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]

Contents:

The following documents are made available to consultees and commentators:

1. **Appeal panel decision**

2. **New evidence provided by Kyowa Kirin Ltd post-appeal**
   a. Refined analyses
   b. Refined analyses appendix

3. **ERG post-appeal addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on mogamulizumab for previously treated mycosis fungoides and Sezary syndrome [ID1405]

Decision of the panel

Introduction

1. An appeal panel was convened on 10 May 2021 to consider an appeal against NICE's final appraisal document, to the NHS, on mogamulizumab for previously treated mycosis fungoides and Sezary syndrome.

2. The appeal panel consisted of:

• Paddy Storrie	Chair
• Dr Mark Chakravarty	Non-executive director, NICE
• Dr Biba Stanton	Health service representative
• Adrian Griffin	Industry representative
• Alan Thomas	Patient representative

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered appeals submitted by Kyowa Kirin (the company), Lymphoma Action and Leukaemia Care (a joint appeal from these patient groups) and the UK Cutaneous Lymphoma Group (UKCLG).

5. Kyowa Kirin was represented by:

- Richard Johnson — General Manager
- Linda McNamara — Market Access Director
- Jan-Paul Rosen — Medical Director
- Edit Remak — Director, Health Economics
- Dr Adela Williams — Legal representative

6. Lymphoma Action & Leukaemia Care were represented by:

- Ropinder Gill — Chief Executive, Lymphoma Action
- Vicki Gregory — Senior Medical Writer, Lymphoma Action
- Stan Cummins — Patient representative
- Zack Pemberton-Whiteley — Chief Executive, Leukaemia Care
- Charlotte Martin — Patient advocacy manager Leukaemia Care

7. UKCLG were represented by:

- Professor Sean Whittaker — Professor of cutaneous oncology, Guy's and St Thomas' NHSFT
- Professor Richard Cowan — Consultant in Clinical Oncology and Director of The Christie School of Oncology
- Dr Stephen Morris — Consultant in Clinical Oncology, Guy's and St Thomas' NHSFT

8. Professor Cowan declared that he had in the past consulted for Kyowa Kirin.

9. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

- Helen Knight — Programme Director, NICE
- Ross Dent — Associate Director, NICE
- Professor Stephen O'Brien — TA Committee Chair, NICE
- Robert Wolff — ERG member, Kleijnen Systematic Reviews

10. The appeal panel's legal adviser Stephen Hocking was also present.

11. The following members of the NICE appeal panel for highly specialised technologies and technology appraisals were present as silent observers during the hearing.

• Professor Jon Cohen	Appeal panel observer (Panel chair)
• Dr Paul Robinson	Appeal panel observer (Industry)
• Jackie Fielding	Appeal panel observer (Non-executive director, NICE)
• Sir Bruce Keogh	Appeal panel observer (Non-executive director, NICE)

12. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

13. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in light of the evidence submitted to NICE.

14. The Vice Chair of NICE (Mr Tim Irish) in preliminary correspondence had confirmed that:

- Kyowa Kirin had potentially valid grounds of appeal as follows: Ground 1a and Ground 2
- Lymphoma Action & Leukaemia Care had potentially valid grounds of appeal as follows: Ground 1a and Ground 2
- UKCLG had potentially valid grounds of appeal as follows: Ground 2

15. The appraisal that is the subject of the current appeal provided advice to the NHS on mogamulizumab for previously treated mycosis fungoides and Sezary syndrome.

16. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Richard Johnson on behalf of Kyowa Kirin, Zack Pemberton-Whiteley on behalf of Leukaemia Care, Stan Cummins on behalf of Lymphoma Action, Prof Richard Cowan on behalf of UKCLG and Prof Stephen O'Brien on behalf of the appraisal committee.

17. The appeal panel were very grateful for Mr Cummins' eloquent and moving description of his experience as a patient with this condition.

Appeal by Kyowa Kirin

Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

Appeal Ground 1a.1: The Committee's decision that allogenic stem cell transplant (aSCT) should not be included in the economic modelling for mogamulizumab because aSCT had not been permitted in the MAVORIC trial is unfair

18. Linda McNamara, for Kyowa Kirin stated that it is important to recognise that even issues which have a small effect on the incremental cost effectiveness ratio (ICER) may act cumulatively to have an impact on the final decision in an appraisal.

19. Dr Adela Williams, for Kyowa Kirin, said that mogamulizumab could be a bridge to transplant in some patients. Whilst this is uncommon, it is important because transplant is potentially curative. In the final appraisal document (FAD), the committee admits that this is an option, but nevertheless did not model it because transplant was not used in the trial and they were concerned about "double counting". Dr Williams stated that the committee addressed this theoretical risk in a scenario

analysis from the Evidence Review Group (ERG) but there was no indication that this was taken into account. She stated that the approach taken in this appraisal was inconsistent with that taken in the appraisal of brentuximab, and that this different approach required explanation and justification.

20. In response to questions from the panel, Dr Stephen Morris, for UKCLG agreed that aSCT is discussed with patients with progressive disease but is only suitable for a small number, perhaps 5-10%.

21. Prof O'Brien, for the appraisal committee, noted that clinical experts had advised the committee that aSCT is not commonly used. He said that including aSCT did not make a substantial difference to the ICER.

22. Robert Wolff, for the appraisal committee, said that the ERG did indeed consider this issue and provided data which was discussed at the committee meeting (as evidenced by the committee meeting slides).

23. Ross Dent, for NICE, said that analyses which included aSCT only affected the ICERs by a few hundred pounds and still gave ICERs >£30,000.

24. In response to questions from the panel, Prof O'Brien said the committee had not considered the issue of consistency with previous appraisals in detail because aSCT was uncommon in this patient group and made a minimal difference to the ICERs. He did not recall discussing the way aSCT was handled in the brentuximab appraisal but noted that the use of aSCT was more common in the care pathway relevant to that appraisal.

25. Edit Remak, for Kyowa Kirin, stated that it seemed strange to disregard a treatment given to up to 10% of patients, and that all benefits of treatment should be incorporated into the evaluation.

26. Dr Williams, for Kyowa Kirin, said that there was no evidence in the FAD that the committee had indeed considered the scenario analysis provided by the ERG, nor an explanation of why it was rejected.

27. Ross Dent, for NICE, said that the committee are presented with many scenario analyses and not all of these can be discussed in the FAD.

28. The appeal panel concluded that the committee had not refused to consider aSCT at all. The committee acknowledged that some patients might go on to aSCT, examined scenario analyses incorporating this and then decided (with reasons) not to include this in the base case. The panel judged that the level of detail provided about this decision in the FAD was sufficient, bearing in mind the relatively small effect of this issue on the ICERs. Regarding consistency with TA577, the panel noted that while NICE processes require a broad consistency between appraisals, the requirement for consistency (or explanation for inconsistency) cannot be set too high. In this case TA577 dealt with CD-30 positive cutaneous T cell lymphoma and relied on a different trial to this appraisal, so the panel judged that there was no relevant requirement for consistency in this instance.

29. The appeal panel therefore dismissed the appeal on this point.

Appeal Ground 1a.3: The Committee's decision not to include carer utilities in the economic model is based on conclusions which are inconsistent with NICE's Methods Guide and inadequately explained

30. Dr Williams stated that the committee's decision not to include carer utilities in the modelling was both inconsistent with the methods guide and inadequately explained. She explained that this condition has a substantial impact on carers because of the need for nursing support and social isolation. The ERG considered the carer utilities provided by the company and expressed no concern about the use of vignettes to generate data. The company was therefore surprised at the committee's assertion that the utilities were "implausibly large", a statement that appears to be based on intuition rather than evidence.

Dr Williams disagreed with the committee's justification that the approach used by the company was not "in line" with the methods guide. In fact, the company's approach (using a vignette study) was consistent with the methods guide, which recommends evaluation of public preferences in assessing utility, and use of the EQ5D.

31. Ross Dent, for NICE, agreed that there is limited guidance on how to assess carer utilities in the methods guide. He explained that it is the valuing of quality of life (in other words how EQ5D scores translate into utility) that the methods guide recommends should be based on public preferences. In the case of patients, the methods guide is very clear that utilities should be based on measurement with the EQ5D. He acknowledged that other appraisals have accepted the use of vignette studies, but this was because in those appraisals the utilities were judged to be plausible, which was not the case here. In response to a question from the panel, he clarified that the sense in which the approach was not "in line" with the methods guide, was that it was not in line with what the methods guide says about measuring patient quality of life.

32. Prof O'Brien, for the appraisal committee, said that the committee were very sympathetic to the idea that the condition affected carers and took that very seriously. He also recalled that they heard from a patient expert who "got on with it" on their own, without major impact on their friends or family. He explained that the carer utility gain presented by the company at the first committee meeting was greater than the gain for patients. They found it difficult to accept that a medication could be more effective for the carer than for the patient (and could not think of a precedent for this). At the second meeting, the carer utility presented was equivalent to that for patients, which they still did not find plausible.

33. In response to questions from the panel, Robert Wolff, for the appraisal committee, disputed the notion that the ERG had "green-lighted" the approach used by the company. Rather, their report noted that this approach "properly avoided the flaws of some other methods".

34. In response to questions from the panel, Prof O'Brien, for the appraisal committee argued that "intuition" was the wrong way to characterise the judgement the committee made. In fact, this was a critical appraisal of data they were being asked to accept.

35. Edit Remak, for Kyowa Kirin, pointed out that the EQ5D was used to evaluate health states in the vignette study, and that the only difference was that this was done in the general population rather than patients or carers themselves. She highlighted the fact that vignette studies had been accepted in TA614, TA615 and HST11 and said that the methods guide does not rule out this approach.

36. Dr Williams, for Kyowa Kirin, stated that that the impact of treatment on carers is clearly a benefit that has not been properly reflected in the model and therefore should have been taken account of in setting the ICER threshold.

37. Helen Knight, for NICE, explained that NICE requires that FADs have a "tag line" for each paragraph, but asked the panel not to put too much weight on these. In this case, she asked the panel to ignore the "tag line" for paragraph 3.17 (which states that all benefits of treatment can be adequately captured in the model) and instead rely on the text in this paragraph in which the committee recalled the burden on carers. This paragraph also points out that even those cost-effectiveness estimates incorporating carer utilities were higher than the middle of the range normally considered cost-effective.

38. The appeal panel concluded as follows. The panel judged that the committee had carefully considered the data on carer utilities and their view that a utility gain for carers greater than that for patients was implausible was fairly expressed and not an unreasonable one. The panel therefore judged that the decision not to include these utilities in the modelling was not unfair. The panel noted that the committee had indeed recognised the burden of this condition on care-givers.

39. However the panel concluded that, having recognised this burden (and chosen not to include carer utilities in the modelling) the committee should have considered this issue qualitatively in their decision-making. The panel were not satisfied that a statement that the committee recognised this burden in itself amounted to evidence of adequate consideration of this issue. The panel were aware that carer utilities made a relatively small difference to the ICERs, but were not convinced that this issue could not have affected the decision. The panel therefore concluded that the failure to show greater consideration of carer burden in the decision-making, and/or to have given more reasoning around what consideration may have taken place, amounted to unfairness.

40. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.4: The committee's conclusion that mogamulizumab is not considered to be a life-extending treatment at the end of life relies on evidence which has not been disclosed and is therefore unfair

41. Dr Williams, for Kyowa Kirin, referred to paragraph 3.13 of the FAD. Here, the committee relies on the professional organisations' response to technical engagement and states that the median survival in patients eligible for second line treatment is three to five years. After reviewing the documents, the company were unable to find any statement to reflect this. Relying on information not available to all consultees would be unfair.

42. Ross Dent, for NICE, said that the statement referred to by Dr Williams was based on the technical engagement response from the Royal College of Pathologists and British Association of Dermatologists. This was included in the papers available to all consultees. He conceded that this statement actually referred to time from diagnosis, rather than time from eligibility to second line treatment.

43. The appeal panel concluded that the committee had not relied on undisclosed evidence and therefore there was no valid appeal point

under Ground 1a. The way in which this evidence was used is considered under Kyowa Kirin appeal point 2.5.

44. The appeal panel therefore dismissed the appeal on this point.

Appeal Ground 1a.6: The Committee's conclusions regarding the appropriate ICER threshold for this appraisal do not assess uncertainty in accordance with paragraph 6.2.16 of NICE's Guide to the Methods of Technology Appraisal

45. Dr Williams, for Kyowa Kirin, highlighted paragraph 3.14 of the FAD, which concludes that based on the "high level of uncertainty associated with MAVORIC analysis" an acceptable ICER would be no higher than the middle of the range usually considered cost-effective. The appeal letter referred to paragraph 6.2.16 of the methods guide, which states that the evidence base will necessarily be weaker for technologies used to treat very rare diseases. Kyowa Kirin argued that the there is no indication in paragraph 3.14 of the FAD that the committee gave any consideration to the rarity of mycosis fungoides and Sezary syndrome when considering uncertainty and its impact on the ICER threshold.

46. In response to questions from the panel, Prof O'Brien said that the committee had been very aware of paragraph 6.2.16 of the methods guide, and had tried to strike a balance between considering rarity and uncertainty. He pointed out that they had not specified an ICER threshold of <£20,000, but rather something in the middle of the range. In fact, none of the ICERs submitted by the company were <£30,000 so this threshold did not affect the final decision. He said that not putting patients with rare conditions at a disadvantage was very much in their thinking.

47. Dr Williams, for Kyowa Kirin, said that there is nowhere in the FAD where the committee say how they weighed rarity in their decision-making. She highlighted the fact that mycosis fungoides and Sezary syndrome meet the definition for ultra-orphan diseases. This is a fundamental issue for this appraisal, so it was vital for the committee to explain how they reached their conclusions. If committees adopt a

process which insists on robust data with no uncertainty, treatments for rare diseases would never be recommended.

48. Ross Dent, for NICE, said that paragraph 3.1 of the FAD demonstrates that the committee were aware that this is a rare disease. He argued that rarity is not a decision modifier in setting an ICER threshold. The methods guide says that above an ICER of £20,000 the committee must consider uncertainty, innovation and benefits that may not have been captured by the model. He disputed the notion that technologies to treat rare diseases face an insurmountable hurdle because if the ICER were <£20,000 (or if there was important innovation or uncaptured benefits) they would be recommended despite some uncertainty in the data.

49. Dr Williams, for Kyowa Kirin, said that while rarity may not be one of the explicit decision modifiers for the ICER threshold listed in the methods guide, it should be considered in relation to uncertainty. (In other words, uncertainty should be given less weight in the case of a rare disease, where there will inevitably be more uncertainty in the data).

50. In response to questions from the panel, Prof O'Brien was not able to recall exactly why the ICER range had changed between the Appraisal Consultation Document (ACD) (which talks about the lower end of the range) and the FAD.

51. Dr Morris, for UKCLG, said that from a clinician and patient point of view, there is no uncertainty about the clinical effectiveness of mogamulizumab.

52. Prof O'Brien, for the appraisal committee, agreed that the MAVORIC trial provided a high level of certainty about the effectiveness of mogamulizumab compared with vorinostat, but the uncertainty was in its effectiveness compared with the UK standard of care.

53. The appeal panel concluded as follows. The panel noted that the uncertainty in the appraisal was not about the effectiveness of mogamulizumab (for which there was robust data) but about the cost-effectiveness when applied in an NHS setting. This distinction was not clear in the FAD. The panel's impression was that the committee had been diligent and thoughtful in their approach and the panel accepted that they had been aware of the issue of rarity. The panel did not accept that the committee was obliged to discount uncertainty in the data solely because of the rarity of the condition. However, the panel judged that rarity is a relevant factor to consider when committees weigh the importance of uncertainty in modifying the ICER threshold. The panel noted that both in the FAD and during the hearing, the committee found it difficult to articulate clearly how this had been factored into their decision-making. The panel noted that there was insufficient discussion and transparency about how the appropriate ICER threshold had been decided upon, and why this had changed between the ACD and the FAD. The panel concluded that the reasoning in the FAD was not sufficient for the reader to understand how the ICER threshold was reached, in particular with regard to how rarity had been weighed in the committee's judgement. Because this issue was of such importance in this appraisal, the panel judged that this lack of reasoning was unfair.

54. The panel therefore upheld the appeal on this point.

Appeal Ground 1a.7 The Committee's conclusions regarding the appropriate ICER threshold for this appraisal lack transparency

55. Dr Williams, for Kyowa Kirin, stated that the ICER threshold is central to any appraisal. Companies need absolute transparency and clarity about this so that they know what they need to do to achieve a positive recommendation. In the appeal letter, they argued that the statement that the ICER threshold would be "no higher than the middle of the range" was insufficiently precise.

56. Prof O'Brien, for the appraisal committee, agreed that the FAD had not specified a precise ICER threshold, but rather said that something in the middle of the range would be reasonable. He said that it was not the role of the committee to determine a precise ICER threshold (and by extension the price of the technology).

57. Later in the hearing, Zack Pemberton-Whiteley said that Leukaemia Action and Lymphoma Care (LALC) interpreted the statement in the FAD as referring to a precise ICER threshold of £25,000.

58. The appeal panel concluded as follows. The panel accepted that it is important for the company to know what they have to do in order to achieve a positive outcome. They must therefore understand the key drivers of the decision. However, NICE methods guide explicitly states that "The Appraisal Committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost effective or below which it would." It is well known that ICERs <£20,000 are accepted as a cost-effective use of NHS resources and that ICERs between £20,000 and £30,000 may be acceptable depending on the criteria set out in the methods guide. In this appraisal, the committee explicitly stated that they would consider ICERs in the middle of that range to be acceptable. The panel noted that one appellant had interpreted that to mean that the ICER had to be below £25,000, and the other had presumably interpreted it to mean (as the committee intended) that it had to be somewhere in the region of £25,000. While the panel found in relation to Kyowa Kirin appeal point 1a.6 that this outcome required further reasoning, it judged that the outcome itself provided sufficient information for the company to understand what would be required to achieve a positive outcome, and therefore that this constituted a fair process. The difference in understanding between appellants was not evidence of any real uncertainty about the threshold. The panel concluded that the target itself was sufficiently clear, even though the reasons that the target had been put where it had were not (see Kyowa Kirin appeal point 1a.6).

59. The appeal panel therefore dismissed the appeal on this point.

Appeal by Lymphoma Action and Leukaemia Care

Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

Appeal Ground 1a2. End of Life (EoL) - Given the committee's comments about median life expectancy of this population being less than 24 months, any committee decision to utilise a lower threshold than the maximum available to a treatment not meeting end of life (£30,000 per Quality Adjusted Life Year (QALY) gained) would be unfair

60. Zack Pemberton-Whiteley, for LALC, said that they believed that the criteria for End of Life had been met (as discussed in LALC appeal point 2.3). However, in the event that NICE conclude that these criteria were not met, he argued that the fact they were close to being met should have had a bearing on decision-making. He drew the panel's attention to the methods guide stating that committees should have regard to whether a treatment meets End of Life criteria. In this case, the committee was aware that median overall survival in the Hospital Episode Statistics (HES) data was 17.83 months. With this in mind, he argued that the decision to use an ICER below the maximum threshold of £30,000 was unreasonable.

61. In response to questions from the panel, Ross Dent, for NICE said that the decision for the committee about whether EoL criteria are met is essentially a binary one. The methods guide does not say that the committee should consider short life expectancy as a modifier of the ICER threshold when these criteria are not met. It explicitly specifies uncaptured benefits, innovation and uncertainty as the potential modifiers of the ICER threshold.

62. Zack Pemberton-Whiteley, for LALC, disagreed with the contention that the committee's decision about EoL is a binary one. He argued that section 6.3.3 of the methods guide suggests that every decision should take account of end of life factors, even if the criteria are not met.

63. Helen Knight, for NICE, stated that this is not the case, and has never previously been done. She said that paragraph 6.3.3 of the methods guide simply refers to the committee deciding whether or not EoL criteria have been met. The EoL criteria are an exception to usual practice, where all QALYs refer to the reference case and all QALYs are equal.

64. The appeal panel concluded as follows. The panel judged that the methods guide does not require committees to consider life expectancy as a modifier of the ICER threshold after, through carefully consideration, they have concluded that the EoL criteria are not met. In this case, the committee had indeed considered the EoL criteria. The reasonableness of this conclusion is discussed separately under Kyowa Kirin appeal point 2.5. The panel accepted that there is nothing in the methods guide to preclude committees from considering life expectancy in their decision-making if they judge that this is particularly relevant in a specific appraisal. The panel were aware that this is not something that has been done in previous appraisals. The panel concluded that this would at best be very exceptional rather than something to be considered routinely. The panel therefore judged that it was reasonable and consistent with NICE processes that, having concluded that the EoL criteria were not met, the committee did not give life expectancy any weight when considering the appropriate ICER threshold.

65. The appeal panel therefore dismissed the appeal on this point.

Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers

66. There was no appeal under this ground.

Appeal by Kyowa Kirin

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal point Ground 2.1: The Committee's conclusion that Kyowa Kirin's analysis using the Hospital Episodes Statistics (HES) database was not adequately matched to the data from the MAVORIC trial is incorrect and therefore unreasonable

67. Linda McNamara, for Kyowa Kirin, said that there are errors of fact in section 3.5 of the FAD concerning the matching of HES data to that from the MAVORIC trial. The FAD states that only one variable was matched, whereas in fact four variables were matched. In addition, age and gender were considered but the scale of the difference between the two sets of data did not require further matching. She argued that further matching would have reduced the sample size and therefore increased the uncertainty associated with the data. Matching for age and gender was later done for the Scottish Medicines Consortium, and the hazard ratio changed by only 0.02.

68. Robert Wolff, for the appraisal committee, said that the statement that only one variable was matched was based on a document dated 27 November 2020 from Kyowa Kirin in response to an information request from the ERG which said they had only matched on the proportions of mycosis fungoides/Sezary Syndrome patients "in order to not further reduce the sample size post-matching unnecessarily".

