NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Contents:

The following documents are made available to consultees and commentators:

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Final appraisal document

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy

1 Recommendations

1.1 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.

1.2 This recommendation is not intended to affect treatment with avelumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

There are no maintenance treatments routinely available for locally advanced or metastatic urothelial cancer that has responded to platinum-based chemotherapy. Clinical trial evidence shows that if people take avelumab it takes longer for their cancer to get worse, and they live longer than if they have best supportive care.

Avelumab does not meet NICE's criteria to be considered a life-extending treatment at the end of life. The most likely cost-effectiveness estimates are much higher than what NICE normally considers an acceptable use of NHS resources. So avelumab is not recommended for routine use.

Issue date: June 2021

Avelumab is not suitable for use within the Cancer Drugs Fund because it is unlikely to be cost effective and further data collection is not an option. So avelumab is not recommended for use within the Cancer Drugs Fund.

2 Information about avelumab

Marketing authorisation indication

2.1 Avelumab (Bavencio, Merck Serono) is indicated 'as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial cancer who are progression-free following platinum-based chemotherapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price is £768.00 per 200 mg/10 ml concentrate for solution for infusion vials (excluding VAT; BNF online, accessed April 2021).

The company has a commercial arrangement. This makes avelumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Merck Serono, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Metastatic urothelial cancer decreases quality of life

3.1 Urothelial cancer causes a number of symptoms, including haematuria (blood in the urine) and increased frequency, urgency and pain associated with urination. The committee was aware that many people with locally advanced or metastatic urothelial cancer are older and may have comorbidities, which can affect treatment decisions. The patient experts explained that chemotherapy is associated with unpleasant side effects such as fatigue, nausea and vomiting and means people are at greater risk of infection. The committee recognised that locally advanced or metastatic urothelial cancer has a substantial effect on quality of life.

There is unmet need for effective treatment options

3.2 The main aim of treatment for locally advanced or metastatic urothelial cancer is to prevent disease progression, maintain health-related quality of life, provide relief from cancer symptoms and extend life. The patient experts explained that the side effects of chemotherapy can have a major negative effect on quality of life and regular hospital visits for treatment disrupts usual activities and affects their ability to work. The committee heard how people whose disease remains stable or responds to first-line chemotherapy must wait for disease progression before having further treatment. The clinical experts noted that maintenance treatments can prevent or delay the need for second-line treatment and there is a population who would benefit from maintenance therapy at this point in the treatment pathway. The committee concluded that there is an unmet need for effective treatment options for people with locally advanced or metastatic urothelial cancer that has not progressed after platinum-based chemotherapy.

Clinical evidence

The JAVELIN Bladder 100 trial is generalisable to clinical practice in the UK

3.3 The clinical effectiveness evidence for avelumab came from 1 phase 3, randomised, open-label, parallel, 2-arm study. This included 700 adults with locally advanced or metastatic urothelial cancer that did not get worse during, or 4 to 10 weeks after, first-line platinum-based chemotherapy. People had either avelumab 10 mg/kg once every 2 weeks (n=350) or best supportive care alone (n=350). The study population included people who had a cisplatin- or carboplatin-based chemotherapy with gemcitabine. This aligns with current NICE recommendations on a platinum-based chemotherapy regimen. The committee agreed this reflected current UK clinical practice. It highlighted that a weight-based dose for avelumab was used in JAVELIN Bladder 100, whereas the licence specifies a fixed dose. It accepted that the fixed licensed dose would have similar clinical outcomes to the weight-based dose and so it was not necessary to adjust for differential efficacy. The company presented interim data from a cut-off date of October 2019. It considered this to be the final analyses because the trial had achieved its primary objectives. The committee concluded that JAVELIN Bladder 100 is generalisable to clinical practice in the UK.

Avelumab and best supportive care improves overall survival compared with best supportive care alone

3.4 The evidence from JAVELIN Bladder 100 had 2 co-primary populations: all the people in the trial and people with PD-L1-positive tumours. The committee noted there was a statistically significant improvement in overall survival for the whole trial population who had avelumab with best supportive care (median 21.4 months; 95% confidence interval [CI] 18.9 to 26.1 months). There was a 31% reduction in the risk of death compared with people who had best supportive care alone (median 14.3 months;

95% CI 12.9 to 17.9 months; hazard ratio [HR] 0.69; 95% CI 0.556 to 0.863; p=0.001). There was also a statistically significant improvement in overall survival for people with PD-L1 positive tumours. This group had a 44% reduction in the risk of death (median not reached; 95% CI 20.3 months to not reached) compared with people who had best supportive care alone (median 17.1 months; 95% CI 13.5 to 23.7 months; HR 0.56; 95% CI 0.404 to 0.787, p<0.001). There was a 15% reduction in risk of death for people with PD-L1 negative tumours. But these results were not statistically significant when comparing people having avelumab and best supportive care (median 18.8 months; 95% CI 13.3 to 22.5 months) with those having best supportive care alone (median 13.7 months; 95% CI 10.8 to 17.8 months; HR 0.85; 95% CI 0.615 to 1.181, p value not reported). The committee concluded avelumab and best supportive care improves overall survival compared with best supportive care alone but may not do so in people with PD-L1 negative tumours.

Avelumab and best supportive care improves progression-free survival compared with best supportive care alone

3.5 There was a statistically significant improvement in progression-free survival (assessed by blinded independent central review) for all people having avelumab compared with best supportive care (median 3.7 months; 95% CI 3.5 to 5.5 months). The risk of progression or death reduced by 38% compared with people who had best supportive care alone (median 2.0 months; 95% CI 1.9 to 2.7 months; HR 0.62; 95% CI 0.519 to 0.751, p<0.0001). There was a statistically significant improvement in progression-free survival for the people with PD-L1-positive tumours. The risk of death reduced by 44% for people having avelumab and best supportive care (median 5.7 months; 95% CI 3.7 to 7.4 months) compared with people who had best supportive care alone (median 2.1 months; 95% CI 1.9 to 3.5 months; HR 0.56; 95% CI 0.431 to 0.728, p<0.0001). There was a 37% reduction in risk of death for people with PD-L1 negative tumours having avelumab and best

supportive care (median 3.0 months; 95% CI 2.0 to 3.7 months) compared with people who had best supportive care alone (median 1.9 months; 95% CI 1.9 to 2.0 months; HR 0.63; 95% CI 0.476 to 0.845, p value not reported). The committee agreed the results showed that avelumab and best supportive care improves progression-free survival compared with best supportive care alone.

