#

6th August 2021

Mr Tim Irish

Vice chair

National Institute for Health and Care Excellence

2nd Floor

2 Redman Place

London E20 1JQ

Dear Mr Irish,

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

**Executive Summary**

MerckSerono and Pfizer (Merck/Pfizer alliance) wish to appeal the above Final Appraisal Document (“FAD”), in which avelumab is not recommended for routine funding. The Merck/Pfizer alliance are disappointed by the Appraisal Committee’s decision and disagree with the various judgements and assumptions the Committee made on key aspects of the evidence-base. Considering the evidence submitted during the appraisal process and the input of experts, the Committee has reached a conclusion based on the most conservative assumptions available. The Merck/Pfizer alliance therefore wishes to appeal this decision on the following grounds:

**Ground 1a**

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

**Ground 2**

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.

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

**Introduction**

A summary of the original Merck/Pfizer Alliance’s submission is provided here. It is not intended to replace the details originally supplied to NICE.

Urothelial carcinoma (UC) is the most common type of bladder cancer in the UK, accounting for over 90% of cases (1). In England, the National Cancer Registration and Analysis Service reported 8,686 bladder cancer cases in 2017, of which 1,464 (16.9%) (2) were Stage IV (disease that has invaded the pelvic or abdominal wall [T4b], has spread to one or more lymph nodes [N1–N3], or has metastasised to distant sites [M1]) (3-5). In addition, approximately 10–15% and 50% of patients diagnosed at Stage I and Stages II–III, respectively are estimated to progress to Stage IV disease. (6, 7)

The estimated age-standardised mortality rates in 2018 for bladder cancer were 14.0 and 4.7 per 100,000 population for men and women respectively (8). Survival is especially poor in patients with locally advanced or metastatic bladder cancer; one- and five-year survival rates for Stage IV disease are 35.7% and <5%, respectively (9-12), with median survival for patients with Stage III–IV UC of just 9.47 months (13).

Systemic platinum-based chemotherapy regimens are the current standard of care (SoC) for UC in the UK. The majority of patients with locally advanced or metastatic UC respond to first-line platinum-based chemotherapy, with reported objective response rates of 24–70% (14-38). However, durable responses following first-line chemotherapy are uncommon, while complicated treatment regimens and severe side effects limit their long-term use (39, 40).

The short response duration and poor survival of locally advanced or metastatic UC patients on first-line chemotherapy demonstrates a clear unmet need for new treatment approaches. Maintenance therapy following first-line induction chemotherapy is already effective in multiple cancer types, including lung, colorectal, ovarian, lymphomas, and squamous cell carcinoma of the head and neck (41-47). Given that response to first-line therapy is a predictor of long-term outcomes in a number of cancers, including UC (48-53), a maintenance therapy that sustains and/or improves response to first-line treatment may significantly improve survival outcomes for patients with locally advanced or metastatic UC. This is particularly relevant when considering that the advanced UC population is typically older and with a high rate of comorbidities and may therefore be unlikely to tolerate second-line therapy. – clinical experts estimate that 60–85% of patients who receive first-line treatment are eligible for second-line therapy (54).

As the first and only maintenance therapy to demonstrate efficacy in locally advanced or metastatic UC (55, 56), avelumab offers an important and efficient new targeted treatment option for patients whose disease has not progressed following first-line platinum-based chemotherapy, as an alternative to watchful waiting. Therefore, the use of avelumab as a maintenance therapy to sustain the benefit of first-line platinum chemotherapy will contribute to addressing the critical unmet need for patients with locally advanced or metastatic UC.

