes all scenarios. KK is now providing this updated model, however compared to the ERG version, a few very minor corrections have been made. These include the following:

- the ERG model assumes aSCT happens at 25 weeks for the comparator arm too to account for wash-out period (ERG correction no. 2), but since a wash-out period is not required for treatments included in the comparator arm, the company model assumed aSCT happens at 18 weeks in this arm;
- the ERG model assumes occurrence of AEs is linked to administrations.

However, these differences are very minor, especially compared to the structural assumptions contested by the ERG.

Table 1 below provides an overview of the differences in assumptions between the ERG's base case and the company base case, while

Table 2 provides the impact of these structural assumptions on the results.

Table 1 Differences in assumptions between ERG and company model

Aspect of the CEM	ERG base case	Company base case	Evidence
Source of efficacy data for comparator arm	Crossover adjusted (TSE method) vorinostat data from MAVORIC trial	10-year NHS England data of all patients (HES database) using MAIC	• Based on the ACD recommendations • HES data reflects current clinical practice, current patient population, does not require crossover adjustment • HES study designed to include all NHS treated (England) patients in target population using inclusion/exclusion criteria based on MAVORIC trial with longest possible follow-up • Remaining difference of MAVORIC data (MF/SS distribution) matched to reflect current patient population • ERG stated: "The data obtained from the HES database can be considered the best source of evidence"
aSCT after current treatment	Excluded	Included	• aSCT after current treatment is current NHS clinical practice as seen in HES data and clinical expert survey • It was not allowed in MAVORIC trial due to PFS as the primary end point, thus effects of aSCT are not counted in mogamulizumab arm • Conservative as benefit of aSCT is double counted in comparator arm • Effect of hypothetical scenario of better responding patients having no benefit from response other than aSCT was explored in scenario analyses with minimal effect on ICER
Carer utilities	Excluded	Included with conservative implementation	• MF/SS places exceptional burden on carers as noted by patients and clinical experts • With recent data, Williams et al 2020 showed statistically significant increase in carer utilities after loss of disease control • ERG agreed that the conservative implementation by KK is the most appropriate as it only takes into account small portion of the effect of carer burden (full implementation in scenario analyses reduced ICER by an additional 34%)
Crossover adjustment for the MAVORIC-based analyses	TSE	IPCW	• 3 observational studies (from UK and North America) support the predictions of the IPCW adjustment

			• The UK HES database analyses based on all MF/SS patients treated in NHS England supports the use of IPCW adjustment • Clinical expert opinion, including the ERG's clinical expert, supports the predictions of the IPCW adjustment
Extrapolation of OS	Different parametric models for the two arms for HES based analyses, but not for MAVORIC-based analyses	Same parametric models for the two arms in both analyses as per ERG request	• The ACD stated that "The committee agreed that the company would need to make a strong case to justify using different parametric curves in each treatment arm." • As per ACD statement, strong justification needs to be provided by the ERG to use different models in the HES-based analyses also

Table 2 Impact of structural assumptions on deterministic results (correcting for identified errors in both ERG and company models)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Assumptions
HES analyses with ERG preferences						
HES analysis with all ERG preferences						No carer utilities
Mogamulizumab	[redacted]	4.42	£86,864	2.27	£38,274	No aSCT after current treatment for either arm
ECM	[redacted]	2.15				OS ECM: lognormal / OS moga: exponential
						NTFS ECM: gen gamma / NTFS moga: lognormal
HES analysis with ERG preferences, but OS ECM exponential						No carer utilities
Mogamulizumab	[redacted]	4.42	£92,536	2.72	£33,961	No aSCT after current treatment for either arm
ECM	[redacted]	1.69				**OS ECM: exponential** / OS moga: exponential
						NTFS ECM: gen gamma / NTFS moga: lognormal
HES analysis with ERG preferences, but with aSCT after current treatment						No carer utilities
Mogamulizumab	[redacted]	4.55	£82,995	2.21	£37,590	**aSCT after current** treatment **for both arms**
ECM	[redacted]	2.35				OS ECM: lognormal / OS moga: exponential
						NTFS ECM: gen gamma / NTFS moga: lognormal
HES analysis with ERG preferences, but with incremental carer utilities						**With incremental carer utilities for additional disease control only**
Mogamulizumab	[redacted]	4.55	£86,864	2.40	£36,233	No aSCT after current treatment for either arm
ECM	[redacted]	2.15				OS ECM: lognormal / OS moga: exponential
						NTFS ECM: gen gamma / NTFS moga: lognormal

