#

27th August 2021

Dr Mark Chakravarty

Lead Non-Executive Director for Appeals

National Institute for Health and Care Excellence

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Dear Dr Chakravarty,

**APPEAL AGAINST THE FINAL APPRAISAL DOCUMENT FOR AVELUMAB FOR MAINTENANCE TREATMENT OF LOCALLY ADVANCED OR METASTATIC UROTHELIAL CANCER AFTER PLATINUM-BASED CHEMOTHERAPY [ID3735]**

Thank you for your letter dated 13 August 2021, in which you provide your preliminary view of the admissibility of the points of appeal set out in the Merck/Pfizer alliance appeal letter submitted on 6 August 2021.

We now provide, as you suggest, additional detail to elaborate, comment on or clarify those points of appeal (listed below) where your preliminary view is that these should not be referred to the appeal panel.

## **Grounds of appeal**

## **Ground 1: In making the assessment that preceded the recommendation, NICE has a) failed to act fairly or b) exceeded its powers**

**1.1 The Committee’s conclusion that a stopping rule is inappropriate for avelumab is inconsistent with previous appraisals for immunotherapies (IOs) in mUC**

You express the preliminary view that this point should not be referred to the Appeal Panel on the basis that: (a) the Committee considered the question of a stopping rule in immunotherapies after platinum-based chemotherapy in urothelial cancer as sufficiently similar to warrant consideration; (b) have given their reasons for not doing so in this case in a substantial paragraph.

While we recognise the committee is aware of past practice with regards to implementation of stopping rules in immunotherapies after platinum-based chemotherapy in urothelial cancer, what we contest strongly is the rationale the committee have provided for their decision to reject a stopping rule for avelumab.

You state that, if two appraisals are “sufficiently similar” an obligation of consistency arises, and reasons for any apparent inconsistency must be stated. We agree with your conclusion, however in certain important respects the committee in this appraisal has failed to provide such reasoning. In particular, while the committee has provided lengthy reasons for its decision to depart from the stopping rules applied in certain IO technologies, the reasons given do not apply to TA525 (atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy). They have accordingly provided no explanation for the inconsistency in approach with TA525, despite the high level of similarity to the current appraisal of avelumab.

We have outlined our argument in detail in our appeal letter. However, to briefly reiterate the key inconsistencies with TA525:

* In paragraph 3.8 of the FAD, the committee “*was concerned that it would be difficult for patients to accept that they would no longer be able to have treatment after 2 years if they were free from disease, and they may fear losing treatment benefit”.*

The committee provides no explanation as to why it would be difficult for patients to discontinue therapy with avelumab after two years (contrary to the evidence from clinicians and patient experts that this would be accepted if it enabled access to avelumab) despite accepting a stopping rule requiring patients to discontinue atezolizumab, after a similar period in TA525.

* In paragraph 3.8 of the FAD, the committee expressed concern that “*People whose disease had not progressed before needing to stop avelumab would not be able to have another immunotherapy in the NHS”.*

However, this is also true for patients receiving atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy, yet this did not preclude acceptance of a stopping rule in TA525.

* In paragraph 3.8 of the FAD, the committee stated that it *“In these [prior] technology appraisals, a stopping rule was included in the trial, or the committee was able to generalise these results to other treatments in the same class used in the same populations and settings. It considered that there was no similar evidence here to support a stopping rule, since JAVELIN Bladder 100 did not include one and the setting and population in this technology appraisal was different to others in this disease area*”.

While the patient population considered in the context of the current appraisal is not identical to that in TA525, both represent patients with locally advanced or metastatic urothelial carcinoma after treatment with first-line platinum-containing chemotherapy.

1. The patient populations for atezolizumab and avelumab are so similar that it is more than reasonable to conclude the population eligible for avelumab is generalisable to the population in TA525 and the appraisal committee has provided no reasons for any different conclusion. The population eligible for first-line maintenance therapy with avelumab represents a sub-population of the patients eligible for atezolizumab after platinum-containing chemotherapy.
2. Like JAVELIN Bladder 100, the IMvigor trials for atezolizumab did not include a stopping rule and yet this was not a barrier to the committee accepting a 2-year stopping rule in TA525.

To summarise, the committee’s reasons for rejecting a stopping rule in this appraisal have disregarded the approach taken in TA525, despite the very substantial similarities in these two appraisals. The fact that lengthy explanations have been given does not satisfy the requirement for procedural fairness if those explanations disregard relevant factors, including inconsistent decisions taken in other appraisals, and are therefore inadequate.

You say in your letter that we “imply that the approach taken in atezolizumab must also be taken here” but that “committees must have room to exercise those own judgment on the facts of each appraisal”. We do not disagree. However, where there is divergence from a prior decision taken in a similar situation, that must be explained, consistent with the requirements of NICE’s Guide to the Methods of Technology Appraisal set out in our appeal letter. Our point of appeal arose from the fact that the committee has provided no reasons for diverging from the stopping rule approach it accepted in TA525.

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

You express the preliminary view that this point should not be referred to the Appeal Panel on the basis that you say that you cannot accept that the lack of a stopping rule in the trial (and hence the SmPC) is positively something which the committee must not take into account when considering whether a stopping rule should be agreed by NICE.

In your letter you have given the example that if the SmPC did have a stopping rule then, unless NICE was to recommend off-label use, its recommendation would also have a stopping rule.