69. Prof O'Brien, for the appraisal committee, said that the committee had commended the company on obtaining this data and doing the best they could with it, but judged that there were important limitations to using proxies for stage of disease and duration of disease. He was happy to accept that age and gender were not very important to the analysis, but he was concerned about disease stage and time from diagnosis.

70. Edit Remak, for Kyowa Kirin, said that the company had considered eleven possible prognostic factors. Not all of these could be examined

directly, but they did their best to select appropriate proxies that clinicians considered valid. In using the HES data, they had gone through two stages relevant to the issue of matching. First, they set up a dataset, and some of these prognostic factors were considered in setting up the analysis. Then they want on to specifically match for only one factor.

71. Robert Wolff, for the appraisal committee, said that NICE processes advise that all known variables should be included in the matching model even if they do not have a major impact.

72. Prof Cowan, for UKCLG, said that the HES dataset is unique and of international value. He said it is which factors are matched for (rather than the number that are matched for) that is important. He stated that the proportion with mycosis fungoides/Sezary Syndrome is important (this was matched in this case) but agreed that matching for disease stage is also important.

73. Edit Remak, for Kyowa Kirin, said that they identified patients with advanced disease by the fact that they were all in secondary care and receiving systemic, second line treatment. They had tried to be very conservative in their model.

74. The appeal panel concluded as follows. The panel agreed that the HES dataset was very useful in reflecting current clinical practice in the UK. The panel judged that the company had taken a thoughtful and reasonable approach to attempting to match the HES data to data from the MAVORIC trial. The panel noted that there was some common ground between the company and the committee at the hearing, particularly with regard to age and gender matching being less important than matching for stage and duration of disease. There had clearly been some difference in the use of language between the company and the committee that led to confusion as to whether one or four variables had been “matched”. However, the more substantive issue seemed to be that the committee were not convinced that the

proxy measures of stage and duration of disease were sufficiently robust to allow adequate matching on these variables. The panel judged that the committee's approach to considering this issue had been thoughtful and clearly articulated. Whilst the company disagreed with their conclusions (and it is conceivable that another committee could have reached a different conclusion) the panel did not judge that these conclusions were unreasonable.

75. The panel therefore dismissed the appeal on this point. However, the panel suggests that it would be helpful if the FAD could be re-worded to more accurately reflect the reasoning of the committee as expressed at the hearing.

Appeal point Ground 2.2: The Committee's reliance on the two-stage estimation method to produce overall survival estimates for survival in the standard care arm of the MAVORIC trial is inconsistent with the available evidence

76. Linda McNamara, for Kyowa Kirin, explained that the trial had a high cross-over, for ethical reasons. NICE processes allow three methods for dealing with cross-over, and the method selected should have supporting data. Here only two of these methods were relevant: the two-stage estimation model (TSE) and the Inverse Probability of Censoring Weighting (IPCW) method. The third method, Rank Preserving Structural Failure Time (RPSFT) was not considered because everyone agreed this did not produce believable results. She said that the TSE model should also have been disregarded because the results it produced were implausible. For instance, median survival from second line treatment was 3.4 years using TSE (versus 1.5 years in the HES data, and 1.8 years using IPCW). In other words, the TSE approach over-estimated survival in the standard of care arm. Despite this, the committee gave equal weight to the TSE and IPCW approaches, saying that they represented the upper and lower range of possible survival.

77. In response to questions from the panel, Edit Remak, for Kyowa Kirin, explained the different approach the company had taken to the RPSFT and TSE methods. She said that the RPSFT method was ruled out a priori based on statistical assumptions, whereas the TSE method was not ruled out on this basis, so they went to the next stage of validating its results against external data.

78. In response to a question from the panel about whether the TSE model could have any informative value, Edit Remak, for Kyowa Kirin, said that she believed a choice had to be made between these two alternative methods.

79. Prof O'Brien, for the appraisal committee, said that the committee had been concerned that the modelled survival with the IPCW method was not plausible. In particular, they had noted a sudden drop in the survival curve at 6 months. The ERG had also thought this was not very plausible. The committee therefore decided to give due consideration to both methods. It did not dismiss IPCW (or make a choice between the two methods) but concluded that reality was probably somewhere in between the two approaches.

80. Robert Wolff, for the appraisal committee, added that IPCW resulted in very low 10-year survival, and that some weights in the IPCW may have been greater than ten, which is known to potentially produce biased results.

81. Prof Cowan, for UKCLG, agreed that the survival curve for the IPCW model looked exaggerated compared with what is seen in clinical practice, although he noted that there can be a rapid decline in outcome leaving a trail of better responders.

82. Edit Remak, for Kyowa Kirin, agreed that the shape of that curve was a statistical artefact but argued that this is an intermediate outcome that does not inform the model directly. Because both methods are highly uncertain, the company judged that validation against external data was of particular importance.

83. The appeal panel concluded as follows. The panel noted that both the company and the committee had given thoughtful and clearly articulated reasons for their respective conclusions about the preferred approach to dealing with the issue of cross-over. It did not accept that the committee had "relied upon" the TSE approach. The committee had clearly considered the TSE and IPCW methods in its decision making. The panel judged that the statement in the FAD that these two methods "represented the upper and lower range of plausible survival in the standard care arm" was not unreasonable.

84. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.3: The Committee's conclusions regarding the disease-modifying effects of mogamulizumab disregard expert evidence and misinterpret the evidence of one patient expert and are therefore unreasonable

85. Jan-Paul Rosen, for Kyowa Kirin, drew the panel's attention to section 3.8 of the FAD which states that "the committee was not convinced that mogamulizumab provided a prolonged benefit after disease progression and could be considered disease-modifying". He stated that the mechanism of action of mogamulizumab means that a prolonged benefit is biologically plausible, and that this is backed up by clinical experience. Data on time to next treatment also shows that this is longer for mogamulizumab than the comparator. He said that the FAD misrepresents a patient expert who stopped treatment for a period of 12 weeks: in fact this patient did have some benefit even after treatment was stopped.

86. Prof O'Brien, for the appraisal committee, said that it is uncertain whether mogamulizumab does something that will make it continue to work after treatment is stopped. This is a theoretical possibility but there is no confirmation of this (median follow up in the trial was 18 months). The committee had heard that when treatment was stopped the disease does indeed recur.

87. Ross Dent, for NICE, stated that the comment from the patient expert was in the ACD and no one raised concerns about this at consultation.

88. Prof Cowan, for UKCLG, said that in oncology practice time to next treatment typically gets shorter with each treatment tried. With mogamulizumab, some patients stay stable for an unusual period of time after stopping treatment. Time to next treatment can be a good proxy for a disease-modifying effect.

89. Prof O'Brien agreed that this is interesting and promising, but said that it remains anecdotal. The committee had not considered this issue in great detail at their second meeting as it was not something that had been raised in consultation.

90. In response to questions from the panel, Robert Wolff, for the appraisal committee, said that the data on time to next treatment had not been used in the modelling.

91. Linda McNamara, for Kyowa Kirin, said that the company had raised this issue in their consultation response.

92. The appeal panel concluded as follows. The panel noted that the presentation slides from the first committee meeting specifically mention this issue and say that the technical team's advice was that that there is "no robust estimate of treatment effect for moga after treatment is stopped" (slide 23). At the hearing, the committee did not dismiss the possibility of a prolonged treatment effect for mogamulizumab but said they had considered this and concluded that there was insufficient evidence to include this in the model. The panel felt the differing positions of the company and committee on this question were both reasonable ones to take.

93. The panel therefore dismissed the appeal on this point.

Appeal point Ground 2.4: The Committee's conclusion that it was not convinced that mogamulizumab provides an overall survival benefit is unreasonable in light of the evidence available

94. This appeal point was discussed together with UKCLG point 2.4 at the hearing.

95. Linda McNamara, for Kyowa Kirin, drew the panel's attention to section 3.9 of the FAD which states that "The committee was not convinced that mogamulizumab provided an overall survival benefit compared with standard care." In fact, all the evidence presented to the committee had demonstrated an overall survival (OS) benefit with mogamulizumab. Section 3.8 of the FAD itself appears to recognise a survival benefit when it describes the upper and lower plausible range of OS in the standard of care arm.

96. Prof Cowan, for UKCLG, said that the FAD states there is inadequate information on the OS benefit of mogamulizumab. If the difference between the study drug and control arm is modest, it may be reasonable to conclude there is too much uncertainty in the data. However, in this case, there is a dramatic difference between OS with mogamulizumab and standard of care (57 months versus 17.3 months). With this degree of difference, it was unreasonable to conclude that the evidence was not strong enough.

97. In response to questions from the panel, Edit Remak, for Kyowa Kirin, confirmed that this data had been submitted after the first committee meeting so was available to the committee.

98. Prof O'Brien, for the appraisal committee, said that although the MAVORIC trial did not show a significant difference in OS between treatment and control arms (which was an active treatment not used in the NHS), the committee accepted that there may well be an OS benefit when compared to NHS current practice. They considered a number of scenarios with an OS benefit, and did not ask for a scenario without OS benefit. He said that the statement in section 3.8

of the FAD should be considered in context. This paragraph was specifically considering the issue of how to adjust for cross-over, so the statement was explaining why it was appropriate to consider the ERG approach to this issue (which showed a lower OS benefit).

99. In response to questions from the panel, Prof O'Brien refuted the notion that the panel had said there was no OS benefit from mogamulizumab. Rather, they were uncertain how much benefit there was. They did not have a problem with accepting a greater than three month survival benefit from mogamulizumab, so decisions about the EoL criteria were based on life expectancy rather than OS benefit. He agreed that the FAD could have been written better, but was clear that the committee had accepted an OS benefit with mogamulizumab. He said that he could not recall seeing the comparison between 50 months and 17.3 months but again emphasised that the committee were open to an important OS benefit with mogamulizumab.

100. In response to questions from the panel, Robert Wolff, for the appraisal committee, confirmed that the ERG preferred scenario did model an OS benefit.

101. The appeal panel concluded as follows. The panel were aware that the MAVORIC trial did not show an OS benefit for mogamulizumab but also that it was not designed to show this. The panel agreed that the magnitude of the difference between OS in the MAVORIC trial and the HES data (see UKCLG point 2.4) was very striking and that it would therefore have been unreasonable to conclude that there was no OS benefit from mogamulizumab. At the hearing the committee said they had accepted an OS benefit from mogamulizumab and the panel noted that they had indeed relied on models with an OS benefit. However, the FAD clearly states that "the committee was not convinced that mogamulizumab provided an overall survival benefit compared with standard care" which seemed to the panel an unreasonable statement. The panel noted the committee's comments

about the context of this statement, but did not think this would be clear to a patient or clinician reading the FAD.

102. Further, the panel was cautious about relying on statements made in an appeal which appear difficult to reconcile with a statement in the FAD. The panel accepts that while the reasoning behind a FAD can, in certain instances, be clarified at an appeal hearing, the FAD is the most important document produced during an appraisal. It therefore needs to reflect the committee's conclusions accurately and clearly. The statement in question appeared clear and yet at odds with the committee's stated approach, and unsustainable on the evidence. The panel understood from his comments during the hearing that Professor O'Brien would agree with this. The panel therefore concluded that the inclusion of this statement in the FAD amounted to unreasonableness. Had the committee in fact proceeded on the basis that mogamulizumab showed or might show no OS benefit compared to standard care that too would have been unreasonable. Whether that benefit can be quantified in any sufficiently robust way to be used in decision making is a matter for the committee.