**Procedural history of the appraisal**

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| --- | --- |
| **Date** | **Event** |
| 6th February 2020 | Referral to NICE |
| 3rd August 2020 | Final scope for appraisal |
| 6th October 2020 | Merck/Pfizer Alliance submission to NICE |
| 15th January – 12th February 2021 | Technical engagement |
| 21st January 2021 | Approval of extension to authorised indication to include “…first line maintenance of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy.”  |
| 14th April 2021 | First meeting of the Appraisal Committee |
| 6th May 2021 | Appraisal Consultation Document issued:“Avelumab is not recommended, within its marketing authorisation, for maintenance treatment of locally advanced or metastatic urothelial cancer that has not progressed after platinum-based chemotherapy in adults” |
| 27th May 2021 | Merck/Pfizer Alliance and other consultees and commentators submit responses to consultation on ACD. |
| 17th June 2021 | Second meeting of the Appraisal Committee |
| 23rd July 2021 | Final Appraisal Document issuedRecommendations unchanged from those in ACD |
| 6th August 2021 | Deadline for submission of appeal |

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

At paragraph 3.8 of the FAD, the Appraisal Committee considers whether a stopping rule should be implemented for avelumab and states:

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

The Committee recognises that stopping rules have been implemented in previous appraisals for IOs in UC, but states:

*“The committee was aware of other examples when decisions about including or excluding stopping rules had been applied for immunotherapies after platinum-based chemotherapy in urothelial cancer. In these 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. The committee concluded that time to stopping treatment should reflect the trial evidence and a stopping rule should not be included in the model.”*

However a stopping rule was previously accepted by Committee D for atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA525) based on the following rationale:

“*The committee understood that for other immunotherapies in the same class as atezolizumab, consideration has been given to stopping treatment after a defined period of time (a 'stopping rule'). In its additional evidence, the company included a 2‑year treatment stopping rule in its revised economic analysis. The committee noted that the evidence for atezolizumab and its summary of product characteristics did not include a stopping rule. The company considered that there is a lack of clinical evidence to show that imposing a stopping rule is of benefit to patients in the long term. However, the committee recognised that in previous NICE technology appraisals clinicians have highlighted growing concern about using immunotherapies beyond 2 years. The Cancer Drugs Fund clinical lead clarified that a 2-year stopping rule is acceptable to both patients and clinicians, and would be implementable. The committee also recognised that NICE guidance for other immunotherapies for metastatic urothelial carcinoma and other cancers include 2-year stopping rules. The committee concluded that it is appropriate to include a 2-year stopping rule in the economic model.”*

In that appraisal therefore, the same Appraisal Committee considering an IO therapy for the same cancer approved a stopping rule in circumstances where:

* As with avelumab, the evidence for atezolizumab did not include a stopping rule;
* However
	+ Growing clinical concerns regarding use of IOs beyond two years were referenced;
	+ As with avelumab, clinicians and patients supported use of a stopping rule; and
	+ The Committee recognised that NICE guidance for UC and other cancers include 2-year stopping rules.

In particular, in contrast to the approach followed in the current appraisal the conclusions of the Committee in relation to atezolizumab did not impose the barrier that results for atezolizumab should be generalisable to other treatments in the same class, used in the same populations and settings and the reference to other cancers further confirms that such an approach was not followed. In fact, the wording of the Committee’s conclusions for atezolizumab indicates that it was concerned to adopt a similar approach to that followed in other appraisals for reasons of consistency and fairness.

The approach followed in relation to atezolizumab reflects general principles of procedural fairness and the requirements of NICE’s Guide to the Methods of Technology Appraisal as stated for example at:

* Section 5: “*The Institute seeks to promote high-quality analysis and to encourage consistency in analytical approaches”*
* Section 5.1.1: “*It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach”*
* Section 6.2.15: “*the Appraisal Committee takes account of how the incremental cost effectiveness of the technology being appraised relates to other interventions or technologies currently or potentially applied in the NHS. In addition, as far as possible, the Committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals”*.

Merck/Pfizer Alliance are aware that the Appraisal Committee is not bound to follow exactly the same approach in different appraisals. However, where it proposes to reach conclusions which are inconsistent it is necessary that adequate reasons are provided to justify that decision. In this case, the same Committee considering two IOs used in very similar patient populations with the same cancer has reached opposite conclusions. No explanation has been given as to why the reasons given by Committee D in considering a stopping rule for atezolizumab would not apply with equal force to avelumab and this inconsistency does not reflect a fair procedure or the requirements of NICE’s Guide to the Methods of Technology Appraisal.

