Xx xxxxx xxxxxxx

Managing Director, UK & Ireland

MSD

Sent by email: [xxxxxxxxxx@merck.com](mailto:xxxxxxxxxx@merck.com)

3 April 2020

Dear xx xxxxxxx

**Re: Final Appraisal Document - Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum - containing chemotherapy [ID1536] (CDF guidance review of TA519)**

Thank you for your letter of 26 March 2020, lodging Merck Sharp and Dohme’s appeal against the above Final Appraisal Document (FAD). I am replying as interim Vice Chair in place of Tim Irish, who is currently acting as interim Chair.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

* 1(a) NICE has failed to act fairly, or
* 1(b) NICE has exceeded powers;
* (2) the recommendation is unreasonable in the light of the evidence submitted to NICE

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information and arguably fall within any one of the grounds, will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn and then summarise the appeal points that I am presently minded to refer at the end of this letter. Thank you for grouping your appeal points thematically in your letter for ease of exposition. I think it may be easier for present purposes if I respond to them in number order grouped under NICE’s three appeal grounds, but it will be for the appeal panel to decide how best to take the valid points in the appeal hearing.

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

**Ground 1a.1 – Fundamental differences with the approach taken in TA525 evidence an inconsistent methodology, in breach of the Methods Guide and the principle of procedural fairness**

A valid appeal point.

Your comments about NICE’s approach to consistency in past appeals are correct. An appeal on grounds of consistency will raise particular challenges for an appeal panel, as it will not have the papers in the comparator appraisal before it. I would like to take this opportunity to try to manage that difficulty as best we can. I will suggest to NICE that the FAD in TA525 should be included with the appeal papers in this case, which I hope will be sufficient. Please confirm that the alleged inconsistencies identified in your letter are all the inconsistencies that you will rely on, as the appeal panel will prepare for those points and may not be able to accept any further or wider instances of inconsistency.

**Ground 1a.2 – It is procedurally unfair to have introduced paragraph 3.19 (“The costs of pembrolizumab are likely underestimated in the model”) in the FAD at a very late stage, without explanation or any opportunity to respond**

A valid appeal point.

***Ground 1b NICE has exceeded its powers***

**Ground 1b.1 – NICE has breached its legal obligations under human rights and equalities laws**

I agree, at least for present purposes, that a treatment such as this is at least within the ambit of Article 2. You accept that Article 2 is unlikely to compel a nation to make a specific treatment available. Your argument is that there is a procedural content to Article 2 in cases such as this.

However I am unsure whether this is a standalone point of exceeding powers, or whether it should instead inform the standard of review that the appeal panel should apply when asking whether the committee has acted unfairly or unreasonably. If the argument is not that Article 2 compels a positive recommendation per se, but rather it compels a particular approach to the evidence or it narrows the range of otherwise reasonable conclusions, is that not better considered as part of the appeal panel’s consideration of your points around unfairness or unreasonableness?

Perhaps you could consider and let me have your further views before I take a final decision on this point.

As to discrimination either under article 14 or the Equality Act, could you elaborate further? Any decision not to recommend a treatment leaves the relevant patient group in a worse position than they would have been in had the treatment been recommended, but I am not sure that that alone establishes unlawful discrimination or a breach of the PSED. Do you have a comparator group in mind who you say has been treated more favourably for an unjustified reason? In so far as the concern is that NICE’s assessment of the evidence is said to be not objectively justified, it seems to me that would fall to be considered under ground 2 in any case. While it could be said that a patient group subject to such an appraisal has been treated less favourably than a patient group who benefited from a well conducted appraisal, I am not sure that discrimination would be the most natural characterisation of what had gone wrong? I don’t yet see any specific discrimination argument here and would benefit from further argument from you on this point before making a decision on admissibility.

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

**Ground 2.1 – The Appraisal Committee’s assessment of duration of treatment effect and its effect on cost-effectiveness is illogical and unreasonable**

A valid appeal point.

**Ground 2.2 – The Appraisal Committee’s analysis of evidence from the clinical expert in paragraph 3.15 of the FAD is internally inconsistent and its conclusions are unreasonable**

I wonder whether this is a standalone point, or is an argument in favour of point 2.1? I would be minded to suggest it is valid but should be considered in the round as part of point 2.1.

**Ground 2.3 – The Appraisal Committee’s decisions that: (i) a range of possible ICERs from £48,518 to £70,520 applies; and (ii) the “most plausible” ICER for pembrolizumab is likely to be above £50,000, are unreasonable in light of the evidence submitted**

Similarly I wonder whether this is a standalone point, or is an argument in favour of point 2.1? Again I would be minded to suggest it is considered in the round under ground 2.1.

**Ground 2.4 – The statement that “the costs of pembrolizumab are likely underestimated in the model” lacks meaningful explanation and evidence and it is unreasonable to have taken it into account for the purposes of assessing cost-effectiveness**

A valid appeal point.

**Ground 2.5 – The conclusion that new data from KEYNOTE-045 “shows the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account” results from a flawed and unreasonable interpretation of the evidence**

A valid appeal point. For guidance, as you will be aware, the question for the panel will be whether the guidance cannot reasonably be justified in light of the evidence, i.e. whether the analysis adopted cannot reasonably be justified. Whether the 2-stage method might also have been a reasonable approach to have taken will at best only be relevant on the margin of this question.

At present I am minded to refer points 1a.1, 1a.2, 2.1 incorporating 2.2 and 2.3, 2.4 and 2.5 to an appeal panel. I am not minded to refer 1b.1.

In respect of the points that I am not yet minded to refer, you are entitled to submit further clarification and/or evidence to me within the next 10 working days, **no later than 5pm Tuesday 21 April 2020,** and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held, although under current circumstances this is likely to be held virtually. It is also possible that the usual timeframe for the hearing will have to be extended given the challenge of securing availability from those working in NHS. The appeals team will be in contact as soon as there is further information on the date for the appeal.

Yours sincerely

Dr Rima Makarem

Interim Vice-Chair, National Institute for Health and Care Excellence