103. The appeal panel therefore upheld the appeal on this point.

Appeal point Ground 2.5: The Committee's conclusion that mogamulizumab is not considered to be a life-extending treatment at the end of life relies on incorrect and irrelevant data and is therefore unreasonable

104. Linda McNamara, for Kyowa Kirin, said that the company had deep concerns about the reasoning about the decision on the EoL criteria set out in section 3.13 of the FAD. This section appears to confuse survival from diagnosis with survival from second line treatment. It is survival from second line treatment which is relevant to this appraisal, as this is the population considered in the scope. The FAD refers to a study from the Cutaneous Lymphoma International Consortium (CLIC) in which median overall survival was 63 months, but this was from diagnosis rather than from second line treatment. Later in the

same paragraph, the FAD refers to the professional organisations' response to technical engagement and say that "median survival for people with disease stage 2B and above eligible for second-line treatment in the NHS was estimated to be between 3 and 5 years." The company questions the basis of this statement. In fact, the data presented suggest survival from diagnosis about 5-6 years, but survival from second line treatment (using the NHS HES data) is about 1.5 years.

105. Prof Sean Whittaker, for UKCLG, said that there is a paucity of data on survival times from different lines of treatment. Most published data is on survival from diagnosis.

106. In response to questions from the panel, Prof O'Brien, for the appraisal committee, accepted that the committee had misunderstood the evidence on survival from the professional organisations' response to technical engagement, and may have expressed this in an unclear way in the FAD. He stated that, following challenges from the company, the committee accepted that survival from the time of initiation of second-line treatment was the relevant parameter for making decisions about EoL criteria. However, the evidence on survival from second-line treatment is not robust. The modelled submission from the company shows that whether survival is less than or greater than two years depends on the methods used (with the IPCW method it is 1.8 years but with the TSE method it is 3.4 years).

107. Dr Williams, for Kyowa Kirin, said that the company can only understand the committee's reasoning from what is written in the FAD. The FAD lists pieces of evidence relied upon in making a decision about the EoL criteria and reaches an overall conclusion. We have heard that some of that evidence did not refer to the correct time frame, so that overall conclusion must be flawed.

108. In response to questions from the panel about whether the committee judged that the HES data supported the EoL criteria being met, Prof O'Brien said that the HES data are not completely robust. The committee thought about this issue carefully, but struggled because of a lack of good evidence on survival from second line treatment. They concluded that they could not find evidence to robustly support life expectancy of less than 24 months.

109. Prof Sean Whittaker, for UKCLG, said that HES data is very important: it provides the first "real world" data that provide information on survival from second line treatment.

110. In response to questions from the panel about whether the ERG had advised that HES should be considered the best source of evidence for the decision about the EoL criteria, Robert Wolff for the appraisal committee said that just because something is the best source of evidence does not necessarily mean it is a good source of evidence. The HES data does have potential limitations.

111. Prof O'Brien, for the appraisal committee, drew the panel's attention to the statement in section 3.13 of the FAD that "the mean extrapolated discounted and undiscounted life years in the standard care arm of the cost-effectiveness model based on the HES data were 2.87 and 3.31 years".

112. The appeal panel concluded as follows. The panel noted that there was agreement that survival from time of initiation of second-line treatment (not time from diagnosis) is the relevant parameter for decisions about the EoL criteria. The panel accepted that data on this is less robust than data on survival from diagnosis and that there may be no perfect source of data. However, the panel were persuaded by the ERG's own view that the HES data provide the best available source of evidence on this question. This is a large, real-world dataset including all patients treated in England for this condition. Whilst the committee were not obliged to prefer the HES data

because of this advice from the ERG, they did not provide reasons in the FAD or during the hearing for why they had not agreed that this was the best source of evidence. The panel was not clear what the committee's concerns about the HES data were (in relation to this purpose), or why it preferred modelled data based on HES for its decision-making. The panel judged that section 3.13 of the FAD suggests that the data from the CLIC and the professional organisations' response to technical engagement had been relied upon in reaching a decision about the EoL criteria, despite the fact that these figures referred to survival from diagnosis rather than from second-line treatment. The panel judged that the final decision about the short life expectancy EoL criterion "did not add up" and was therefore unreasonable.

113. The panel therefore upheld the appeal on this point.

Appeal by Lymphoma Action and Leukaemia Care

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal point: Given the rarity of this condition, unmet need and limited treatment options for these patients we believe the imposition of a "middle of the range" ICER threshold to be unfair.

114. This appeal point was originally submitted under Ground 1a (and was referred to as point 1a1 during the hearing) but following initial scrutiny was accepted for consideration under Ground 2.

115. At the hearing, this point was discussed together with Kyowa Kirin appeal point 1.6, so the following should be read in conjunction with that section of this decision letter.

116. Zack Pemberton Whiteley, for LALC, said that this decision sets a worrying precedent for rare cancers. It was unreasonable of the committee to apply a lower ICER threshold that the £30,000 that was open to the committee. Instead the committee had argued that because of uncertainty in the data, an ICER no higher than £25,000

was acceptable. LALC acknowledge the importance of uncertainty, but note that the methods guide states that evidence will necessarily be weaker for rare disease. While committees should consider uncertainty, they should not penalise rare conditions in doing so.

117. As set out in paragraph 45, Prof O'Brien said that the committee had been very aware of this statement in the methods guide, and had tried to strike a balance between considering rarity and uncertainty. He pointed out that they had not specified an ICER threshold of <£20,000, but rather something in the middle of the range. In fact, none of the ICERs submitted by the company were <£30,000 so this threshold did not affect the final decision. He said that not putting patients with rare conditions at a disadvantage was very much in their thinking.

118. As set out in paragraph 48 Ross Dent, for NICE, said that paragraph 3.1 of the FAD demonstrates that the committee were aware that this is a rare disease. He argued that rarity is not a decision modifier in setting an ICER threshold. The methods guide says that above an ICER of £20,000 the committee must consider uncertainty, innovation and benefits that may not have been captured by the model. He disputed the notion that technologies to treat rare diseases face an insurmountable hurdle because if the ICER were <£20,000 (or if there was important innovation or uncaptured benefits) they would be recommended despite some uncertainty in the data.

119. The appeal panel considered closely related issues under Kyowa Kirin appeal point 1.6. This appeal point was upheld on the basis the reasoning in the FAD was not sufficient for the reader to understand how the ICER threshold was reached, in particular with regard to the transparency of how rarity had been weighed in the committee's judgement. Here, the panel considered the specific point raised by LALC that it was unreasonable to use an ICER threshold <£30,000 because of uncertainty in the data in the case of a rare disease. The panel was not persuaded that the committee was obliged to discount uncertainty in the data to the extent argued by LALC because of the

rarity of the condition. The panel therefore did not judge that it was unreasonable to use an ICER threshold of <£30,000 (even though the lack of reasoning about how rarity had been weighed in this decision was unfair).

120. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.3: A decision not to consider mogamulizumab to be a treatment 'indicated for patients with a short life expectancy' is unreasonable in the light of the evidence submitted to NICE.

121. Zack Pemberton-Whiteley, for NICE, said that it was unreasonable for the committee not base its decision on EoL criteria on the median overall survival from the HES data, which was 17.8 months. He said that the committee had preferred to use mean survival figures (from the modelled HES data). He argued that there was a precedent for using median rather than mean survival in other appraisals (e.g. TA541).

122. Prof O'Brien, for the appraisal committee, said that committees regularly debate whether to use median or mean survival figures for EoL decisions. From a health economic perspective, using medians will tend to under-estimate costs and over-estimate benefits. The methods guide does not specify whether medians or means should be used.

123. Ross Dent, for NICE, said that means are preferred because cost-benefit analyses use the mean and committees want to be consistent.

124. Dr Stephen Morris, for UKCLG, explained that patients who go to have an autologous stem cell transplant will achieve very prolonged remission, resulting in a right shift in the data. Consequently, medians may be more appropriate than means for examining survival in this condition.

125. Prof O'Brien, for the appraisal committee said that the median survival figure used in TA541 was 6.7 months which is well below the EoL threshold (unlike in this appraisal). In response to questions from the

panel, he said that the committee did consider median survival, but decided to base their decision primarily on mean survival data.

126. The appeal panel concluded as follows. The panel considered the weight given to HES data in reaching a decision about the EoL criteria as part of Kyowa Kirin appeal point 2.5, which was upheld. Here, the panel considered the specific issue of whether it was unreasonable of the committee to prefer median rather than mean figures in reaching a decision about survival with regard to the EoL criteria. The panel was persuaded that the committee had not disregarded median survival. It had considered median survival, but gave a reasoned explanation for why it had preferred to use mean survival data. Whilst it is possible that a different committee could have reached a different decision, the panel did not judge that this decision was unreasonable.

127. The panel therefore dismissed the appeal on this point.

Appeal by UKCLG

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal point Ground 2.1/2.2: The Committee's treatment of the evidence in which Vorinostat was a comparator led to an unreasonable recommendation. The Committee's judgement of the comparator in the MAVORIC trial led to an unreasonable recommendation.

128. These points were originally submitted separately but following initial scrutiny were accepted for consideration as a single point of appeal.

129. Prof Cowan, for UKCLG, noted that the hearing had been dominated by discussion of uncertainty. The committee make the reasonable statement that vorinostat (the comparator in the MAVORIC) trial is not part of UK practice. However, the trial was designed in this way for good reasons: in order to conduct an international study, compromises have to be made. The important point is that vorinostat is equivalent to the standard treatments in UK practice. Phase II data suggest a virtually identical outcome with bexarotene (which is one of

the drugs used in the UK) and vorinostat. There is no good data on other drugs used in the UK, like methotrexate. On this basis, the choice of comparator should not be perceived as a limitation of the MAVORIC trial or as something that creates undue uncertainty in interpreting its results.

130. Dr Stephen Morris, for UKCLG, said that the committee seem to be assuming that we are using something more effective than vorinostat in UK clinical practice and that this is not plausible.

131. Prof O'Brien, for the appraisal committee, said that the committee had not ruled out a positive decision because of the use of this comparator. The committee completely understood why the trial had been done in this way. The question is whether the committee can safely assume that vorinostat is the same as what is used in the NHS. Without Phase III comparative data, you have to make some assumptions. The committee did not feel completely comfortable with assuming that vorinostat was exactly the same as UK standard of care. This was a reasonable possibility, but evidence was lacking. He went on to say that the committee's conclusions about uncertainty in the MAVORIC data were not just based on the comparator, but also on the short follow-up and high rate of cross-over.

132. Robert Wolff, for the appraisal committee, drew the panel's attention to section 3.3 of the ERG report which has a long discussion about this issue. He said that the problem is that there remains uncertainty about this point.