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

The Committee’s conclusion at paragraph 3.8 of the FAD that it would not implement a stopping rule for avelumab relies on the fact that the JAVELIN Bladder 100 trial did not include a stopping rule and accordingly, the SmPC does not include one. These are irrelevant considerations.

These two facts are closely linked, because whether the trial includes a stopping rule is likely to determine the inclusion of such a rule in the SmPC. However, the inclusion of a stopping rule in the design of a clinical trial and/or in the SmPC is wholly distinct from whether such a rule should be included in NICE’s recommendations. A stopping rule is likely to be included in a clinical trial or SmPC for reasons related to the safety of the medicinal product, whereas NICE includes stopping rules principally for reasons related to cost-effectiveness. This was recognised by the NICE Appeal Panel that considered the recent appeal against the FAD for tafamidis for treating transthyretin amyloidosis with cardiomyopathy. The Appeal Panel stated in paragraph 37 of its decision:

*“The panel accept Pfizer’s reasoning that the decision to adopt or reject stopping rules for a medication should not be driven on the content of the marketing authorisation. It is possible (indeed usual) to have a stopping rule for health economic reasons that is not to be found in the marketing authorisation.”*

The reliance on the JAVELIN Bladder 100 trial and the SmPC for avelumab as reasons not to implement a stopping rule in the context of the current appraisal, clinical expert opinion and anticipated real-world use is unfair and conflicts with NICE’s procedures, as confirmed by the Appeal Panel.

**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**

At paragraph 3.8 of the FAD, the Committee also refers to its concern “*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*” and also stated that “*people whose disease had not progressed before needing to stop avelumab would not be able to have another immunotherapy in the NHS”*.

No adequate reasons for the Committee’s concerns has been provided even though:

* The Committee’s views conflict with the evidence given by the clinical and patient experts, who stated “*that they would accept a similar stopping rule if this would enable access to avelumab*”, a position confirmed by two patient organisations.
* The Committee recognises that stopping rules have been implemented for other IOs, including those used for the treatment of urothelial cancer after platinum-based chemotherapy; it is unclear why it would be difficult for patients to discontinue avelumab after 2 years but would not be difficult for them to discontinue treatment with these other IOs.
* The clinical lead for the Cancer Drugs Fund accepted that “*for other immunotherapies a rule to stop treatment at 2 years has been implemented in the NHS*”.
* The statement at paragraph 3.8 of the FAD that “…*people whose disease had not progressed before needing to stop avelumab would not be able to have another immunotherapy in the NHS*”, applies equally to patients receiving second-line IO treatment (with atezolizumab) for which the Committee have previously decided to implement a 2-year stopping rule.

In summary therefore, the Committee has rejected the submissions of the clinical and patient experts and the patient organisations that a stopping rule would be accepted if this enabled access to avelumab, without adequate reasons. Such lack of transparency, which does not permit a comprehensive response to the Committee’s conclusions prejudices Merck/Pfizer Alliance and is inconsistent with standards of procedural fairness.

**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)**

The implementation of a stopping rule to improve cost effectiveness is a central issue in this appraisal. However:

* The Appraisal Committee rejected the submissions of the clinical and patient experts and the patient organisations that a stopping rule would be accepted if it enabled access to avelumab; and
* While it accepted the evidence of the clinical experts

*“…that stopping treatment after 2 years might be reasonable for some people for reasons such as fatigue from fortnightly hospital visits or the adverse effects of the treatment”,* it stated that *“it was not clear whether this would apply to people with urothelial cancer in general, or the population considered here of people whose disease has responded to chemotherapy and is continuing to respond to maintenance treatment.”*

While therefore the stopping rule was of substantial importance in this appraisal, the Committee was concerned about whether such a rule could be implemented and questioned clinical evidence that certain patients would elect to discontinue treatment. Nevertheless and despite these areas of uncertainty for the Committee, the stopping rule and patient discontinuance was barely mentioned during the public part of the second Appraisal Committee meeting. The unfairness resulting from the limited consideration given to this issue was substantially increased as a result of the absence of the clinical and patient experts from that meeting, with the result that the Committee was unable to test its concerns regarding implementation of a stopping rule or clarify whether patients eligible for avelumab maintenance therapy would voluntarily discontinue treatment after two years.