Assumptions in the economic model

The generalised gamma and log-normal models are both acceptable for extrapolating overall survival

3.6 In the economic model, the company used parametric distributions to extrapolate data on overall and progression-free survival from JAVELIN Bladder 100. In its original submission the company stated that overall survival estimates were expected to be between 20% and 30% at 5 years and between 10% and 15% at 10 years for people having avelumab. For watchful waiting (people having best supportive care alone) overall survival was expected to be between 5% and 15%, and 10-year overall survival between 2% and 7%. The company originally selected the generalised gamma curve to extrapolate both avelumab and watchful waiting overall survival in its base case because the 10-year survival predictions were in line with clinical estimates. It stated that the generalised gamma was the only model that predicted 10-year overall survival estimates in the region of clinical estimates for avelumab (10% to 14%). It noted the 5-year (15%), and 10-year (6.48%) generalised gamma estimates for watchful waiting were optimistic. But it noted the estimates for avelumab may be considered pessimistic, based on clinical expectations. It preferred to use the same parametric model for both treatment groups. The ERG considered this may overestimate overall survival for both avelumab and watchful waiting, because it predicted 5-year and 10-year survival estimates that were close to the upper end of clinical expectations. The ERG preferred the log-normal curve for watchful waiting because the 5-year (10.71%) and 10-year (2.90%) predictions

were closer to the mid-point of clinical expectations and because it had the best statistical fit. In response to technical engagement, the company accepted that both the generalised gamma and log-normal curves were helpful for decision making. But it revised its base case to use the log-normal model, aligned with the ERG's preferred base case. Both the company and ERG stated there was little to distinguish between each model. The committee agreed that there is little to distinguish between the extrapolations in terms of statistical fit. But changing the model reduced the mean life years for people who had not had avelumab from 35.4 months (generalised gamma) to 27.82 months (log-normal). At the second committee meeting, the company confirmed it would prefer the log-normal extrapolation model. However, the committee considered it was reasonable to use the generalised gamma. It could be plausible that survival estimates for watchful waiting are at the upper end of clinical ranges. For this reason, the committee concluded that both models should be considered plausible for extrapolating overall survival data.

Progression should be defined by blinded independent central review

3.7 In the company's model, progression-free survival curves were fitted for 2 alternative definitions of progression: blinded independent central review and investigator-assessed progression. The company's original base-case analysis considered blinded independent central review defined progression because it was expected to give the most unbiased assessment of disease progression. The ERG noted that treatment decisions in clinical practice are more likely to be based on investigator-assessed progression. In response to technical engagement, the company provided feedback from 8 UK-based oncologists who supported the ERG's preference for using investigator-assessed progression. The committee noted that in open-label trials, investigator-assessed progression has the potential for biased decisions. After an initial investigator assessment, all subsequent assessments of progression in JAVELIN Bladder 100 were based on blinded independent central review. This is consistent with greater internal validity as noted in NICE's guide to

the methods of technology appraisal. The committee recalled that blinded independent central review defined progression was the preferred approach in many published technology appraisals. For this reason, it concluded that progression should be defined by blinded independent central review.

Time to stopping treatment should reflect the trial

3.8 In its original economic model, the company assumed that 95% of people will stop treatment with avelumab at 2 years whether or not their disease has progressed, and all remaining people would stop treatment with avelumab at 5 years. The company also assumed that people would continue to benefit from avelumab for the remainder of their lifetime, even after stopping treatment. The committee noted that this did not reflect JAVELIN Bladder 100 and the summary of product characteristics does not include a stopping rule. Data from the trial showed substantially more people were having treatment at 2 years than the 5% assumed in the company's model. But the exact figures are considered confidential by the company, so cannot be reported. The model captured the benefits these people had from continuing avelumab treatment, but the costs were not included. The clinical experts explained 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. The committee agreed, but 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. The clinical lead for the Cancer Drugs Fund explained that the company's assumptions about stopping avelumab treatment could not be implemented in the NHS. He noted that for other immunotherapies a rule to stop treatment at 2 years has been implemented in the NHS. The clinical and patient experts stated that they would accept a similar stopping rule if this would enable access to avelumab. This was confirmed by 2 patient organisations in response to consultation, although 1 group noted that the people it represented would

prefer avelumab to be made available without a stopping rule. The committee was aware that the company had not provided a scenario analysis when all patients stopped having treatment at 2 years. It 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. Also, people whose disease had not progressed before needing to stop avelumab would not be able to have another immunotherapy in the NHS. The committee noted that other NICE technology appraisals of avelumab have preferred no stopping rules. The committee would prefer the model to base time to stopping treatment on the trial data. But, it was also concerned that because people cannot have further immunotherapy, treatment in the NHS may continue beyond radiographical progression. One clinical expert noted that they would prefer to continue avelumab until symptomatic progression. The committee therefore asked the company to provide the progression-free survival and time to stopping treatment curves presented on the same graph to assess the relationship between the 2 in the trial. After consultation, the company confirmed that their initial assumption around treatment duration was not intended to be a stopping rule but to reflect the likely treatment duration of people in clinical practice. It proposed a 2-year stopping rule based on expectations that in clinical practice people will stop treatment by then. It noted this was in line with immunotherapies for other indications. The committee recalled that there were many people in JAVELIN Bladder 100 whose disease had not progressed at 2 years, but a slightly lower number were still having treatment after 2 years. It acknowledged that some of these people may stop having avelumab for other reasons than disease progression. 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.