133. In response to questions from the panel, Prof O'Brien said that the additional uncertainty caused by the use of vorinostat as the comparator in MAVORIC was not a key driver of the committee's decision.

134. Edit Remak, for Kyowa Kirin, responded by pointing out that the first page of the FAD highlights the committee's concern that "the clinical trial evidence is very uncertain because mogamulizumab is compared

with vorinostat". She argued that the uncertainty concerns whether vorinostat may be better than standard of care, so using vorinostat as a comparator must be a conservative approach.

135. The appeal panel concluded as follows. The panel noted that the uncertainty in the appraisal was not about the effectiveness of mogamulizumab (for which there was robust data) but about the clinical and cost-effectiveness when applied in an NHS setting, given there is no trial evidence of mogamulizumab v NHS standard of care. This distinction was not made sufficiently clear in the FAD, but was particularly important to this appeal point. The panel accepted UKCLG's argument that the choice of comparator in the trial did not introduce uncertainly about whether mogamulizumab is effective for this indication. However, they also accepted the committee's argument that this comparator did introduce uncertainty about clinical and cost-effectiveness estimates in an NHS setting. The committee had not rejected the MAVORIC data, but had considered it carefully and judged that this uncertainty was a factor in their decision-making (but not a key driver of the decision). The panel judged that this was not unreasonable.

136. The appeal panel therefore dismissed the appeal on this point. However, the panel suggests that it would be helpful if the FAD could be re-worded to clarify that the uncertainty referred to by the committee concerns cost-effectiveness in an NHS setting rather than the clinical effectiveness of mogamulizumab.

Appeal point Ground 2.3: The Committee's conclusions in respect of the cross-over trial design rendered its decisions on both the end of life criteria and its recommendation unreasonable

137. Prof Cowan, for UKCLG, stated that the committee devalued evidence from MAVORIC based on the cross-over design. It is well recognised that this design compromises the ability to measure overall survival but it is done in the best interests of the patients. If

NICE perceive that this cross-over approach is a barrier to reaching positive decisions, this would not be in the best interests of patients.

138. Prof O'Brien, for the appraisal committee, said that he would not want to deter triallists from using cross-over designs. There are established methods for dealing with this problem which were applied in this appraisal.

139. In response to questions from the panel, Prof O'Brien agreed that this inevitably introduces additional uncertainty to the data but said that committees work very hard to reach a decision despite this uncertainty. He emphasised that the committee had certainly not "ruled out" the MAVORIC data because of the cross-over issue but had just tried to use the best possible approach to accounting for this in the modelling.

140. Prof Cowan, for UKCLG, said that clinicians have to rely on the reasoning given in the FAD. In this FAD, the uncertainty resulting from the cross-over design was emphasised, so it appears to have been important in the committee's decision.

141. The appeal panel concluded as follows. The committee acknowledged the rationale for a cross-over design in the MAVORIC study and had not dismissed or ruled out the data on this basis. It is accepted that high cross-over necessitates statistical approaches to adjust for the effect of cross-over in the modelling, as was done in this case. It is also accepted that these approaches introduce uncertainty into the data. The panel felt that the FAD could have been clearer in specifying that this uncertainty concerned the cost-effectiveness estimates rather than implying uncertainty about whether mogamulizumab is effective. However, the panel did not judge that it was unreasonable for the committee to have considered this uncertainty as one factor in their decision-making.

142. The panel therefore dismissed the appeal on this point.

Appeal point Ground 2.4: The final appraisal document (FAD) indicates that there was no evidence to suggest that mogamulizumab could prolong life in this group of patients. We strongly disagree with this interpretation. Specifically, mogamulizumab dramatically changes the course of disease in patients for whom, hitherto, we have had no effective treatment.

143. This appeal point was discussed together with Kyowa Kirin point 2.4 at the hearing, so this section should be read in conjunction with consideration of that point in this decision letter.

144. The appeal panel's conclusions on this issue are set out in paragraph 101-103 of this letter.

145. The appeal panel therefore upheld the appeal on this point.

Appeal point Ground 2.5: The FAD did not take into account a distinct cohort of patients in the MAVORIC trial with an aggressive leukaemic CTCL variant, Sezary syndrome, who did obtain an excellent clinical benefit from mogamulizumab therapy

146. Prof Cowan for UKCLG, drew the panel's attention to the forest plot in report of the MAVORIC trial in Lancet Oncology which shows a greater magnitude of benefit from mogamulizumab in the sub-group of patients with Sezary Syndrome. More recently, members of UKCLG have written a paper confirming that mogamulizumab is most effective in patients with the worst disease. Normally, patients with blood involvement (as in Sezary Syndrome) have worse outcomes and poorer response to treatment. With mogamulizumab, patients with blood involvement seem to respond better. This is biologically plausible based on the mechanism of action of mogamulizumab.

147. Prof O'Brien, for the appraisal committee, said he particularly recalled Mr Cummins' testimony about his experience of mogamulizumab for Sezary syndrome, and explained that the committee had been very aware that this was a potential sub-group of patients in which treatment might be more cost-effective. Unfortunately, the company

did not put forward specific data for this sub-group so there was no case that the committee could consider.

148. Jan-Paul Rosen, for Kyowa Kirin, said that the data was not available at the time for the company to be able to do this.

149. Prof Cowan, for UKCLG, again highlighted how striking the additional benefit for Sezary Syndrome patients was in the forest plot and pointed out that this was available to the committee.

150. Ross Dent, for NICE, stated that the committee specifically said they would like to see analyses based on disease type in section 3.5 of the ACD. There was no response to this request at consultation from any of the stakeholders.

151. The appeal panel concluded as follows. The panel accepted UKCLG's position that the data available to the committee suggested that patients with Sezary Syndrome may get greater benefit from treatment with mogamulizumab. The committee themselves had also recognised this, and had appropriately asked for specific data on this sub-group at the consultation stage. At the hearing, Kyowa Kirin acknowledged that they had not been able to provide specific data for this sub-group during the appraisal. The panel noted with interest emerging data on this issue, but the committee could not consider data that was not available to them at the time of the appraisal. It was therefore not possible for the committee to reach a separate decision for this sub-group of patients. The committee's approach was not unreasonable.

152. The panel therefore dismissed the appeal on this point.

Conclusion and effect of the appeal panel's decision

153. The appeal panel therefore upholds the appeal on the following grounds: Kyowa Kirin ground 1a.3, Kyowa Kirin ground 1a.6, Kyowa Kirin ground 2.4, Kyowa Kirin ground 2.5 and UKCLG ground 2.4. The appeal is dismissed on all other grounds.

154. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to correct the issues identified above. Specifically:

1a.3 (Kyowa Kirin) The committee must rework its decision to make clear how carer utilities were included in its decision making.

1a.6 (Kyowa Kirin) The committee must rework its decision to make clear how it decided on the appropriate ICER threshold, with particular reference to uncertainty and disease rarity.

2.4 (Kyowa Kirin and UKCLG) The committee must revisit its decision, making clear its thinking that there is likely to be an OS benefit for treatment with mogamulizumab when compared to NHS standard care and how that impacts on its reasoning.

2.5 (Kyowa Kirin) The committee must revisit its decision on the applicability of the EoL criterion of short life expectancy, being clear that the relevant period is survival from second-line treatment, stating what data they use to decide whether that criterion is met and what their conclusion on life expectancy is. If they decide the EoL criteria are met they must apply the EoL policy when formulating their recommendation.

155. The committee may additionally wish to consider clarifying the FAD as suggested in paragraphs 74 and 135 above.

156. The Institute and/or the committee will need to consider whether these steps will require a second ACD or whether the committee can fairly proceed directly to issue a second FAD.

157. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.

Refined analyses and additional clarifications in response to the NICE Appeal Decision (and accepted by NICE to submit 13th August 2021)

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

Single Technology Appraisal (STA)

Submitted by Kyowa Kirin

National Institute for Health and Care Excellence

Submitted 13 August 2021

Contents

Background

Mycosis fungoides (MF) / Sézary syndrome (SS) is an orphan disease[1] with 125 patients annually in England and Wales. There is a very high unmet need with only clinical trials or recycled treatment options are available after second line treatment for MF patients and after one line of treatment for SS patients who are ineligible for, or refractory to, treatment with brentuximab vedotin. MF and SS are associated with short life expectancy (median of 18 months based on all NHS England patients) (see details in the NHS England budget impact analysis submission, Jan 2020, Final ERG Report 18/03/2020, Section 2.3).

Mogamulizumab is an effective treatment providing benefits in terms of overall survival (OS), next-treatment-free and progression-free survival (NTFS and PFS), quality of life and bridging to allogeneic stem cell transplant(aSCT) (see details in Company evidence submission, Jan 2020, and Mogamulizumab ID1405 Appeal Panel Decision, paragraph 101, June 2021).

All orphan indications carry an inherent higher uncertainty due to the low patient numbers. According to the Appeal Decision, rarity and uncertainty are two key factors in the decision making, that need to be balanced (see Mogamulizumab ID1405 Appeal Panel Decision, paragraph 53 and 154, June 2021).

As a rare disease, due to the small patient population, MF/SS has significant challenges in gathering data. Despite such challenges, Kyowa Kirin has conducted not only the largest randomised clinical trial ever conducted in any subgroup of patients with CTCL (the pivotal MAVORIC trial), but also the analyses of all MF and SS patients treated in England in the NHS secondary care system over a recent 10-year period, from the Hospital Episode Statistics (HES) database. The HES data was deemed the best available evidence by both the Evidence Review Group (ERG) and the Appeal Panel (Mogamulizumab ID1405 Appeal Panel Decision Paragraph 112, Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma – ERG comments on additional evidence 09/12/2020). This was reinforced by the clinical expert representatives, who emphasised not only the unique nature of this dataset, but also its international value (Mogamulizumab ID1405 Appeal Panel Decision Paragraphs 72, 109, June 2021).

Consistent with the decision of the Appeal Panel and the discussions with NICE, Kyowa Kirin would like to make a further submission to refine the existing HES-based analyses to reduce uncertainty and provide more information on the life expectancy of patients in this rare haematological malignancy disease, given the consensus opinion expressed during the appeal that HES data represent the best available data for this patient population.

We believe, this information will assist the Committee in fairly balancing rarity and uncertainty in accordance with the decision of the Appeal Panel.

Clarifications on MAIC according to the Appeal

An important uncertainty discussed in the appeal meeting, was the inclusion of age and sex in the matching-adjusted indirect comparison (MAIC) between the mogamulizumab arm of the MAVORIC trial and the HES data representing standard of care. Refining the MAIC analysis by including sex and age, reduces the perceived uncertainty of the analysis of the HES data, the best available source of evidence.

Kyowa Kirin has previously submitted the MAIC using the HES data. As there were differences in the proportion of patients with MF vs. SS disease type between the trial and the HES datasets (see Additional information request-Company response, 27th November 2020) and this is a known prognostic factor[2–4], 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 [2,3], these were very similar between the two data sources (difference in age: 2 years, in sex: 4%). Therefore, it was decided to only perform the matching on the proportion of MF and SS patients in order not to further reduce the sample size post-matching unnecessarily. After matching, the age difference increased by only by 2.5 years, while the gender difference decreased by 3.4%.