The Appraisal Committee has a discretion to invite the clinical and patient experts to attend its second meeting. It is unclear whether any consideration was given to issuing such invitations in this case or, if so, why the clinical and patient experts were not in fact invited. In particular, if the Committee considered that any of the statements made during the first meeting or the ACD consultation by the clinical experts were unclear, these should have been clarified at the second Committee meeting had such experts been invited to attend. Therefore, based on the uncertainties expressed in the FAD and the Committee’s rejection of the clinical and patient evidence, we believe that the Committee should have exercised its discretion to invite the clinical and patient experts to the second meeting and that its failure to do so resulted in procedural unfairness.

**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)**

At paragraph 3.14, the FAD refers to the evidence of the clinical experts at the first committee meeting regarding life expectancy and the Committee concern that this evidence might not apply to patients eligible for maintenance treatment with avelumab.

 *“At the first meeting, the committee was concerned that the overall survival values from existing clinical trials and estimates provided by the clinical experts may not accurately reflect people who are eligible for maintenance treatment with avelumab. It considered that these estimates might include people whose cancer had not responded well to chemotherapy and so have a short prognosis and therefore would not be eligible for maintenance treatment.”*

However the concerns of the Committee disregard evidence given by the clinical experts during the first Committee meeting (14th April) who confirmed they were considering the correct patient population and referenced the LaMB study which also only included patients who had responded to first-line chemotherapy. Therefore, based on the uncertainties expressed in the FAD and the Committee’s rejection of the clinical and patient evidence, we believe that the Committee should have exercised its discretion to invite the clinical and patient experts to the second meeting and that its failure to do so resulted in procedural unfairness.

**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).**

At paragraph 3.12 of the FAD, the Committee concludes:

*“It was not appropriate to pool health-state utilities across treatment arms”.*

The explanation provided by the Committee *is*

*“The ERG noted utilities before progression were slightly higher in the avelumab with best supportive care arm compared with best supportive care alone. But values after progression were lower for avelumab with best supportive care compared with best supportive care alone. The committee noted people who had best supportive care in JAVELIN Bladder 100 would also have immunotherapies or chemotherapy if their disease progressed. The committee considered that this might explain the difference in utility values for people who had avelumab with best supportive care or best supportive care alone.”*

The FAD goes on to state that:

*“After consultation, the company maintained its preference for using pooled health-state utilities. It noted that pooled values have previously been accepted in NICE’s technology appraisal guidance on pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. However, the committee noted in that appraisal, the same treatments were available to people in both study groups whose disease progressed”*

The Committee refers to the NICE’s technology appraisal guidance on pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy which accepted pooled utility values. In this pembrolizumab appraisal, the pre-progression health state (second-line treatment) compared treatment with pembrolizumab and standard of care. By accepting pooled utility values for this health-state the Committee have inferred that there is no utility benefit for treatment with a second-line immunotherapy versus standard of care treatments. This is contrary to the rationale the Committee has given in the FAD whereby they suggest the small difference in utilities in the post-progression health state (second-line treatment) could be explained by use of subsequent immunotherapies in the best supportive care arm. This explanation was hypothesised by the committee and not substantiated by the empirical data.

Additionally, the FAD states that:

*“The ERG noted it was reasonable to consider the effect of treatment-specific utilities on cost-effectiveness estimates, if any uncertainty might be introduced by combining health-state utilities across treatment arms. “*

And

*“The committee considered the views of the company and clinical experts and the ERG and concluded, on balance, it was not appropriate to pool health-state utilities across treatment arms.”*

However, in the ERG critique of the company’s response to Technical Engagement found in the committee papers for the first committee meeting, it is stated:

*“The ERG notes that the ICER is not particularly sensitive to the post-progression utilities and, on balance, the ERG agrees with the company’s view that it is appropriate to pool health state utilities across the treatment arms for use in the economic model.”*

Consequently, the Committee conclusion is in conflict with both the opinion of the Expert Review Group as well as the prior appraisal in mUC.