However, the appraisal committee did not simply consider the trial data (and therefore the SmPC) in the way you suggest in your letter. Instead the appraisal committee appeared to consider that it was bound to follow the design of the trial. The committee states at paragraph 3.8 of the FAD:

*“The committee concluded that the time to stopping treatment should reflect the trial evidence and a stopping rule should not be included in the model”*

In other words, the fact that a stopping rule was not part of the JAVELIN Bladder 100 clinical trial, was not simply a factor taken into account by the committee. It was a fundamental reason for the decision, even though the design of the clinical trial (and SmPC) is not a relevant consideration.

As detailed in the Merck/Pfizer Alliance appeal letter, NICE includes stopping rules principally for reasons related to cost-effectiveness and this can differ from the SmPC in the absence of safety concerns. Furthermore, there is precedence in previous appraisals of NICE recommending a stopping rule when this is not included in the associated SmPC and trial (separately to TA525).

Merck/Pfizer therefore believe that the reliance on the JAVELIN Bladder 100 trial and the SmPC for avelumab as reasons not to implement a stopping rule is unfair and inconsistent with prior appraisals and NICE’s procedures.

**1.3 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**

In your preliminary view of this point, you state that you do not accept that an obligation to give reasons extends not only to indicating a disagreement with a certain piece of evidence, but also to giving reasons for that disagreement. We disagree. A fundamental part of the requirement to give reasons is to demonstrate that decisions are made for rational reasons and are not arbitrary. If reasons for disagreeing are not provided, it is not possible to test whether such disagreement is reasonable.

In this particular example, we assume you are suggesting that the committee is not required to provide a rationale for disagreeing with the patient and clinical experts regarding the viewpoint that patients would find it difficult to accept that they would no longer be able to have treatment after 2 years. This cannot be correct. Rigorous decision-making requires that the decision-maker explains its viewpoint with appropriate reasoning, particularly when this viewpoint is in direct contradiction to the patient and clinical experts who have extensive personal and professional experience in this area and have been invited to participate and shares these experiences in this appraisal. It is patently unfair that the viewpoint of a committee on whether patients would be concerned about a treatment stopping rule should, without reason, overrule the viewpoint of the very patients who would be taking this drug (and who have clearly stated they would accept a stopping rule if it meant they could have access to avelumab) and the clinicians who treat them.

**1.4 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 (17th June 2021)**

In your preliminary assessment of this point of appeal, you express the view that there would be a requirement to invite the patient and clinical experts to attend the second meeting of the appraisal committee only if “there was something that they needed to say that they had not had the chance to say or that the committee had not properly informed itself of some relevant issue…”. You suggest that neither of these situations was applicable in the current appraisal. We do not agree.

Firstly, while you say that the ‘stopping rule/duration of treatment topic was in play at the ACD stage and the views of the patients and clinicians were known’, the stopping rule was included in the company’s base case only in response to consultation on the ACD and could not therefore be considered at the first meeting of the appraisal committee.

The potential implementation of a stopping rule was a key issue at the second meeting of the appraisal committee, but without input from the patient and clinical experts it was barely discussed during the public part of the meeting. It is the position of the Merck/Pfizer Alliance that the committee was not in a position to adequately consider the implementation of a stopping rule in the context of the companies’ revised base case in the absence of appropriate patient/clinical advice and that this constituted a procedural flaw in the appraisal. For completeness, this view is supported by the lack of proper explanation for the committee’s assertion that it would be difficult for patients to accept a stopping rule disregarding contrary evidence from patient and clinical experts at the first committee meeting.

**1.5 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)**

We do not agree with the preliminary view expressed in your letter. However, we note your suggestion that this issue may be considered as part of appeal point 2.1 and will proceed on that basis.

**1.6 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).**

You express the preliminary view that the preference for pooled utilities or those from separate treatment arms is an expert judgment for a committee that can only be taken in the light of the data available in each appraisal. You suggest that there can only be a requirement for consistency in this context if the committee is dealing with the very same trial data.

We disagree with your preliminary view. The issue in this point of appeal is the inconsistent approach to utility benefit deriving from immunotherapies after platinum-based chemotherapy in the same disease. It is Merck/Pfizer Alliance’s position that there is no scientific basis for approaching this issue differently in the context of pembrolizumab (TA692) and avelumab - irrespective of the trial data - and the committee provides no reason for doing so. This inconsistency is clearly unfair.

## **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**

Your preliminary view is noted.

**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**

In your letter you express the preliminary view that you are not persuaded that the inaccuracy in the FAD may amount to unreasonableness although you say it “may” be grounds for a factual correction.

With respect, this cannot be right. The conclusion expressed in the FAD is incorrect. It is therefore clearly unreasonable. It is not possible to say whether this was simply an error in preparing the FAD or if it was an erroneous conclusion by the committee and, if it was the latter, what effect that had on the committee’s reasoning. In particular, it cannot be right to dismiss such a point at the initial scrutiny stage without giving proper consideration to these legitimate concerns.

Thank you for your consideration of the issues raised in this letter. We hope that the additional clarification we have provided will persuade you that our points of appeal should be permitted to proceed to a hearing and look forward to receiving your final views on admissibility.

Yours sincerely,

Merck/Pfizer Alliance