Waning of treatment effect should not be included in the model

3.9 Related to the assumptions about stopping treatment, the company originally assumed a lifetime treatment benefit for avelumab in its base case, even after stopping treatment. The company and ERG provided several scenario analyses in which the treatment effect for avelumab was capped at different time points. The clinical experts explained that for immunotherapies, it is common for the treatment benefit to continue when treatment stops. But the committee agreed that it was implausible that the treatment effect for avelumab would continue for a person's lifetime after stopping treatment. It noted that in other technology appraisals of immunotherapies, a treatment cap between 2 and 5 years had been applied when a stopping rule had been applied. After consultation, the company proposed waning of treatment benefit should be applied at 5 years. Any treatment benefit would stop 3 years after stopping treatment, aligned with its proposed 2-year stopping rule. The ERG noted the true duration of benefit after stopping treatment is unclear. It provided several scenario analyses varying the duration of continued benefit. These varied from no benefit after stopping treatment, to 5 years after stopping treatment, which was included in other technology appraisals of immunotherapies for metastatic urothelial cancer. It also provided a gradual waning of treatment effect in line with the company's original scenario analysis. The committee noted that there is substantial uncertainty about the most appropriate treatment benefit capping assumptions. It concluded that since a stopping rule had not been accepted, a waning of treatment effect should not be included in the model.

The SACT dataset does not reflect the maintenance setting in which avelumab would be used in clinical practice

3.10 The company model included the costs of subsequent treatments after progression based on JAVELIN Bladder 100, adjusted to reflect the treatments available in UK clinical practice. The ERG noted that the proportion of people having subsequent treatments in the trial would likely to be higher than that seen in clinical practice. People in the trial had more stable disease and so were considered fitter than those in clinical practice and were monitored more closely. So, they were more likely to have subsequent treatment after progression. The company provided estimates from the systematic anti-cancer therapy (SACT) dataset. This showed that 41.9% of people in UK clinical practice have a second-line therapy after first-line platinum-based chemotherapy. This was lower than the proportion in JAVELIN Bladder 100. The clinical experts explained that only people with stable disease would have been eligible to be included in JAVELIN Bladder 100 because people whose disease progressed during or very shortly after first-line chemotherapy were not eligible. As a result, the number having subsequent treatments in JAVELIN Bladder 100 would have only included people who had stable disease (and therefore may be considered fitter and more likely to have subsequent treatment). This was not directly comparable with those in the SACT dataset, which includes people whose disease has progressed during or immediately after chemotherapy. The SACT dataset was collected before NICE recommendations that increased the treatment options in metastatic urothelial cancer to include immunotherapies. Also, the hazard ratios and incremental cost-effectiveness ratios (ICERs) that the cost-effectiveness results were based on came directly from those in JAVELIN Bladder 100. The committee agreed the data used to inform the proportion of people having subsequent treatment in the model should come from JAVELIN Bladder 100. It concluded that the SACT dataset does not reflect the maintenance setting in which avelumab would be used in clinical practice.

The costs of subsequent treatments in the model should reflect the treatments used in JAVELIN Bladder 100

3.11 Some people had immunotherapies after disease progression on avelumab in JAVELIN Bladder 100. In the economic model, the company removed the cost of these immunotherapy treatments to reflect NHS clinical practice. The clinical experts confirmed that in clinical practice people would not have a second-line immunotherapy after disease progression on avelumab. The committee recognised that in the NHS people would not have further immunotherapy after avelumab. However, it considered that people may have had some benefit from immunotherapy treatment after avelumab, but that the model had not been adjusted to account for this. It was aware of discussions from NICE's technology appraisal guidance on pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. These concluded that it was inconsistent to include the potential benefits of subsequent immunotherapy treatment without the costs, so both should either be included or excluded. So, the committee concluded that the costs of immunotherapies used after disease progression on avelumab should be included in the model.

It is not appropriate to pool health-state utilities across treatment arms

3.12 The company submission stated that overall health status and health-related quality of life were similar between both arms of JAVELIN Bladder 100. So the company used pooled utility values to inform the model. However, it also provided health-state utility data for each arm of the study, split by before progression and after progression states. 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 clinical experts explained that lower utility after progression on avelumab was clinically plausible because people would be having less effective chemotherapy treatment, and this may affect their health-related quality of life. The clinical experts stated that it would be reasonable to include health-state utilities from each arm of the trial. 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 company also suggested the difference in utilities before and after progression from JAVELIN Bladder 100 might be explained by fewer observations of people after progression in the avelumab arm of the trial. But the committee considered the data was still robust enough to allow conclusions to be drawn. 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. It provided a scenario analyses exploring this uncertainty. Using pooled data for the health-state utilities slightly increased the ICER for avelumab. 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.

End of life

Avelumab extends life by at least 3 months

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of

technology appraisal. The committee agreed based on the evidence that was available and the views of the clinical experts that the overall survival gain with avelumab would likely be more than 3 months. The data from the company's model suggested there was an increase in mean overall survival of 12 months (median 6.9 months). The committee agreed that avelumab meets the criterion for a life-extending treatment because it increases overall survival by more than 3 months.

Avelumab does not meet the short-life expectancy criterion and so is not considered to be a life-extending treatment at the end of life

3.14 The company confirmed that mean estimates were not available from JAVELIN Bladder 100, but the median overall survival for people who had best supportive care alone was 14.3 months. It noted that people in the trial would generally be fitter than in UK clinical practice. The company's original base case predicted a mean overall survival of 35.4 months and a median of 15.9 months for people having best supportive care. The ERG's base case predicted a mean overall survival of 27.82 months and a median of 15.6 months. The committee noted mean estimates are very rarely available from clinical trial data directly. In situations such as this, the options available will usually involve alternative measures of survival, such as landmark survival times or using a restricted mean survival time. The alternative is to use extrapolation models to estimate the mean. It acknowledged that this involves assumptions and uncertainty. The economic model was based on the results from JAVELIN Bladder 100, which the company considered included people who were fitter than those in clinical practice. The mean estimates of overall survival were higher than 24 months and the cost-effectiveness analyses are based on mean survival estimates. Most survival distributions will have a skewed distribution where the mean is often higher than the median. The skew can be more pronounced with immunotherapies (that people in the comparator arm have when their disease progresses). This is because of the small number of people whose disease sustains a durable response to treatment. This is a key benefit of these therapies, and the cost-