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Assumptions
HES analyses with company preferences						
HES analysis with all company preferences						With incremental carer utilities for additional disease control only aSCT after current treatment for both arms OS ECM: exponential / OS moga: exponential NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	4.75	£88,034	2.84	£31,030	
ECM	[redacted]	1.92				
HES analysis with company preferences, but with no carer utilities						**No carer utilities** aSCT after current treatment for both arms OS ECM: exponential / OS moga: exponential NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	4.58	£88,034	2.66	£33,043	
ECM	[redacted]	1.92				
HES analysis with company preferences, but no aSCT after current treatment						With incremental carer utilities for additional disease control only **No aSCT after current treatment for either arm** OS ECM: exponential / OS moga: exponential NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	4.63	£92,178	2.94	£31,353	
ECM	[redacted]	1.69				
HES analysis with company preferences, but OS ECM lognormal						With incremental carer utilities for additional disease control only aSCT after current treatment for both arms **OS ECM: lognormal** / OS moga: exponential NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	4.75	£82,663	2.40	£34,375	
ECM	[redacted]	2.35				
HES analysis with company preferences, but both OS lognormal						With incremental carer utilities for additional disease control only aSCT after current treatment for both arms **OS ECM: lognormal** / **OS moga: lognormal** NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	5.50	£93,544	3.15	£29,695	
ECM	[redacted]	2.35				

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Assumptions
MAVORIC -based analyses						
MAVORIC -based analysis with all ERG preferences						Cross-over adjustment method: TSE No carer utilities No aSCT after current treatment OS ECM: exponential / OS moga: exponential NTFS ECM: gen gamma / NTFS moga: lognormal
Mogamulizumab	[redacted]	3.63	£68,547	0.85	£80,555	
ECM	[redacted]	2.78				
MAVORIC -based analysis ERG preferences, but with IPCW cross-over adjustment						**Cross-over adjustment method: IPCW** No carer utilities No aSCT after current treatment OS ECM: exponential / OS moga: exponential NTFS ECM: gen gamma / NTFS moga: lognormal
Mogamulizumab	[redacted]	3.63	£87,218	2.04	£42,812	
ECM	[redacted]	1.60				
MAVORIC based analysis with all company preferences						Cross-over adjustment method: IPCW With incremental carer utilities for additional disease control only aSCT after current treatment OS ECM: exponential / OS moga: lognormal NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	4.66	£93,300	2.86	£32,634	
ECM	[redacted]	1.80				
MAVORIC based analysis company preferences, but with OS moga exponential						Cross-over adjustment method: IPCW With incremental carer utilities for additional disease control only aSCT after current treatment OS ECM: exponential / **OS moga: exponential** NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	4.02	£83,870	2.23	£37,690	
ECM	[redacted]	1.80				
MAVORIC based analysis company preferences, but with no carer utilities						Cross-over adjustment method: IPCW **No carer utilities** aSCT after current treatment OS ECM: exponential / OS moga: lognormal NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	4.48	£93,300	2.68	£34,809	
ECM	[redacted]	1.80				
MAVORIC based analysis company preferences, but with no aSCT after current treatment						Cross-over adjustment method: IPCW With incremental carer utilities for additional disease control only **No aSCT after current treatment** OS ECM: exponential / OS moga: lognormal NTFS ECM: gen gamma / NTFS moga: gen gamma
Mogamulizumab	[redacted]	4.53	£97,311	2.93	£33,185	
ECM	[redacted]	1.60				

References

[1] National Institute for Health and Care Excellence. Technology appraisal: Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma (ID1405). NHS England budget impact analysis submission. 6 Jan 2020

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Maastricht University

Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma – Addendum (post-ACD)

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Rider on responsibility for report

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Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Mickaël Hiligsmann, Ben Wijnen, Charlotte Ahmadu, Steve Ryder and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker, Regina Leadley and Vanesa Huertas Carrera acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Isabel Syndikus provided clinical expertise. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Company's response and updated cost effectiveness results

The ERG appreciates that the company have corrected the error in their model and provided a wide range of analyses including ERG preferences. The ERG is satisfied that the company's new results are likely correct.