In line with the discussions with NICE, Kyowa Kirin has now also conducted a scenario analysis including age and sex. For the simple matching based on disease classification (MF/SS) alone, the same weight was estimated based for all MF and the same weight for all SS patients to ensure matching the proportions of each

disease class in the HES dataset. In the sensitivity analyses, a more sophisticated matching-adjusted indirect comparison (MAIC) was conducted including disease type, sex and gender using the method of moments methodology described Signorovitch et al. (2010) and the NICE Technical Support Document 18.[5,6]

The results are presented in Table 1 below. The sensitivity analysis including age and sex had negligible effect on the hazard ratio compared to the base case analysis but reduces the uncertainty of the MAIC and further increases the comparability of the MAVORIC trial and the HES data.

Table 1. Results of the unanchored indirect comparison.

	Median survival in months (95% CI)	**Data first presented**	**Hazard ratio (95% CI)**
	Unadjusted		
Mogamulizumab	57.2 (40.1, NA)	ID1405_mogamulizumab for treating MF or SS CTCL_Survival analyses incl SCT Appendix 3, Feb 2020	0.43 (0.31 to 0.60)
Standard of care	17.83 (12.37, 24.03)	Technical engagement meeting, 29 May 2020	
	Base case: Adjusted for MF/SS		
Mogamulizumab	NA (51.7, NA)	ID1405 Mogamulizumab additional ACD requested analysis respot_Kyowa Kirin_v1.0_Final, Aug 2020	0.36 (0.24 to 0.53)
Standard of care	17.83 (12.37, 24.03)	Same as above	
	Sensitivity analyses: Adjusted for MF/SS, age, sex		
Mogamulizumab	NA (40.06, NA)	In current document	0.38 (0.25 to 0.59)
Standard of care	17.83 (12.37, 24.03)	Same as above	

Refined analyses including [redacted]

As both the Appraisal Committee (represented by Prof O'Brien) and the Appeal Panel agreed on the need to balance rarity and uncertainty (Mogamulizumab ID1405 Appeal Panel Decision, Paragraph 46 and 53, June 2021), Kyowa Kirin would like to

provide additional clarifications for the population with the greatest unmet need, where this balance is clearer.

While in 2nd line in advanced MF and in SS, there is already a high unmet need for an additional treatment option, patients with advanced disease following at least two prior systemic therapies for MF and one prior systemic therapy for SS, who are clinically ineligible for, or refractory to, treatment with brentuximab vedotin were identified by the ERG and clinical experts as the population for whom only clinical trials or recycled treatment options are available (see FAD, Section 3.1 and the Final ERG Report 18/03/2020, Section 2.3), resulting in extreme unmet need.

Kyowa Kirin would like to provide further clarifications for this optimised population for the Committee in the determination of the end-of-life criteria submitted previously in the Technical engagement response (see Response form submitted 5th June 2020, in response to question 6) and in the estimation of cost-effectiveness.

[redacted]

Methods

The same methods were used for this refined analysis including patients with advanced MF with at least 2 prior systemic treatments and SS patients with at least 1 prior systemic treatment as previously for the patient population of advanced MF and SS with at least 1 prior systemic treatment including the following steps:

- Unanchored MAIC of the mogamulizumab arm of the MAVORIC trial with the 10-year survival information for MF and SS available from the HES database adjusting for proportion of patients with MF/SS, sex and age as per ERG request (Final Appraisal Determination, Section 3.5, February 2021),
- Survival analyses to extrapolate results for OS, NTFS, PFS and time to treatment discontinuation (TTD),
- Incorporation of the results into the economic evaluation.

Details of the analyses are available in Appendix 1.

The base case of this refined cost-utility analyses was based on:

- the Appeal Decision recommendation of focusing on the HES data, as the best source of evidence for this ultra-orphan population,
- Clinical experts' recommendation for the population with the highest unmet need,
- Best fitting distribution for NTFS according to the data, and
- FAD for all other settings (Table 2).

Table 2. Base case for the optimised analyses in line with the Final Appraisal Determination

	Original scenario	**Optimised scenario**	**Source of requirement**
Data source for comparator	Vorinostat arm of the MAVORIC trial / HES data	HES data	Appeal Decision
Population	Advanced MF or SS following at least one prior systemic therapy, who are clinically ineligible for, or refractory to, treatment with brentuximab vedotin	Advanced MF or SS following at least two prior systemic therapy for MF and one for SS, who are clinically ineligible for, or refractory to, treatment with brentuximab vedotin	According to clinicians: the population with greatest unmet need, no other treatment options available and short life expectancy
Carer utilities	No	No	FAD/Appeal Decision base case
aSCT after current treatment	No	No	FAD/Appeal Decision base case
OS	ECM: exponential Moga: exponential	ECM: exponential Moga: exponential	FAD base case
NTFS	ECM: gen gamma Moga: lognormal	ECM: loglogistic Moga: lognormal	Best fitting distributions[1]
MAIC	Matched on histology	Matched on histology, age and gender	Appeal discussion, reducing uncertainty
Patient access scheme (discount)	[redacted]	[redacted]	Kyowa Kirin submission

[1] Better statistical fit was cited for choosing distributions for extrapolation for the two treatment arms by the ERG (ID1405 Mogamulizumab Final ERG report v0.1 180320 PS [ACIC], page 99, section 5.2.6.5.6 Extrapolation of NTFS). The choice remained in FAD base case.

Key: HES, Hospital Episode Statistics; MF, mycosis fungoides; SS, Sezary Syndrome; ECM, established clinical practice; FAD, Final Appraisal Determination; Moga, mogamulizumab; aSCT, allogeneic stem cell transplant; OS, overall survival; NTFS, next-treatment-free survival.

The refined analysis includes no new data. All HES data used were submitted previously in both Word and Excel format on 19th August 2020 as part of the reference pack:

- Data used submitted on 19th August 2020 as part of the reference pack: 2_CTCL Analysis Cohort A -final version including additional OS analyses from 2nd progression_17Aug2020.xlsx
- Report on data used submitted on 19th August 2020 as part of the reference pack: 2_FINAL_HES CTCL report_including additional OS analyses from 2nd progression_v1 0_17Aug2020.pdf
- Life expectancy for 3rd line was requested and submitted in the Technical engagement response form on 5th June 2020, in response to question 6.

Life expectancy

For this optimised population, the median life expectancy is significantly below the 24-month threshold (1.1 years) based on the best source of evidence, the HES data directly according to the recommendations of the Appeal Decision (Table 3) (Mogamulizumab ID1405 Appeal Panel Decision Paragraph 112, June 2021).

While the mean life expectancy is slightly higher than two years (by 0.3 years or four months), according to clinical experts, it is skewed by “super-survivors”, the long survival of app.10% of patients receiving the only potentially curative treatment, aSCT after current and subsequent treatment in the HES database (Mogamulizumab ID1405 Appeal Panel Decision Paragraph 124, June 2021).

Additionally, the mean life expectancy is based on modelling with an inherent uncertainty. It also lacks consistency with the cost-utility analyses, as the survival benefit of patients receiving aSCT after current treatment was excluded from the mogamulizumab arm of the cost-utility analyses as per the recommendations in the FAD. Therefore, the median survival in this case is a more appropriate measure.

Table 3. Life expectancy with standard of care (End-of-life criterion 1)

	Median	Mean	Comments
HES data	13 months 1.1 years	28 months 2.3 years	Direct from HES data as per Appeal Decision* For mean extrapolated using exponential distribution

Key: HES, Hospital Episode Statistics

* Mogamulizumab ID1405 Appeal Panel Decision Paragraph 112

Cost-utility results

In the cost-utility analyses, with the [redacted], mogamulizumab resulted in an incremental cost-effectiveness ratio (ICER) of £28,233/QALY (Table 4). These results are conservative as:

- The results include OS consequences of the only curative treatment, aSCT, after current treatment only for the standard of care arm (5.2% in the HES data), but not for the mogamulizumab arm. However, based on the significantly higher response rate with mogamulizumab[7], the clinical experts' opinion based on experience with mogamulizumab[8] and the assumption of higher response rate leading to higher rates of aSCT used in the previous NICE Technology appraisal for MF/SS[9], mogamulizumab will lead to higher aSCT rate than current clinical practice. The current analysis assumes 0%, i.e., a smaller aSCT rate after mogamulizumab than after standard of care.
- The results exclude carer burden, which is significant once patients progress on 2nd line systemic treatments[10]. According to the Appeal decision, carer burden in this case should be considered qualitatively as it has the potential to affect the decision (see Mogamulizumab ID1405 Appeal Panel Decision, paragraph 39).

Table 4: Base-case results (discounted) [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Established clinical management	[redacted]	2.46	1.60				
Mogamulizumab	[redacted]	6.85	4.68	£86,998	4.38	3.08	£28,233

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

Detailed results and sensitivity analyses are presented in the Appendix 2.

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Appendix 1: MAIC and survival analysis – 3rd line advanced MF and 2nd line SS population

Please see separate document provided with this submission.

Appendix 2: Cost-utility analysis: Detailed results and sensitivity analyses

Detailed results

Compared to standard of care in England, mogamulizumab results in a discounted QALY gain of 3.08 (Table 5).

Table 5. Discounted disaggregated quality-adjusted life-years (QALYs)

	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	**4.68**	**1.60**	**3.08**	**100%**

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

Including the [redacted], the discounted incremental costs were £86,998 driven by the drug costs ([redacted]) and the disease monitoring costs [redacted] (Table 6). 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 6. Discounted disaggregated costs [redacted]

	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]	**£86,998**	**100%**

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

With the [redacted], mogamulizumab resulted in an incremental cost-effectiveness ratio (ICER) of £28,233/QALY (Table 7).

Table 7: Base-case results (discounted) [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Established clinical management	[redacted]	2.46	1.60				
Mogamulizumab	[redacted]	6.85	4.68	£86,998	4.38	3.08	£28,233

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).

Probabilistic sensitivity analysis

The probabilistic results for the base case are presented in Table 8 and are similar to the deterministic results. The results are presented on the cost-effectiveness plane in Figure 1. The probability of mogamulizumab being cost-effective at the £30,000/QALY threshold is 68.3%, while at the £50,000/QALY threshold 99.8% (Figure 2).

Table 8: Comparison of the probabilistic and deterministic results [redacted]

	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALYs)	ICER (£/LYs)
Deterministic results	86,998	3.08	4.38	28,233	19,841
Probabilistic results	86,147	3.06	4.36	28,116	19,780

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

Figure 1: Cost-effectiveness plane [redacted]

Figure 2: Cost-effectiveness acceptability curves (CEACs) [redacted]

Deterministic sensitivity analysis

The tornado diagram showed that the results are most sensitive to survival extrapolations, the utility and the disease management / monitoring costs for the 'Subsequent treatment' health state (Figure 3).