effectiveness estimates are normally very sensitive to this specific effect of these drugs. It is important for the committee to consider the mean survival since using mean life years is a key part of the NICE methods for assessing cost effectiveness. The committee also recognised the value in looking at 2-year landmark survival. It noted that 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. After consultation, the company highlighted 2 NICE technology appraisals that had documented median overall survival in the sections of the guidance considering end of life criteria. In both NICE's technology appraisal guidance on pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy and isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma, median overall survival was less than 24 months. The committee noted that in these 2 examples, data available in the committee papers shows that the mean overall survival was also less than 24 months. The same was true in NICE's technology appraisal guidance on inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia mentioned by a patient organisation in their consultation response. The clinical expert submission received at technical engagement stated that median overall survival in JAVELIN Bladder 100 was taken from the time of randomisation. Randomisation happened within 4 to 10 weeks after 4 to 6 cycles of chemotherapy. The committee considered what this meant for interpreting overall survival estimates. In clinical practice, chemotherapy is given for 4 to 6 cycles, with 3 weeks between each cycle. Measuring survival from starting chemotherapy would add an estimated extra 4 to 7 months to the survival outcomes. This would mean the median values from JAVELIN Bladder 100 would be more than 20 months and the mean survival from the modelling estimates more than 30 months. However, the committee

considered that the important point is that from the time of randomisation, only people whose cancer responded well to chemotherapy remained in the study. 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. After consultation, the company provided several sources of median survival data for people with advanced or metastatic urothelial cancer, although only 1 related specifically to people whose disease had responded well to chemotherapy. These showed that median survival estimates ranged from 9.3 to 18 months. The company also submitted feedback from 8 clinicians who said that overall survival for people whose disease responds to chemotherapy was between 12 and 18 months. A patient organisation also provided similar estimates from 2 clinicians The committee 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. 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 committee concluded that the short life expectancy criterion had not been met based on the extrapolations of JAVELIN Bladder 100 from the point of randomisation. Therefore avelumab could not be considered a life-extending treatment at the end of life.

Cost-effectiveness estimates

The ICER using the committee's preferred assumptions is substantially higher than £20,000 per QALY gained so avelumab cannot be recommended for routine use

3.15 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The company's deterministic base-case ICERs, compared with watchful waiting, were above the higher end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). Because of confidential discounts for subsequent therapies, the cost-effectiveness results cannot be reported here. The committee agreed that its preferred assumptions included:

- overall survival extrapolated using either the generalised gamma or log-normal model (see section 3.6)
- progression assessed by blinded independent central review (see section 3.7)
- the proportion of people having treatment after progression based on JAVELIN Bladder 100 (see section 3.10)
- including costs of immunotherapies for people having avelumab whose disease had progressed (see section 3.11)
- no stopping rule and no waning of treatment benefit (see section 3.8 and section 3.9)
- health-state utilities before and after disease progression based on each arm of JAVELIN Bladder 100 (see section 3.12).

The cumulative effect of the committee's preferred assumptions increased the company's base case significantly above what is normally considered

a cost-effective use of NHS resources. The ICER was £72,933 per QALY gained (including the discount for avelumab). The ICER was higher than this when confidential discounts for subsequent treatments were included. The committee therefore concluded that avelumab could not be recommended for routine use in the NHS.

Cancer Drugs Fund

Avelumab does not meet the criteria to be included in the Cancer Drugs Fund

3.16 Having concluded that avelumab could not be recommended for routine use, the committee considered if it could be recommended within the Cancer Drugs Fund. It discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The most plausible ICER including the committee's preferred assumptions was significantly above the range normally considered a cost-effective use of NHS resources and so there was no plausible potential for routine use. The committee noted that there are no planned or ongoing studies that could address the uncertainties identified. It concluded that avelumab did not meet the criteria for inclusion in the Cancer Drugs Fund.

Innovation

The treatment benefit from avelumab has been adequately incorporated into the model

3.17 The committee considered whether avelumab was innovative. It noted that maintenance treatment after platinum-based chemotherapy is a step-change compared with current treatment options. Avelumab is not a novel compound because it is available as a treatment option for other types of cancer. The company stated that innovation should be considered separately for each indication. The committee agreed with the company that in this case, the innovation is in using avelumab as maintenance

treatment for people whose disease had not progressed 4 to 10 weeks after having first-line chemotherapy. The company considered that avelumab was innovative because there is an unmet need for people with metastatic urothelial cancer and there are no other treatment options for disease that has not progressed. The committee considered that the benefits of avelumab, related to improvements in length and quality of life, have already been incorporated into the model. It concluded that the treatment benefit from avelumab for this indication has been adequately incorporated into the model.

Other factors

3.18 No equality or social value judgement issues were identified.

Review of guidance

3.19 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Lindsay Smith
Chair, appraisal committee
June 2021

4 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Victoria Gillis-Elliott
Technical lead

Sally Doss
Technical adviser

Louise Jafferally
Project manager

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]: Decision of the panel

Introduction

1. An appeal panel was convened on 28 September 2021 to consider an appeal against the final appraisal document (FAD), to the NHS, on avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735].

2. The appeal panel consisted of:

• Alan Silman	Chair
• Elaine Inglesby-Burke	Non-executive director of NICE
• Chris Rao	Health service representative
• Adrian Griffin	Industry representative
• Alan Thomas	Lay representative

3. None of the members of the appeal panel had any competing interests to declare.

4. The panel considered appeals submitted by Merck Serono Ltd, Fight Bladder Cancer, Association of Cancer Physicians, British Uro-Oncology Group, and Action Bladder Cancer UK.

