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

1. None of the members of the appeal panel had any competing interest to declare.
2. 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).
3. 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

1. 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

1. 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

1. Professor Cowan declared that he had in the past consulted for Kyowa Kirin.
2. 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

1. The appeal panel’s legal adviser Stephen Hocking was also present.
2. 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)

1. 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.
2. 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.

1. 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

1. 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.
2. 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.
3. 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

1. 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.
2. 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.
3. 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%.
4. 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.
5. 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).
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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

1. 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.
2. 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.
3. 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.
4. 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”.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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

1. 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.
2. 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.
3. 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.
4. 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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).
6. 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.
7. Dr Morris, for UKCLG, said that from a clinician and patient point of view, there is no uncertainty about the clinical effectiveness of mogamulizumab.
8. 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.
9. 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.
10. 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

1. 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.
2. 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).
3. 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.
4. 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).
5. 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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

1. 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

1. 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.
2. 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”.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. Linda McNamara, for Kyowa Kirin, said that the company had raised this issue in their consultation response.
8. 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.
9. 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

1. This appeal point was discussed together with UKCLG point 2.4 at the hearing.
2. 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.
3. 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.
4. 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.
5. 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).
6. 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.
7. In response to questions from the panel, Robert Wolff, for the appraisal committee, confirmed that the ERG preferred scenario did model an OS benefit.
8. 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.
9. 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.
10. 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

1. 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.
2. 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.
3. 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).
4. 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.
5. 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.
6. 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.
7. 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.
8. 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”.
9. 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.
10. 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.

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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).
7. 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.

1. Zack Pemberton-Whiteley, for LALC, 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).
2. 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.
3. Ross Dent, for NICE, said that means are preferred because cost-benefit analyses use the mean and committees want to be consistent.
4. 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.
5. 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.
6. 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.
7. 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.

1. These points were originally submitted separately but following initial scrutiny were accepted for consideration as a single point of appeal.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.

1. 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.
2. The appeal panel’s conclusions on this issue are set out in paragraph 101-103 of this letter.
3. 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. The panel therefore dismissed the appeal on this point.

## Conclusion and effect of the appeal panel’s decision

1. 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.
2. 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.

1. The committee may additionally wish to consider clarifying the FAD as suggested in paragraphs 74 and 135 above.
2. 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.
3. 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.