Comparator data based on MAIC using HES data

The company criticise the ERG preference for the use of the MAVORIC trial data for the comparison with standard care. They also claim that there were inaccuracies in the ERG critique of the MAIC, citing the ACD and the original company submission. However, the ERG would point out that the MAIC was not conducted until after the ACD. Most importantly, although more information has been provided by the company in terms of the variables considered and chosen for adjustment, several apparently key variables, such as ECOG PS, remain unadjusted and no evidence has been provided as to the likely effect on any bias. As the ERG stated, quoting TSD 18: "Submissions using population-adjusted analyses in an unconnected network need to provide evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects, and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison" (p.62)

Of course, the MAVORIC trial data are also limited and therefore it is a matter of judgement as to which of the two data sources is preferable.

Cross-over adjustment methods

If using MAVORIC, analyses have to be adjusted for cross-over. It is worth noting that the aim of cross-over adjustment is not to estimate effectiveness of a different treatment (here ECM) in a different population (UK clinical practice), but instead it is to estimate treatment effectiveness (of vorinostat) of the patients in the trial population if they had not crossed over. It is then worth reiterating that unadjusted OS for patients allocated to vorinostat was actually longer than OS for patients allocated to mogamulizumab. Using the RPSFTM method for cross-over adjustment, the difference between vorinostat and mogamulizumab OS became even larger, as RPSFTM assumes that treatment multiplies survival time. These results did not appear plausible to clinical experts and the RPSFTM was ruled out. Based on the ERG's clinical expert, the IPCW method also did not result in plausible OS estimates considering the observed MAVORIC data. Both TSE and IPCW rely on assumptions. As stated in the ERG report regarding the IPCW method: *"Based on the information provided by the company it was not possible to fully assess how these weights were obtained. However, it appears that some* "extreme weights" *were obtained for those patients randomised to vorinostat that did not switch but were potentially eligible for switching.*[58] *The company did not provide the proportion of patients who did not switch out of those eligible for switching, which, if low, is an indicator for the IPCW method potentially being biased. The proportion of patients switching in the advanced population was 71.5% (133 patients in that subgroup).*[50] *According to TSD 16 and other literature, weights larger than 10 could mean that the IPCW method produces biased results.*[61, 76, 77] *This, paired with a potentially high proportion of patients that switched compared to those eligible for switching, may indicate that the use of IPCW could be inappropriate in this setting."*

With regards to the TSE method, it was stated in the ERG report that: *"The ERG acknowledges that the TSE method not only requires the* "no unmeasured confounders" *assumption (as the IPCW method does) but also requires the existence of a* "secondary baseline"*, that is the time after which switching was allowed.*[1] *Progression status was one of the main criteria for switching, and the majority of patients appeared to have switched because of progression, which supports the existence of a secondary baseline. Furthermore, for the TSE method, the* "no unmeasured confounders" *assumption is important*

at the time of the secondary baseline, which may be more easily satisfied than at other time points where other variables may not have been measured (required for the IPCW method).”

It appears that the important assumptions may be fulfilled for the TSE method whilst doubts remain over the IPCW method. In addition, the ERG clinical expert considered TSE results most plausible. The TSE method is therefore used in the ERG base-case, and IPCW method in a scenario.

Survival analysis

The ERG wishes to clarify that the approximately 10% OS at 5 years were mis-attributed to the ERG clinical expert. The ERG has not changed its mind. The distribution with the second-best model fit was chosen because the one with the best model fit was deemed clinically implausible. To re-iterate the argument made for selection of cross-over adjustment methods, the aim of selection of distributions to model OS is not to estimate effectiveness of a different treatment (here ECM) in a different population (UK clinical practice), but instead it is to estimate treatment effectiveness (of vorinostat) of the patients in the trial population.

Conclusion

The ERG considers that substantial uncertainty remains about the long-term overall survival of mogamulizumab over established clinical management. Whilst there are limitations to the MAVORIC study that cannot be addressed fully, such as the bias introduced by cross-over and the comparator not reflecting UK clinical practice, there are also limitations to the use of HES data, namely the lack of clarity on whether a comparison between the mogamulizumab arm and the HES data is appropriate.