In summary, the same Committee have considered that second-line immunotherapies provide no utility benefit versus standard of care in previous metastatic urothelial cancer appraisals which conflicts with the FAD for avelumab. This inconsistency does not reflect a fair procedure or the requirements of NICE’s Guide to the Methods of Technology Appraisal.

## **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**

Paragraph 6.2.10 of NICE’s Guide to the Methods of Technology Appraisal defines the first end of life criterion as:

*“the treatment is indicated for patients with a short life expectancy, normally less than 24 months"*.

However in considering avelumab, the Appraisal Committee’s application of the first criterion is not reasonable. Our reasons for this conclusion are set out below.

### (a) NICE’s procedures do not determine how a short life expectancy is to be measured

NICE’s procedures do not define the approach to be followed by the Committee. In particular the procedures do not specify whether any determination should be based on mean versus median data and there is a lack of clarity in relation to the weight to be attached to real world evidence and clinical expert opinion as well as data from clinical trials. However the overall assessment procedure must be reasonable in the context of what this is required to achieve.

Although we are unable to fully evaluate all prior End of Life decisions by NICE due to the limited information available in redacted submissions and Final Appraisal Documents. The publicly available study (Bovenberg et al., 2021) has systematically reviewed how end of life guidance was implemented over the past 10 years at NICE. The findings of the study suggest that for the life expectancy criterion median overall survival data from the trial was applied in 46 cases whereas mean estimations from the economic modelled were applied in 39 cases, followed by estimates from clinical experts (in 14 cases).

Based on these findings, it is clearly incorrect that mean data are necessarily the most appropriate approach, this is not required by NICE’s procedures and the fact that alternative methods have been used in the majority of cases where the end of life criteria have been implemented should have been taken into account by the Appraisal Committee considering avelumab.

### (b) The Committee’s conclusion that it should base its decision on mean life expectancy because the cost-effectiveness results are based on mean QALYs is unreasonable

At paragraph 3.14 of the FAD, the Committee states:

“*It considered that the best estimate of expected survival came from modelling mean life-expectancy based on the trial, because the cost-effectiveness results are based on mean quality adjusted life years and costs”*.

The End of life modifier reflects societal preference for treatments for patients who are close to the end of their life and this determination should be based on the current life expectancy of patients in UK clinical practice. The assessment of cost effectiveness has very substantial differences from the determination of eligibility for the end of life criteria:

* The assessment of cost effectiveness involves a determination of the comparative effectiveness of the technology under consideration; we accept that such comparisons should be based on clinical trial data obtained using the same type of analysis (i.e. both mean or both median);
* Determination of whether a technology satisfies the end of life criteria involves different considerations to the assessment of cost effectiveness including
	+ That, in contrast, median data from clinical trials or real-world evidence will reflect more realistic life expectancy for most patients receiving treatment in clinical practice in England.
	+ The fact that mean estimations, which include data from outliers, which skew the overall results, do not reflect life expectancy for most patients with the condition under consideration in the real world in England.
	+ That participants in clinical trials are likely to be fitter than patients eligible for treatment in clinical practice in England and that using real-world evidence is more likely to reflect the experience of such patients.

In these circumstances, a decision to base eligibility under the end of life criteria solely on mean data from the clinical trial, without taking into account evidence from other sources more relevant to the experience of English patients eligible for maintenance treatment with avelumab is unreasonable.

### (c) It is necessary to **consider** the totality of the available evidence

When the totality of the evidence from clinical trials and real-world experience are taken into account, the overwhelming majority of the estimates indicate that the life expectancy of patients eligible for avelumab maintenance treatment is less than 24 months. The evidence available to the Committee on life expectancy in people eligible for maintenance treatment with avelumab are summarised in the table below