Figure 3: Tornado diagram [redacted]

Refined analyses and additional clarifications in response to the NICE Appeal Decision (and accepted by NICE to submit 13th August 2021)

Appendix 1: MAIC and survival analysis – 3rd line advanced MF and 2nd line SS population

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

Single Technology Appraisal (STA)

Submitted by Kyowa Kirin

National Institute for Health and Care Excellence

Submitted 13 August 2021

Contents

Introduction

The previous matching-adjusted indirect comparison (MAIC) and survival analyses have been updated to provide further clarifications for the optimised population of patients with advanced MF or SS following at least two prior systemic therapies for MF and one prior systemic therapy for SS, who are clinically ineligible for, or refractory to, treatment with brentuximab vedotin for the Committee in the determination of the end-of-life criteria submitted previously in the Technical engagement response (see Response form submitted 5th June 2020, in response to question 6) and in the estimation of cost-effectiveness.

Methods

The analyses follow the same methods as described in the Additional Manufacturer Evidence and Analyses Requested by the Committee submitted on 19th August and 27th November 2020:

- ID1405 Mogamulizumab additional ACD requested analysis resport_Kyowa Kirin_v1.0 Final 19th August 2020.docx
- ID1405_mogamulizumab_Response to ERG requests_27thNov20_FINAL.docx

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]).

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.

For detailed description of the dataset please see the extended HES Report[1]. For the description of additional analyses, please see Section 8.4.1, page 44. Data for SS patients with one prior line of treatment was submitted in the ACD response

reference pack on 19 August 2020 (see Excel document titled 2_CTCL Analysis Cohort A -final version including additional OS analyses from 2nd progression_17Aug2020.xlsx). For the data used in the current analyses for MF patients after two prior lines of treatment, please see the attached Excel document (titled 'CTCL Analysis Cohort A - additional OS analyses from 3rd progression_26March2021.xlsx).

To match the optimised target population in the UK for mogamulizumab, third-line, advanced MF and second-line 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[1]) 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.

While mean age and gender distribution were very similar between the two data sources, based on the requirements in the Final Appraisal Determination Document (Section 3.5, February 2021) the matching was performed on the proportion of MF and SS patients, age and sex. The MAVORIC trial was reweighted to represent these patient characteristics as observed in the 3rd line MF patients and 2nd line SS patients in the HES data.

For the simple matching based on disease classification (MF/SS) alone, a simple weighting was estimated based on the inverse probability of being in a given disease class in the HES dataset. In this analyses, similarly to the previous sensitivity analyses, a more sophisticated MAIC was conducted including disease type, sex and gender using the method of moments methodology described Signorovitch et al. (2010) and the NICE Technical Support Document 18.[2,3]

The overall survival (OS) parameters for the standard of care 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.

Reweighting of the MAVORIC trial data

As expected based on the original analyses results of the MAVORIC trial, focusing on the selected population and 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, age and sex on MAVORIC trial mogamulizumab arm for 3rd line advanced MF and 2nd line SS

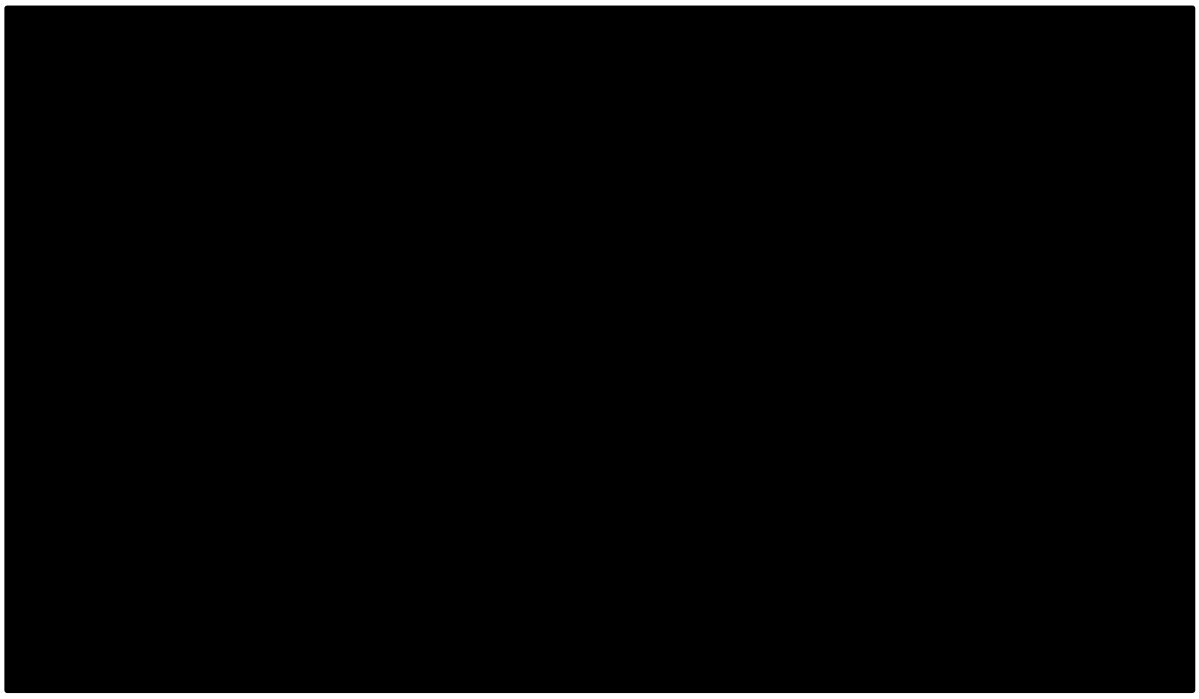

Figure 2: Impact of reweighting according to HES MF/SS proportions on MAVORIC trial vorinostat arm for 3rd line advanced MF and 2nd line SS

Survival analyses

In line with the original submission as well as guidance from NICE DSU 14[4], 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

Figure 3 presents the re-weighted unadjusted KM curves based on MAVORIC for mogamulizumab and HES data for the comparator arm. The median survival was not reached in the mogamulizumab arm.

Figure 3: Re-weighted MAVORIC Kaplan-Meier data, 3rd line advanced MF and 2nd line SS population

Key: KW-0761, mogamulizumab; OS, overall survival; MF, mycosis fungoides; SoC, standard of care; SS, Sezary syndrome

Diagnostic plots for these data are presented in Figure 4. When considering the statistical fits (Table 1), the exponential provides the best fit to the re-weighted mogamulizumab OS.

Figure 4: Diagnostic plots for re-weighted MAVORIC trial OS - 3rd line advanced MF and 2nd line SS population

Key: MF, mycosis fungoides; SS, Sezary syndrome

Table 1: AIC and BIC statistics OS – 3rd line advanced MF and 2nd line SS population

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

Key: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion; MF, mycosis fungoides; SS, Sezary syndrome; OS, overall survival.

Parametric survival models shown alongside observed data are provided in Figure 5. The statistically best fitting exponential curve provided a good fit visually and was clinically plausible. Therefore, it was chosen to be the base case for mogamulizumab.

Figure 5: Re-weighted MAVORIC OS, 3rd line advanced MF and 2nd line SS population

Key: OS, overall survival; AIC: MF, mycosis fungoides; SS, Sezary syndrome.

For the comparator arm 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. 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, 3rd line advanced MF and 2nd line SS population

Key: HES, Hospital Episode Statistic; OS, overall survival; MF, mycosis fungoides; SS, Sezary syndrome.

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Figure 7: Comparison of OS extrapolations between re-weighted MAVORIC mogamulizumab arm and HES data, 3rd line advanced MF and 2nd line SS population

Key: ECM, established clinical management; OS, overall survival; HES, Hospital Episode Statistic; mycosis fungoides; SS, Sezary syndrome

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Next-treatment-free survival

Figure 8 presents the KM curve of NTFS by randomised treatment arm.

Figure 8: Re-weighted MAVORIC NTFS Kaplan-Meier data, 3rd line advanced MF and 2nd line SS population

Key: NTFS, next-treatment-free survival; MF, mycosis fungoides; SS, Sezary syndrome

Diagnostic plots for these data are presented in Figure 9. Table 2 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 log-logistic models provide the best statistical fit according to AIC/BIC statistics, while for the mogamulizumab arm, the log-normal model provides the best fit. Therefore, these were selected as the base case.

Table 2: AIC and BIC statistics for PSM fits to NTFS Kaplan-Meier data, 3rd line advanced MF and 2nd line SS population

Model	AIC V	AIC M	Joint	BIC V	BIC M	Joint
Exponential						
Weibull						
Log-normal						
Log-logistic						
Generalised Gamma						
Gompertz						

Key: AIC; Akaike Information Criterion, BIC: Bayesian Information Criterion; NTFS, next-treatment-free survival; MF, mycosis fungoides; SS, Sezary syndrome; V, vorinostat; M, mogamulizumab.

Figure 9: Diagnostic plots for re-weighted MAVORIC trial NTFS, 3rd line advanced MF and 2nd line SS population

Key: NTFS, next-treatment-free survival; MF, mycosis fungoides; SS, Sezary syndrome

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

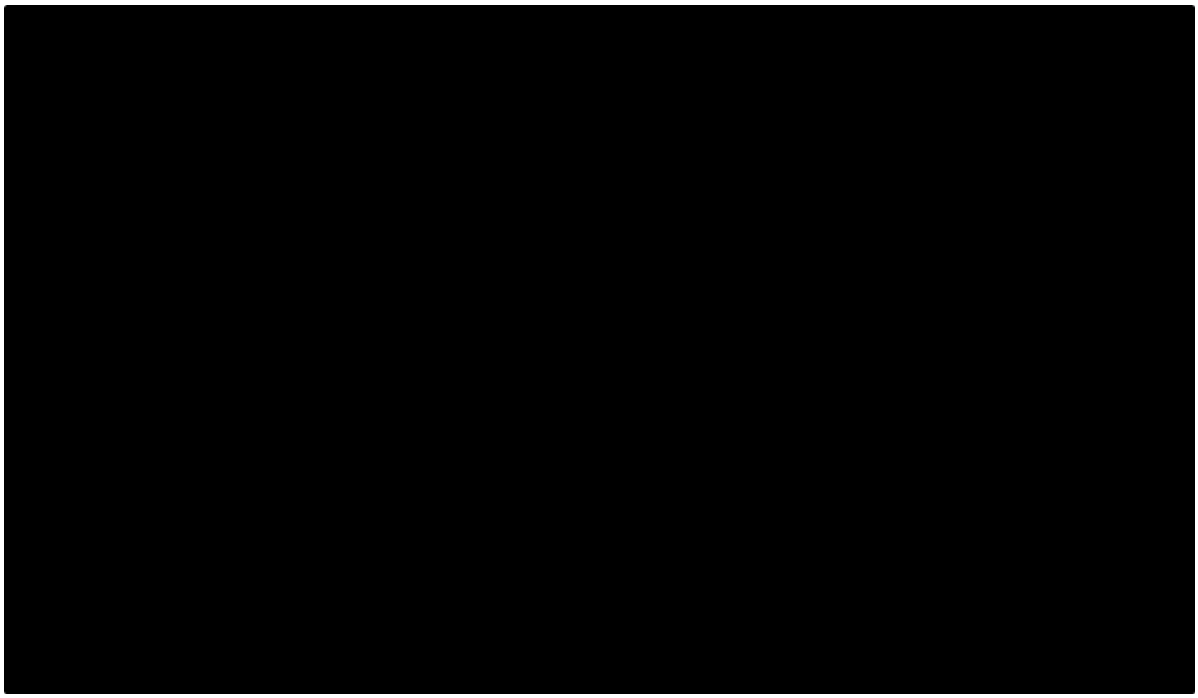
Figure 10: Reweighted MAVORIC NTFS, 3rd line advanced MF and 2nd line SS population

Key: NTFS, next-treatment-free survival; MF, mycosis fungoides; SS, Sezary syndrome

Progression-free survival

Figure 11 presents the KM curve of PFS by randomised treatment arm.