5. Merck Serono Ltd were represented by:

• Amerah Amin	Market Access and Pricing Director Merck Serono UK
• Anthony Eccleston	Senior HTA Manager, Pfizer, UK

- Bihani Kularatne — Oncology Medical Affairs Manager, Pfizer, UK
- Simon Crabb — Associate Professor of Medical Oncology, University of Southampton
- Adela Williams — Legal representative, Partner, Arnold and Porter

6. Association of Cancer Physicians were represented by:

- Mark Linch — Associate Professor and Consultant Medical Oncologist, University College London Hospital

7. British Uro-Oncology Group were represented by:

- Alison Birtle — Secretary of British Uro-Oncology Group, Honorary Clinical Professor and Consultant Oncologist Rosemere Cancer Centre

8. Fight Bladder Cancer were represented by:

- Lydia Makaroff — Chief Executive, Fight Bladder Cancer
- Anne MacDowell — Corporate Partnerships (volunteer), Fight Bladder Cancer
- Melanie Costin — Support Services Manager and bladder cancer patient, Fight Bladder Cancer
- Sana Gilfillan — Policy and Communications Manager, Fight Bladder Cancer

9. Action Bladder Cancer UK were represented by:

- Kevin Gorman — Trustee, Action Bladder Cancer UK

10. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

- Lindsay Smith — Technology Appraisal Committee D Chair, NICE
- Helen Knight — Programme Director, Technology Appraisals and Highly Specialised Technologies, NICE
- Ross Dent — Associate Director, Technology Appraisals, NICE
- Giles Monnickendam — Technology Appraisal Committee D Member, NICE

11. The panel's legal adviser Stephen Hocking, DAC Beachcroft LLP, was also present.

12. The following member of the NICE appeal panel for technology appraisal and highly specialised technologies were present as a silent observer throughout the hearing and panel discussions:

    - Alina Lourie — Non-executive director, NICE

13. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

14. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in light of the evidence submitted to NICE.

15. Mark Chakravarty, NICE Lead Non-executive Director for Appeals, in preliminary correspondence had confirmed that Merck Serono Ltd,

Action Bladder Cancer UK, Fight Bladder Cancer, Association of Cancer Physicians, and the British Uro-Oncology Group all potentially had valid grounds for appeal under Ground 2.

16. The appraisal that is the subject of the current appeal providing advice to the NHS was on the use of avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy.

17. Avelumab is a checkpoint inhibitor anti-cancer immunotherapy agent that activates immune cells by blocking the PD-L1 receptor on their surface. It is used in patients who have had a good response to first-line chemotherapy for locally advanced or metastatic bladder cancer to prevent disease progression.

18. Action Bladder Cancer UK, Fight Bladder Cancer, the Association of Cancer Physicians, and the British Uro-Oncology Group, were invited by the panel chair to describe the impact of metastatic bladder cancer on patients; although he emphasised that these comments were 'scene setting' for the panel to appreciate the impact of the disease on patients, their families and carers and would not be considered as stand-alone grounds for the appeal. The panel would like to thank the patient representatives and clinicians for their insights into living with metastatic and locally advanced bladder cancer. The panel was left in no doubt about the poor prognosis associated with locally advanced and metastatic bladder cancer, its significant effect on quality-of-life, the impact that it has on the psychological and social well-being of patients and their families and the limitations of existing therapies.

19. Before the appeal panel inquired into the detailed appeal points the following made preliminary statements: Amerah Amin on behalf of Merck Serono Ltd, and Lindsay Smith on behalf of NICE. Action Bladder Cancer UK, Fight Bladder Cancer, the Association of Cancer Physicians, and the British Uro-Oncology Group were invited by the chair to make preliminary statements but did not have additional points

to raise not covered in the statement of Amerah Amin on behalf of Merck Serono Ltd and the patient impact statements previously delivered.

20. The appeal panel chair proposed that given the similarity of the two appeal points raised by each of the five appellants under ground 2, that the appeals under each point should be heard together. No objections were raised by any participant.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Merck Serono Ltd appeal point 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)

Action Bladder Cancer UK appeal point 1a.1: Rejection of a stopping rule was unfair in light of past practice and the evidence of patients and clinicians

Association of Cancer Physicians appeal point 1a.1: A stopping rule was rejected but one has been proposed in past appraisals without difficulty

British Uro-Oncology Group appeal point 1a.2: The failure to allow for a stopping rule was not consistent with TAs 525 and 492 (atezolizumab) or TA 692 (pembrolizumab)

21. (Whilst initially raised on Ground 1a, Mark Chakravarty, NICE Lead Non-executive Director for Appeals, during initial scrutiny, considered these appeal points more appropriately related to whether the NICE appraisal committee had acted reasonably. Consequently, these appeal points were considered by the panel under Ground 2)

22. Bihani Kularatne, on behalf of Merck Serono Ltd, stated that the decision of the appraisal committee not to apply a stopping rule was inconsistent with the decisions of appraisal committees previously. She stated that whilst the JAVELIN Bladder 100 trial did not include stopping rules this was also the case for the other trials on which previous technology appraisals that included stopping rules were based. She stated that these prior technology appraisals relate to the

same patient population, the only difference being that maintenance immunotherapy with avelumab is brought forward in the treatment pathway. As the same population of patients have accepted a stopping rule for immunotherapy in other appraisals, it should be assumed that they will accept a stopping rule for immunotherapy no matter what its place is in the care pathway. She stated that the committee did not explain why evidence relating to atezolizumab, also a second line immunotherapy agent, was not relevant to this technology appraisal.

23. Bihani Kularatne stated that the committee also did not consider the evidence from patient groups and clinical experts, who all felt that application of a stopping rule in clinical practice would be accepted.

24. Bihani Kularatne concluded by stating that the guidance was inconsistent with previous appraisals with no proper explanation offered and therefore unreasonable.

25. Simon Crabb, on behalf of Merck Serono Ltd, stated that in the patient population under consideration the only option was immunotherapy, and the question was whether to give it now (i.e., maintenance) or to give it later (i.e., “rescue” after progression). There is no evidence from atezolizumab, where a decision was made to implement a stopping rule in order to allow access to this immunotherapy, that there were practical problems in implementing a stopping rule in this patient population. He stated that experience from applying the stopping rule for the past three years is that patients understand the rationale for the stopping rule and find it acceptable provided it is explained in advance.