|  |  |  |
| --- | --- | --- |
| **Source** | **Population** | **Life Expectancy** |
| JAVELIN Bladder 100 trial (55) | Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy | Median = 14.3 months |
| Committee preferred ERG/Company aligned CEM Base Case using log-normal | Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy | Median = 15.6 monthsMean = 27.82 months |
| **Real world evidence from NHS England Systemic Anti-Cancer Therapy Database (SACT)** |
| England Standing Cohort Study (13) | Adult patients in England diagnosed with Stage III–IV UC between 2013 and 2017.  | Median OS = 9.5 months |
| **Published literature**  |
| LaMB - Powles *et al*. 2017 (57) | Patients with metastatic urothelial bladder cancer - patients with radiologic progression of disease during chemotherapy were excluded | Median OS = 11.8 months |
| Bamias *et al*. 2013 (16) | Patients with inoperable, metastatic or relapsed urothelial cancer | Median OS DD-MVAC = 19 monthsMedian OS DD-GC = 18 months |
| EORTC Intergroup study 30987 - Bellmunt *et al.* 2012 (20) | Gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy | Median OS = 12.7 months |
| Sterberg *et al.* 2001 (22) | MVAC in Advanced Urothelial Tract Tumors | Median OS = 14.1 months |
| Dreicer *et al.* 2004 (23) | M-VAC in patients with advanced carcinoma of the urothelium | Median OS = 15.4 months |
| Siefker-*Radtke et al*. 2002 (24) | M-VAC in patients with Metastatic or Unresectable Urothelial Cancer | Median OS = 12.5 months |
| Bamias *et al.* 2004 (34) | MVAC With G-CSF in Advanced Urothelial Carcinoma | Median OS = 14.2 months |
| Von der Maase *et al.* 2005 (39) | GC vs MVAC in patients With Bladder Cancer | Median OS GC = 14.0 monthsMedian MVAC = 15.2 months |
| De Santis 2012 (58) | GC vs M-CAVI in Patients With Advanced Urothelial CancerWho Are Unfit for Cisplatin-Based Chemotherapy | Median OS GC = 9.3 monthsMedian M-CAVI = 8.1 months |
| Galsky *et al.* 2013 (59) | Patients With MetastaticUrothelial Cancer Treated With First-Line Cisplatin-Based Chemotherapy | Median OS = 13.5 months |
| KEYNOTE-052 - Vuky *et al.* 2020 (60) | First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer | Median OS = 11.3 months |
| IMvigor210 -Balar *et al*. 2018 (61) | Atezolizumab in first-line cisplatin-ineligible or platinum-treated locally advanced or metastatic urothelial cancer | Median OS = 16.3 months |
| IMvigor130 - Galsky *et al.* 2020 (62) | Atezolizumab with or without platinum-based chemotherapy versus placebo plus platinum-based chemotherapy in first-line metastatic urothelial carcinoma | Median OS atezo + chemo = 16.0 monthsMedian OS chemo = 13.4 months |
| KEYNOTE-361 – Loriot *et al.* 2021 (63) | Post hoc analysis of long-term outcomes in patients with CR, PR, or SD to Pembrolizumab or platinum-based chemotherapy as first-line therapy for advanced urothelial carcinoma | Median OS chemo CR/PR = 18.6 monthsMedian OS chemo SD = 11.1 months |
| **Clinical experts and PAG feedback and estimates**  |
| Interviews with eight UK-based clinicians | Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy | 12-18 months |
| Clinician estimates from ACM1 | Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy | Life expectancy 11 – 16 months |
| Clinician response to TE (64) | Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy | Prof Alison J Birtle: Life expectancy = 12-14 monthsDr Syed A Hussain: Life expectancy = 14-15 months |
| Fight Bladder Cancer response to ACD (65) | Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy | Dr Simon Crabb: These patients live for a median of 12-18 months. Less than 20% longer than 2 years.Prof Alison J Birtle: These patients live for an average of around 14 months |

The real-world evidence, estimates from the literature, the median overall survival reported in the JAVELIN Bladder 100 trial as well as clinical expert opinion all suggest that life expectancy for the population under assessment is less than 24 months, with the only outlier being the modelled mean OS which is affected by a long survival tail, due to a small number of patients who have benefitted from an enduring response. Estimates of life expectancy should be based on the totality of the evidence relating to standard of care including the clinical trial, cost-effectiveness model, the clinical opinion from 10 experts (including 2 experts at NICE Committee) and real world evidence which has been presented in our original submission and in our response to the ACD.

