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6 September 2021

Dear Merck/Pfizer Alliance

**Re: Final Appraisal Document –** **avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]**

Thank you for your letter of 27 August 2021. This letter is 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 conclusion that a stopping rule is inappropriate for avelumab is inconsistent with previous appraisals for immunotherapies (IOs) in metastatic urothelial cancer (mUC).*

I have considered your additional material carefully. It still seems to me that it is impossible to argue that any inconsistency there may be between this and previous appraisals is unfair or a breach of any of NICE’s procedures. I cannot agree that “the committee has provided no reasons for diverging from the stopping rule approach it accepted in TA525.” They have done as you acknowledge.

I take your argument to be that the reasons given are flawed. That is a valid appeal argument but it falls under ground 2, because you are challenging the substance of the committee’s decision. (Put another way, in order to agree with you that “no reasons” have been given, the appeal panel would have to be persuaded that the reasons that have been given are essentially void. In turn, to do so they would have to conclude that the committee had acted unreasonably. Once they had reached that conclusion it would add nothing to go on and say that there was also a failure to explain an inconsistency versus a previous appraisal.)

Therefore, I will refer this point to an appeal panel but under ground 2.

* 1. *The Committee has relied upon irrelevant considerations in deciding that it would not implement a stopping rule for avelumab*

I am afraid I do not agree that the FAD wording you have quoted implies the committee felt bounded in the conclusion they could reach. Furthermore, if that were the case then there would have been no need for them to have discussed other considerations bearing on the possibility of a stopping rule, which they do extensively.

I therefore conclude this is not a valid appeal point.

* 1. *The Committee has provided no explanation for its concern that it would be difficult for patients to accept discontinuance of treatment after 2 years and for rejecting the evidence of the clinical and patient experts and patient organisations*

I broadly agree that “Rigorous decision-making requires that the decision-maker explains its viewpoint with appropriate reasoning”, but the question is what is appropriate. Here we can see that the committee are aware of the opinions of patients and experts, and we can see they disagree, or at any rate that those opinions do not carry the day. I still take the view that this is the degree of reasoning that is required by fairness. I do have to note that the committee expressed the same view in the ACD and you did not challenge it as unfair at that point, or say that you were prevented from engaging with the appraisal because of a lack of reasoning here. I am also not sure how much more reasoning could be given on this point. I assume it is obvious why the withdrawal of treatment from all patients after two years is potentially problematic, and it seems to me very much a matter of judgement how problematic it may be. Patients and clinical experts took the view that if well managed it would not be very difficult, and the committee felt that might be overly optimistic. I do not think much more can be said, so far as giving reasons is concerned.

I therefore conclude this is not a valid appeal point.

* 1. *In view of the Committee’s view that it would be difficult for patients to accept a stopping rule for avelumab at 2 years, despite substantial evidence to the contrary, the clinical and patient experts should have been invited to attend the second meeting of the Appraisal Committee*

I do not agree that the committee is required as a matter of fairness to hear from experts again simply because they propose to disagree with them. That disagreement had been made clear in the ACD and was raised by at least one consultee (although not your company). Consultees had a chance to challenge the disagreement in writing and the committee had all of the relevant material before them. This is not a case where the experts views were unclear, but rather they were not agreed with. So far as fairness is concerned it seems to me that the committee did all that they are required to do.

I therefore conclude this is not a valid appeal point.

* 1. *In questioning whether the evidence of clinical experts regarding life expectancy corresponded to the population eligible for maintenance treatment with avelumab despite evidence to the contrary, the clinical and patient experts should have been invited to attend the second meeting of the Appraisal Committee (17th June 2021)*

Your comment is noted thank you.

* 1. The Committee’s conclusion that it is not appropriate to pool health-state utilities across treatment arms is inconsistent with previous appraisals for immunotherapies (IOs) in metastatic urothelial cancer (mUC).

I note your position that there is no scientific basis for approaching this issue differently in the context of pembrolizumab (TA692) and avelumab but cannot agree this is arguable. At FAD 3.12 the committee discuss this issue and note that in TA 692 patients on each arm of the trial went on to receive the same treatments, and that this was not the case here. In any event, for an issue of technical judgement such as whether or not to pool health state utilities across treatment arms I am very wary of the danger of elevating a difference of judgement into a matter of fairness. The greater the element of judgement the less there is to say about a difference in approach, and in my view the committee have said enough here.

I therefore conclude this is not a valid appeal point.

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

*2.1 In considering the application of the end of life criteria, the Committee has misapplied the relevant test and reached a conclusion which does not reflect the balance of the evidence..”*

Already agreed to be valid.

2.2  *The Committee’s conclusion that it is not appropriate to pool health-state utilities across treatment arms may have been impacted by a misunderstanding of the impact this has on the ICER*

I have reviewed your comments and the ACD and FAD. In the ACD the committee noted, “Using treatment-specific utilities slightly increases the ICER”, in the FAD they say, “Using pooled data for the health-state utilities slightly increased the ICER for avelumab”. There is no material or discussion that would suggest they intended to change their minds and no explanation for why they would have gone from a correct understanding to a misunderstanding. I feel confident this is a drafting error, and the change from referring from treatment-specific to pooled data has not been carried through into changing “increases” into “decreases”.

Therefore, the final valid appeal points are 1.1 (under ground 2) and 2.1.

Yours sincerely

Dr Mark Chakravarty

Lead Non-executive Director for Appeals

National Institute for Health and Care Excellence