Figure 11: Re-weighted MAVORIC Kaplan-Meier plot for PFS, 3rd line advanced MF and 2nd line SS population



Key: PFS, progression-free survival; MF, mycosis fungoides; SS, Sezary syndrome.

Diagnostic plots for these data are presented in Figure 12. **Key:** PFS, progression-free survival; MF, mycosis fungoides; SS, Sezary syndrome.

Table 3 shows AIC and BIC statistics for the model fits. PFS data is almost complete; therefore, all fits were close to one another. For the vorinostat arm log-logistic models provide the best statistical fit according to AIC/BIC statistics, while for the mogamulizumab arm, the log-normal model provides the best fit. Therefore, these were selected as the base case.

Parametric survival models shown alongside KM data are provided in Figure 13.

Figure 12: Diagnostic plots for re-weighted MAVORIC trial PFS, 3rd line advanced MF and 2nd line SS population

Key: PFS, progression-free survival; MF, mycosis fungoides; SS, Sezary syndrome.

Table 3: AIC/BIC values for re-weighted MAVORIC PFS, 3rd line advanced MF and 2nd line SS population

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

Key: AIC, Akaike Information Criterion, BIC: Bayesian Information Criterion; PFS, progression-free survival; MF, mycosis fungoides; SS, Sezary syndrome; KW-0761, mogamulizumab.

Figure 13: Re-weighted MAVORIC PFS extrapolations, 3rd line advanced MF and 2nd line SS population

Key: PFS, progression-free survival; MF, mycosis fungoides; SS, Sezary syndrome.

Time on treatment

As time of treatment Kaplan-Meier curves were complete no extrapolation was required, and the Kaplan-Meier estimates were used directly in the cost-

effectiveness model (see Figure 14: Re-weighted MAVORIC Kaplan-Meier plot for ToT, 3rd line advanced MF and 2nd line SS population).

Figure 14: Re-weighted MAVORIC Kaplan-Meier plot for ToT, 3rd line advanced MF and 2nd line SS population

Key: ECM, established clinical management; ToT, time on treatment; MF, mycosis fungoides; SS, Sezary syndrome.

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in collaboration with:

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

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

Authors

Robert Wolff, Managing Director, KSR Ltd, United Kingdom (UK)
Sabine Grimm, Health Economist, Maastricht University Medical Center+ (UMC+), The Netherlands
Willem Witlox, Health Economist, Maastricht UMC+, The Netherlands
Mickaël Hiligsmann, Health Economist, University of Maastricht, The Netherlands
Ben Wijnen, Health Economist, Maastricht UMC+, The Netherlands; Trimbos Institute, Utrecht, The Netherlands
Charlotte Ahmadu, Health Economist, KSR Ltd, UK
Steve Ryder, Health Economist, KSR Ltd, UK
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Steven Duffy, Information Specialist, KSR Ltd, UK
Dr Isabel Syndikus, The Clatterbridge Cancer Centre National Health Service (NHS) Foundation Trust, UK
Manuela Joore, Health Economist, Maastricht UMC
Jos Kleijnen, Director, KSR Ltd, UK

Correspondence to Kleijnen Systematic Reviews Ltd
FAO Robert Wolff
Unit 6, Escrick Business Park, Riccall Road, Escrick
York, UK
YO19 6FD

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Rider on responsibility for report

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Company's response and updated cost effectiveness results

The company presented a new cost effectiveness model for a new, 'optimised', population, using the HES data to inform the comparator arm and [redacted]

Optimised population

The company presented analyses for a so-called 'optimised population', who appear to be *"…patients with advanced disease following at least two prior systemic therapies for MF and one prior systemic therapy for SS, who are clinically ineligible for, or refractory to, treatment with brentuximab vedotin…"* (page 6 of refined analyses post appeal).[1]

ERG comment: It appears as though the company did not change the patient baseline characteristics in their model in line with the optimised population. This would impact on a number of model aspects, including the calculations for drug dosing and utility calculations. The company should provide clarification over whether patient baseline characteristics were adjusted, and if not, provide adjusted analyses.

End of life

The company argues that life expectancy for the optimised population is likely to be less than 24 months, thus fulfilling the EOL criterion. This is on the basis of median survival estimated from the HES data despite the mean estimated using the cost effectiveness model being greater than 24 months (by four months, see Table 1).

Table 1: Life expectancy with standard of care (End-of-life criterion 1)

	Median	Mean	Comments
HES data	13 months 1.1 years	28 months 2.3 years	Direct from HES data as per Appeal Decision* For mean extrapolated using exponential distribution
HES, Hospital Episode Statistics * Mogamulizumab ID1405 Appeal Panel Decision Paragraph 112			

They support the lack of attention that should be given to the mean by citing clinical expert opinion that it is *"skewed by "super-surivors, the long survival of app.10% of patients receiving the only potentially curative treatment, aSCT after current and subsequent treatment in the HES database (Mogamulizumab ID1405 Appeal Panel Decision Paragraph 124, June 2021)".*(page 8 of refined analyses post appeal).[1] The company also cited the judgment in the FAD that the survival benefit of patients receiving aSCT after current treatment should be excluded from the mogamulizumab arm of the cost-utility analyses.[2]

ERG comment: The ERG dispute grounds for the lack of attention that should be given to mean life expectancy. This is on the basis that the so-called 'super-survivors' are part of the same cohort for which life expectancy is estimated and therefore their life expectancy is not a bias to but part of the life expectancy of the whole cohort.

It is true that the FAD stated that *"…in the model it preferred removing allogeneic stem cell transplant after current treatment, to avoid double-counting survival benefit in MAVORIC and to reduce potential bias."* (page 9 of FAD)[2] However, this recommendation was intended to remove any potential bias in the estimate of the *difference* between mogamulizumab and standard care in QALYs and cost and did not imply that the *absolute* estimate of life expectancy with standard care was biased by the inclusion of aSCT. Indeed, the potential for bias existed because of the discrepancy between standard care where aSCT would take place and the source of data for mogamulizumab, i.e. MAVORIC, where it did not.

Clarifications on MAIC according to the appeal

In line with the discussions with NICE, Kyowa Kirin has conducted a scenario analysis including age and sex. The results are shown in Table 2.

Table 2: Results of the unanchored indirect comparison

	Median survival in months (95% CI)	Data first presented	Hazard ratio (95% CI)
Unadjusted			
Mogamulizumab	57.2 (40.1, NA)	ID1405_mogamulizumab for treating MF or SS CTCL_Survival analyses incl SCT Appendix 3, Feb 2020	0.43 (0.31 to 0.60)
Standard of care	17.83 (12.37, 24.03)	Technical engagement meeting, 29 May 2020	
Base case: Adjusted for MF/SS			
Mogamulizumab	NA (51.7, NA)	ID1405 Mogamulizumab additional ACD requested analysis respot_Kyowa Kirin_v1.0_Final, Aug 2020	0.36 (0.24 to 0.53)
Standard of care	17.83 (12.37, 24.03)	Same as above	
Sensitivity analyses: Adjusted for MF/SS, age, sex			
Mogamulizumab	NA (40.06, NA)	In current document	0.38 (0.25 to 0.59)
Standard of care	17.83 (12.37, 24.03)	Same as above	

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

Survival analysis

The company's survival analyses based on the refined MAIC appear to be in line with methodological recommendations. The ERG has nothing to add regarding NTFS, PFS and TTD and agrees with the company's choice of distributions.

However, regarding OS, the ERG wishes to highlight a remaining area of uncertainty. The company's selected distribution for both arms (the exponential) indeed makes the best fit for the mogamulizumab arm, but for the comparator it provides the worst fit. Differences in long-term extrapolated survival are large between the different distributions. The ERG considers that exploration of alternatives is therefore indicated.

The ERG prefers to use the distributions with the best statistical fit. However, the company dismissed the best-fitting generalised gamma for the HES arm based on its long, clinically implausible tail, which would imply that more than 10% of patients would essentially be cured (no more OS events after approximately 10 years). This may or may not be clinically plausible and the ERG notes the company's statement: *"super-surivors, the long survival of app.10% of patients receiving the only potentially curative treatment, aSCT after current and subsequent treatment in the HES database (Mogamulizumab ID1405 Appeal Panel Decision Paragraph 124, June 2021)"* (page 8 of refined analyses post appeal).[1]

The lognormal makes the second-best fit for both arms (AIC and BIC are indeed very close), and the ERG uses this in its preferred analysis (Table 3).

The ERG acknowledges that this is a matter of judgement and other scenarios may be plausible. The ERG also considers a scenario using the log-normal for both arms.

Conclusion

The ERG considers that substantial uncertainty remains about the long-term overall survival of mogamulizumab over established clinical management. Partly, this is represented by the scenario analyses around the chosen distributions for overall survival. Limitations around the use of HES data in the MAIC remain and this uncertainty has not been fully explored in the economic modelling.

Table 3: Cost-effectiveness results of ERG analyses (deterministic unless indicated)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's refined base-case					
Mogamulizumab	[redacted]	4.68	£86,998	3.08	£28,233
ECM	[redacted]	1.60			
ERG preferred analysis: lognormal for HES arm OS					
Mogamulizumab	[redacted]	4.68	£81,292	2.58	£31,475
ECM	[redacted]	2.10			
ERG preferred analysis: lognormal for HES arm OS (probabilistic)					
Mogamulizumab	[redacted]	4.69	£80,663	2.56	£31,509
ECM	[redacted]	2.13			
Scenario 1: generalised gamma for HES arm OS					
Mogamulizumab	[redacted]	4.68	£73,368	2.00	£36,720
ECM	[redacted]	2.68			
Scenario 2: lognormal for both arms OS					
Mogamulizumab	[redacted]	5.63	£94,773	3.53	£26,859
ECM	[redacted]	2.10			

ECM = established clinical management; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; QALY = quality-adjusted life year

References

[1] Kyowa Kirin. *Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]. Refined analyses and additional clarifications in response to the NICE Appeal Decision (and accepted by NICE to submit 13th August 2021). Single technology appraisal (STA)*: Kyowa Kirin, 2021

[2] National Institute for Health and Care Excellence. *Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome. Final appraisal document [Internet]*. London: National Institute for Health and Care Excellence, 2021 [accessed 28.6.21] Available from: https://www.nice.org.uk/guidance/gid-ta10305/documents/final-appraisal-determination-document