 The Committee states, at paragraph 3.14 of the FAD that it

*“recognised that there was potential value in real-world evidence to help inform its decision making and noted that these corresponded with the median estimate from the trial. But it was concerned about the differences between median overall survival and the mean estimates produced in the model”.*

However, the value of real-world evidence submitted and the fact that it corresponded with the median overall survival from JAVELIN Bladder 100 is not reflected in the Committee’s decision, which focusses on extrapolation from the clinical trial. The Committee’s reliance on the most extreme estimate of survival to inform its overall conclusion, in circumstances where this does not reflect the experience of the majority of patients with the condition under consideration is not reasonable.

### (d) The Committee has unreasonably concluded that, in circumstances where more than a very small number of people are expected to survive more than 2 years, the first end of life criterion would not be met.

At paragraph 3.14 of the FAD, in the context of its consideration of criterion one of the end of life criteria, the Committee noted:

*“…overall survival extrapolations from the economic model predicted 37% (generalised gamma) and 35% (log-normal) of people who did not have avelumab were likely to live longer than 2 years. It considered that this did not suggest that only a very small number of people are expected to survive beyond 2 years”.*

However, the implications of the analysis referenced by the Committee is that the majority of patients (i.e. 65%) are expected to live less than two years and the fact that a minority of patients do well, does not in any way reduce the impact of the disease or the grim prognosis for the majority. The Committee’s reliance on these data to support its view that the first end of life criterion is not met is therefore unreasonable. In fact a proper interpretation of these data is that life expectancy reflects the experience of the majority - i.e. less than two years.

### (e) The Committee has misinterpreted the first criterion as imposing a fixed threshold of 24 months and has then applied this to the most extreme estimate of survival

The first end of life criterion requires that “the treatment is indicated for patients with a short life expectancy, normally less than 24 months”. This does not impose an absolute and inflexible limit of two years but simply states that life expectancy will “normally” be less than this. The Committee however has disregarded the word “normally” and treated the criterion as excluding any treatment indicated for patients with a life expectancy over the threshold. This is inconsistent with the wording of NICE’s procedures and therefore unreasonable.

The arbitrariness of the Committee’s approach is demonstrated by the fact that the majority of estimates of life expectancy fall below two years, as explained under (c) above. Furthermore, while it is Merck/Pfizer Alliance’s position that the Committee was not acting reasonably in choosing to rely on a mean estimation of overall survival derived from the clinical trial, the ERG’s estimation of overall survival in the best supportive care arm from the JAVELIN Bladder 100 trial was 27.82 months, which is close to the 24 months specified in the first end of life criterion. The fact that the Committee concluded that this estimation (applying the flexibility incorporated in the first criterion) together with all the other available evidence did not meet the first end of life criterion was unreasonable.

**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**

The Committee states, at paragraph 3.12 of the FAD that:

*“Using pooled data for the health-state utilities slightly increased the ICER for avelumab.”*

However this is incorrect as the inclusion of pooled data for health-state utilities results in a slight decrease in the ICER for avelumab versus the use of treatment-specific utilities. This misunderstanding could have influenced the Committee decision who may have thought they were selecting the more optimistic scenario for avelumab when this wasn’t the case. This misunderstanding may have led to an inappropriate evaluation of the evidence presented.

## **Conclusion**

The Merck/Pfizer Alliance requests that this appeal should be determined at an oral hearing.

We firmly believe that, in certain respects, the procedure followed in this appraisal has been unfair and that the conclusions are unreasonable in light of the evidence provided. We therefore respectfully request the Panel to uphold our appeal and to return this appraisal to the Appraisal Committee for further consideration of (i) the 2-year stopping rule, (ii) the End-of-Life criteria and specifically the full evidence provided on the overall survival of patients with urothelial cancer treated in England and (iii) the use of pooled health state utilities across treatment arms consistent with previous appraisals.

We thank you in advance for considering the company’s submissions in this appeal. We are available to answer any questions you may have or provide further clarifications.

Yours sincerely,

Merck/Pfizer Alliance

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