­Sent by email to: [XXXXXXXXXXXXXXXXXXXXXXXXXXXX](mailto:Linda.McNamara@kyowakirin.com)X

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Kyowa Kirin

19 April 2021

Dear XX XXXXXXXX

**Re: Final Appraisal Document –** **Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]**

Thank you for your letter of 12 April 2021, responding to my initial scrutiny letter. This letter represents my final decision on initial scrutiny.

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

* 1. **The Committee’s decision that allogenic stem cell transplant should not be included in the economic modelling for mogamulizumab because aSCT had not been permitted in the MAVORIC trial is unfair**

Already accepted as valid.

* 1. **The Committee’s conclusion that the IPCW-adjusted curve was not clinically plausible for the average person in the modelled population with severe disease is unexplained**

I accept the statement that reasons must “*enable the reader to understand why the matter was decided as it was and what conclusions were reached on the “principal important controversial issues*”. I remain of the view that the application of this test is context dependent (so here the question is not whether reasons are adequate for the average citizen, but for a reader with some knowledge of the analysis of clinical trial data). I am also of the view that the context includes all of the appraisal documentation, although naturally I accept that, say, a document from the company or from the ERG cannot be said to contain committee reasons unless it is adopted or disagreed with by the committee.

In the MAVORIC trial there was a great deal of patient crossover, for unavoidable ethical reasons. Anyone with knowledge of clinical trial analysis will know that that potentially introduces confounding factors, that these must be corrected for statistically, that there are various ways to do so and that (as a rule) there is no one obviously “best” way. It was also obvious that this was an issue in play in the appraisal, and I accept (for scrutiny purposes at least) that it was an important issue.

However, there is extensive discussion of this issue in the FAD (and I note it was raised in consultation and at the committee’s public meeting). You have focused on one sentence “*The committee was not convinced that the IPCW adjusted curve was clinically plausible for the average person in the modelled population with severe disease*” but in doing so you have not done justice to the discussion at FAD 3.8, all of which has to be read to understand the committee’s position on correcting for crossover. It still seems to me you are focusing on reasons for reasons. Reading the whole of FAD 3.8 one can see that the committee’s conclusion is “*that the results from the 2-stage estimation and IPCW methods represented the upper and lower range of plausible overall survival in the standard care arm*.” In other words, it allowed both your preferred method and the ERG method to inform its analysis, by setting an upper and a lower bound on OS in the comparator arm. That (at best) is the decision for which reasons must be given, not the statement that the IPCW curve may not have been clinically plausible. (I say at best because I consider it is arguable that even this statement is in fact the reason called for, and so the discussion in FAD 3.8 may already be reasons for reasons. However I am not proceeding on that basis.) It seems to me that FAD 3.8 clearly gives sufficient reasons for the committee’s approach which include but are not limited to clinical plausibility. The reasons given may or may not be good reasons, of course, but that falls to be considered under ground 2.

Therefore I am still of the view this is not a valid appeal point.

* 1. **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**

Thank you for your additional comments. Particularly in light of the reference to the methods guide and to past practice I agree this is a valid appeal point.

* 1. **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**

Already accepted as valid.

* 1. **The Committee’s conclusions regarding the appropriate ICER threshold for this appraisal do not take into account the factors identified at paragraph 6.3.3 of NICE’s Guide to the Methods of Technology Appraisal**

I have considered your additional comments carefully, but am still not satisfied that it is arguable that the Committee has not acted fairly here. The committee indicates where it would have found an acceptable ICER to be and gives adequate reasons for that. I do not think fairness requires any farther discussion of the factors set out in para 6.3.3 of the methods guide. Therefore I am still of the view this is not a valid appeal point.

* 1. **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**

Already accepted as valid.

* 1. **The Committee’s conclusions regarding the appropriate ICER threshold for this appraisal lack transparency**

Already accepted as valid.

* 1. **The Committee’s conclusions regarding the most plausible ICER for this appraisal lack transparency**

I have considered your additional comments carefully, but remain firmly of the view that fairness cannot require more precision in the most plausible ICER(s) than a committee reasonably considers possible. Here the committee identifies considerable uncertainty and accordingly offers a considerable range. I do not agree there is any lack of clarity surrounding the committee’s preferred assumptions. Paragraph 3.14 and indeed the FAD more broadly discusses uncertainty, assumptions and the different models and inputs quite clearly. Therefore I am still of the view this is not a valid appeal point.

* 1. **The Committee’s statement that the relevant benefits associated with mogamulizumab could be adequately captured in the model disregards its own conclusions, is inconsistent with NICE’s procedures and lacks transparency**

I have considered your additional comments but they seem to me to repeat for initial point, that by the committee saying that benefits “could be” captured in the model the committee was in some way casting doubt on whether they had been captured. I am afraid I simply do not agree the FAD can be read as you are reading it.

Nor do I think that excluding carer benefit from the model can be unfair (whether it is reasonable is of course a different question). It is apparent from the FAD that the committee were not satisfied with how you had modelled those benefits, and why that was. Your comments seem to suggest it is for the committee to establish that a product is not cost effective, which is not the case. A committee must assess the case made to it and in this case (rightly or otherwise) it concluded your case on carer utility could not be accepted, leaving it with no quantitative analysis on this point. Whether this required special consideration at FAD 3.17 was an issue raised in consultation, and it seems to me rightly rejected. If a company provides an analysis on a particular issue which the committee rejects and excludes from the model, it is clearly a circular argument to say that the model then no longer captures all; the benefits of treatment and so the rejected benefits have to be reintroduced under the equivalent of FAD 3.17. There is no unfairness here as carer utility was an issue raised in the course of the appraisal and you had the opportunity to put your case as you wished.

Therefore I am still of the view this is not a valid appeal point.

***Ground 2: the recommendation is unreasonable in the light of the evidence submitted to NICE***

* 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**

Already accepted as valid.

* 1. **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**

Already accepted as valid.

* 1. **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**

In light of your additional comments I agree this is a valid appeal ground.

* 1. **The Committee’s conclusion that it was not convinced that mogamulizumab provides an overall survival benefit is unreasonable in light of the evidence available**

Already accepted as valid.

* 1. **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**

Already accepted as valid.

NICE will now contact you to make arrangements for an oral appeal hearing, which is likely to be conducted remotely. Your appeal points will be shared in advance with any co-appellants, and you will in turn receive the appeal points that have been accepted from any co-appellants, to help with preparing for the appeal day. The chair of the appeal panel is likely to want to group points that raise similar issues to be taken together, so that the day can be conducted most effectively, and may be in touch in this regard.

Ordinarily appeals are conducted on the basis of the appellants’ written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be before the panel that you would wish to rely on you must let NICE know by return of letter, indicating what the material is, why it is desirable to submit it, and when it will be available, by no later than **Monday 26 April 2021**. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

Many thanks

Yours sincerely

Tim Irish

Vice Chair

National Institute for Health and Care Excellence