26. Simon Crabb stated that patients do not find it acceptable to have access to effective therapies denied. He stated that he did not recognise the assertion by the appraisal committee - made in the preliminary statements of this appeal - that the understanding of patients’ attitudes to stopping rules may have changed in the intervening period since the application of stopping rules in previous appraisals. He stated that he felt patients would find a stopping rule for

immunotherapy just as acceptable in the context of a maintenance therapy, as for a second line therapy given when there was disease progression. In response to questioning from the panel chair he stated that he accepted that patients would find it difficult to accept a stopping rule if they were told after two years of therapy that it had to stop. However, if it was explained to patients before the medication was started that it would be stopped at two years, and the rationale, in his experience, patients found this acceptable. He also stated in response to questioning from the panel chair that he did not think that application of a stopping rule in the context of a maintenance therapy would be any different from a second line therapy given for disease progression. He stated that in this situation patients would understand that a stopping rule would apply if they received immunotherapy for disease progression and therefore would accept that it should apply in the context of maintenance therapy.

27. Anthony Eccleston, on behalf of Merck Serono Ltd, stated that application of a stopping rule would reduce and give certainty to the modelled cost of avelumab, and that different scenarios for treatment effect waning could be modelled, as had been undertaken in previous technology appraisals.

28. Lydia Makaroff, on behalf of Fight Bladder Cancer, described how in her organisation's weekly team meetings she heard stories of patients who had died in the last week. She stated that the NICE decision not to apply a stopping rule was inconsistent with the approach taken for atezolizumab.

29. Lydia Makaroff stated that the assertion by NICE that a stopping rule could not be applied in practise for avelumab was inconsistent with evidence from both clinicians and patients heard by the appraisal committee. She stated that she believed that patients would accept a stopping rule if they were told about it in advance.

30. Alison Birtle, on behalf of the British Uro-Oncology Group, stated that the assumption that all patients would currently have second line therapy if they experienced disease progression was false. She stated that when disease progression was recognised, only 30% would be fit enough to be started on second line therapy. She also stated that less than 5% of patients taking avelumab would be on therapy at two years, and therefore the assumption that all patients would be receiving avelumab at two years was false.

31. Alison Birtle stated that if patients were told prior to starting therapy about a stopping rule, and the reason for the rule, then application of a rule would be acceptable. Finally, she stated that application of a stopping rule would be entirely consistent with immunotherapy technology appraisals in this disease area. She stated that the examples cited by the appraisal committee to explain their concerns about the practical application of stopping rules (Merkel cell carcinoma and renal cell carcinoma) related to different diseases and patient populations and therefore were not relevant in this case.

32. Mark Linch, on behalf of the Association of Cancer Physicians, explained that he had discussed stopping rules extensively with fellow cancer clinicians and their attitude to stopping rules depended on how the discussion was framed. He stated that whilst many clinicians would prefer not to have stopping rules, they would readily apply stopping rules if this was the only way to have access to an effective therapy. He stated that it was not a difficult conversation to have with patients at the start of their treatment with avelumab. Thus, if they were to survive for two-years on therapy then this would be a very good outcome, compared to their normal life expectancy with current standard of care, for metastatic or locally advanced bladder cancer. He stated that it would not be a difficult discussion to have with patients at two years to stop avelumab, as they would have enjoyed two years of quality of life that they would not have had without avelumab. In response to questioning from the chair he stated that a conversation about stopping

therapy following two years of therapy was not without challenge. However, many aspects of clinical medicine were challenging, and this is the type of conversation that he and his colleagues have with patients frequently.

33. Mark Linch stated that immunotherapies were intended to train the patient's immune system to fight cancer and therefore the effect of the immunotherapy was often maintained following cessation of therapy. This was supported by Alison Birtle, speaking on behalf of the British Uro-oncology group, who stated that the treatment effect was durable and that some patients maintained a good response despite stopping immunotherapy. Giles Monnickendam, on behalf of NICE, later challenged this stating that there was no evidence from any clinical trial of a prolonged effect of immunotherapy following cessation of therapy and the only trial to investigate this effect had been negative.

34. Mark Linch stated that CheckMate153 was not relevant to the appraisal of avelumab as the response of metastatic non-small cell lung cancer to therapy was entirely different to metastatic or locally advanced bladder cancer.

35. Kevin Gorman, on behalf of Action Bladder Cancer UK, stated that whilst stopping rules were logical, they could be difficult to explain to patients with bladder cancer. Patients with bladder cancer had a strong preference for receiving some therapy, even for a limited period, rather than not having access to therapy at all. He would find the current FAD hard to explain to patients.

36. Melanie Costin, on behalf of Fight Bladder Cancer, stated that patients would accept a stopping rule. She stated that it was less unfair for patients to have a stopping rule imposed on them then to have no access to avelumab at all.

37. Simon Crabb, on behalf of Merck Serono Ltd, stated that patients would have a choice whether to start maintenance therapy with a

stopping rule or to not start therapy in the hope of receiving second line immunotherapy. He stated that patients were capable of understanding and making this choice.

38. Alison Birtle, on behalf of the British Uro-Oncology Group, stated that the discussion about whether to have immunotherapy now or later with a stopping rule was not a difficult discussion to have with patients. All treatment had a duration. In response to a question by the appeal panel chair about whether patients who were having maintenance immunotherapy would have access to other therapies, should they have disease progression; she said that they were options in the context of clinical trials. She added however only a fraction of patients were still taking maintenance therapy at two years either because of disease progression or toxicity.

39. Lindsay Smith, on behalf of NICE, stated that the proportion of patients in the JAVELIN bladder 100 trial that were still taking avelumab was 20% at two years rather than 5%. Alison Birtle, on behalf of the British Uro-Oncology Group, stated that the proportion of patients taking therapy at 2 years was 51/350 (14.6%). Helen Knight, on behalf of NICE stated that when censored data was accounted for using a Kaplan-Meir estimation it was 20% which was the correct way to estimate the number of patients still taking avelumab. Amerah Amin, on behalf of Merck Serono Ltd stated that when estimated using the Kaplan-Meir method it was 18%, however most clinicians felt that in practice this would be approximately 5%. Amerah Amin, stated in response to questioning from the panel chair that this was because patients in the JAVELIN bladder 100 trial were fitter than other patients with metastatic and locally advanced bladder cancer. Bihani Kularatne, on behalf of Merk Serono Ltd, subsequently stated that this was often the case with clinical trials.

40. Lindsay Smith, on behalf of NICE, stated that in the FAD no reference was made to any difficulty that clinicians may have in applying a

stopping rule. He stated that the appraisal committee have every confidence that clinicians had the appropriate communication skills and training and would be able to apply a stopping rule. He added however that the concern of the appraisal committee was whether patients would accept a stopping rule at two years. He stated that patient experts had said they would not be happy to accept a stopping rule at two years. Mark Linch, on behalf of the Association of Cancer Physicians, subsequently challenged Lindsay Smith's statement about the FAD, drawing the attention of the panel to section 3.8.

41. Helen Knight, on behalf of NICE, stated that different approaches were required for different immunotherapies. She stated that the general approach to stopping rules had changed as the government had received petitions from patient groups that were not happy to accept a stopping rule at two years. She added that the appraisal committees had been asked to be mindful about the application of stopping rules.

42. Lindsay Smith, on behalf of NICE, in response to questions from the panel chair, stated that that there was a combination of reasons behind the decision not to implement a stopping rule for avelumab. He said a significant number of patients would be affected by a stopping rule, and that 1 in 5 of patients would have to be salvaged with second line therapy. Thus, if a stopping rule was used it would be difficult to apply in clinical practice. He stated that avelumab was different from atezolizumab as patients tolerated the former treatment better. He stated that there was no evidence from similar populations that a stopping rule could be applied to avelumab. In response to questioning from the panel chair he said that it was an important factor that the JAVELIN bladder 100 trial did not have a stopping rule. He added therefore there was no clinical trial evidence to justify a stopping rule. He stated that there was no clinical justification for a stopping rule, the only rationale was to reduce the uncertainty around the cost of avelumab. He said that whilst in 2017 a stopping rule was justified on cost grounds for atezolizumab, patients felt increasingly unhappy about

being asked to stop therapy for economic reasons and that the appraisal committee did not have this experience when TA525 was formulated.

43. Simon Crabb on behalf of Merk Serono Ltd, challenged the assertion in Lindsay Smith's evidence that the patient population in the technology appraisal of avelumab was different to the population in atezolizumab (TA525). He therefore questioned the justification for not applying a stopping rule in the case of avelumab.

44. Helen Knight, on behalf of NICE, stated that TA492 (Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable) did not have a stopping rule. Bihani Kularatne, on behalf of Merk Serono Ltd, later challenged this.

45. Adela Williams, on behalf of Merk Serono Ltd, stated that the fact that the SmPC (Summary of product characteristics) does not include a stopping rule (which was mentioned in the FAD) is an irrelevant consideration. The European Medicines Agency which agreed the SmPC is primarily concerned with safety, emphasising factors such as toxicity and side-effects whereas NICE is concerned with economic evaluation. NICE therefore would have a different rationale for applying a stopping rule. She stated that this was a relevant matter as whilst the content of the SmPC may not have been a major factor, it was a factor in the appraisal committee's decision making. Ross Dent, on behalf of NICE, stated that the absence of a stopping rule in the SmPC was not the reason why the appraisal committee chose not to include a stopping rule.

46. The appeal panel concluded as follows:

47. The panel acknowledge that there is no obligation for an appraisal committee to adopt the same approach that previous committees have used to appraise a technology. However, patients, clinicians and industry can reasonably expect that a broadly consistent approach

should be adopted in technology appraisal. This is so that all key stakeholders are aware of the criteria required for NICE to recommend adoption of a technology, or, where an inconsistent approach is adopted, that adequate and rational reasons will be given.

48. Stopping rules are widely applied in the NICE technology appraisals for systemic cancer therapy, including for comparable therapies for apparently similar populations (Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525], and Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA692]).

49. Whilst there is no obligation for the appraisal committee to apply a stopping rule in the case of avelumab because they have been widely applied previously, it is reasonable to expect that the appraisal committee should fully explain their rationale for not doing so.

50. In the view of the panel this could include an explanation of why application of a stopping rule for avelumab would be flawed based on new information addressing the difficulties in the health service with the practical application of stopping rules in clinical practice, or their theoretical basis, that was not considered during the development of TA525 and TA692.

51. Alternatively, the panel consider that it could be reasonable for the appraisal committee to explain why avelumab represents a sufficiently different technology from atezolizumab or pembrolizumab; that the proposed application in this technology appraisal is different from TA525 and TA692; or that the population is distinct in this appraisal from that envisaged in TA525 and TA692, in order to explain why a stopping rule is not applicable in this technology appraisal.

52. The panel can express no view as to whether any such explanations, if given, would be reasonable.

53. The appeal panel heard evidence that the committee were increasingly aware about the broader difficulty in applying stopping rules in particular the acceptance of stopping rules by patients at two-years following the start of treatment. However, no evidence was presented in the FAD or the documents associated with the appraisal committee meetings to support the reasonableness of a change in approach to the application of stopping rules in NICE technology appraisals. If the reason was patients petitioning the Department of Health and Social Care against stopping rules, then the panel considered that to be irrelevant. NICE is independent of the Department of Health and Social Care. Thus, while NICE can consider if a stopping rule might create practical difficulties in implementation for the NHS, it should not consider other difficulties created for other bodies. Patients may well lobby many bodies for access to many treatments, but that lobbying should not be a factor in a technology appraisal.

54. Finally, the appeal panel accepted that modelling a stopping rule in the case of avelumab is problematic, in particular modelling what if any effect avelumab continues to have after cessation of treatment. However, the panel noted from the slides of the appraisal committee meeting, that it was possible to model a number of different scenarios. Whilst it might be reasonable to adopt a conservative modelling approach in view of the uncertainty, the appeal panel do not feel that it is reasonable to reject a stopping rule only on the basis of the difficulties associated with modelling the effect of avelumab following the cessation of treatment. The appeal panel believe it would have been preferable to have considered the various scenarios and used them to inform a decision.

55. Consequently, the appraisal committee finds that insufficient justification was given in the FAD for adoption of an approach in the appraisal of avelumab that was not broadly consistent with previous comparable technology appraisals, and accordingly this inconsistency is unreasonable.

56. The appeal panel therefore upheld the appeal on these points.

Merck Serono Ltd appeal point 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.

Action Bladder Cancer UK appeal point 2.1: It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.

Fight Bladder Cancer appeal point 2.1: It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.

Association of Cancer Physicians appeal point 2.1: It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.

British Uro-Oncology Group appeal point 2.1: It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.

57. Anthony Eccleston, for Merck Serono Ltd, stated that there were two key tests for eligibility for the NICE end of life criteria. Firstly, that the life expectancy must be extended by more than three months, and secondly that life expectancy should be normally less than 24 months. He stated that clearly avelumab meets the first criterion because it extends life-expectancy by seven months. He stated that the appellants disagree that the 24-month criterion was not met. He stated that it is not explained how to assess the patient's life expectancy in NICE guidelines. He stated that the committee received 20 estimates of life-expectancy from clinical trials, epidemiological studies, clinical expert testimony. However NICE chose to adopt an estimate from the modelled mean, ignoring the majority of the other evidence. He stated that the mean data does not reflect the real-world patient data. In response to questioning from the panel chair, Anthony Eccleston stated that life expectancy should be measured from the point at which avelumab would be started.

58. Simon Crabb, for Merck Serono Ltd, stated that the decision by NICE that life-expectancy was greater than 24 months for patients with

metastatic bladder cancer had been met with incredulity by the oncology community. He stated that both median and mean survival are only estimates and that the appraisal committee should evaluate the totality of the data to assess if end of life criteria had been met. He stated that the LaMB trial represented the best long-term estimates of survival in an NHS population, and this suggests that survival would normally be 12 to 18 months. He stated that bladder cancer patients in his clinic often ask him "how long they have got left?". He stated that his response was that 12 to 18 months is a reasonable estimate of life-expectancy and anyone who told patients that they would normally expect to survive two years would be misleading them.

59. Alison Birtle, for the British Uro-Oncology Group, stated that she was comfortable with the use of 12 to 18 months as an estimate for the normal life expectancy of a patient with metastatic bladder cancer based on data from the LaMB study. She also stated that this was congruent with European and US data.

60. Mark Linch, for the Association of Cancer Physicians, stated that he uses the median to explain likely life expectancy to patients as this is representative of what most patients will experience, but draws the survival distribution and explains the long tail and the hope that the individual patient will be "in the tail".

61. Adela Williams, for Merck Serono Ltd, stated that the word "normally" in this context could have two meanings. Firstly, that 24 months is not a rigid threshold for application of end of life criteria by NICE. Secondly, that "normally" could refer to the life expectancy that a patient would usually anticipate.

62. Lydia Makaroff, for Fight Bladder Cancer, stated that the mean of 27.8 months fails to account for what the majority of patients will experience, and it is unreasonable to extrapolate from an economic model to estimate life expectancy. Melanie Costin, also on behalf of Fight

Bladder Cancer, confirmed that patients have a reasonable expectation that the median would be used.

63. Lindsay Smith, for NICE, stated that there has been considerable debate over the period that he has been a member of the appraisal committee about whether it would be more appropriate to use the median or the mean and that both have been used in the last two years. It is easier if both the median and the mean are less than two years but more problematic if the mean is greater than two years and the median is less.

64. Lindsay Smith stated that in the other technology appraisals referenced by the appellants in initial scrutiny (TA692 and TA658) both the median and the mean were less than two years. He stated that the appraisal committee has to take into account both the clinical and cost effectiveness. He stated that the appraisal committee fully accepted the clinical effectiveness of avelumab, and the increase in life expectancy was greater than 3 months. He noted that the Office of National Statistics presents means in their survival data. Of more relevance to the committee discussion was the requirement to use the mean, over the median in their preferred approach to the cost-effectiveness analysis.

65. Giles Monnickendam, for NICE, was asked by the panel chair about whether the committee must necessarily use the same analytical framework to assess whether an intervention fulfils the NICE end of life criteria as to perform the economic analysis. Giles Monnickendam stated that life expectancy is currently measured using the mean, as this captures all data. By contrast, in clinical trials the median is often used as there is incomplete follow-up, but this does not take into account the heterogeneity of data. He stated that NICE need to use the same approach, as the mean unlike the median captures the totality of the data for the whole population. He stated that this is why the Office of National Statistics use the mean. He stated that, clinical trials do not

report the mean and only report the median as they generally do not follow-up patients until death, and that is why they are often used in the decision about whether a technology fulfils end of life criteria.

66. Giles Monnickendam challenged the assertion by the appellants that the 20 sources of evidence suggesting a survival (mean or median) under 24 months had been rejected by the appraisal committee in favour of using their modelled mean. He stated that 16 of the studies referred to were not in the population of interest. He added that the LaMB study was old and predated the introduction of immunotherapy for metastatic and locally advanced bladder cancer. He further stated that the expert opinions of median survival were entirely consistent with the modelled mean used to assess whether the technology met the end of life criteria.

67. In response to questioning from the panel chair with regards to the report of the ERG in which they stated "…A judgement call is therefore required as to whether avelumab satisfies the first criteria for end of life consideration, but on balance the ERG consider it plausible that criteria 1 is met." Lindsay Smith, on behalf of NICE, stated that it depends on what model to accept, and they were both plausible. He stated that he was not sure whether the ERG in making this statement about the plausibility of end of life criteria being met were referring to the fact that the modelled mean was close to the 24-month threshold, or that the median was less than 24 months.

68. Lindsey Smith stated that it was important to be consistent. You cannot use the median and have the "benefit" of 12 to 18 month life-expectancy to fulfil end of life criteria, and then have the benefit of the mean 2 to 3 year survival from the cost-effectiveness analysis.

69. Giles Monnickendam, for NICE, in response to questioning from the panel chair stated that end of life criteria would have a significant effect on whether the technology was considered cost-effective because the cost-effectiveness threshold would move from approximately

£30,000/QALY to £50,000/QALY. He added however he did not feel this was appropriate as the mean was the most appropriate measure of life expectancy.

70. Giles Monnickendam stated that significant work had been done to assess whether the mean was truly a fair representation of life expectancy and if survival was skewed by a small number of patients in a particularly long tail of the survival curve, then it would not have been used. However as 65% of patients died before two years, he did not feel that the distribution was being disproportionately skewed by a long tail of the survival curve.

71. Giles Monnickendam, stated in response to questioning from the panel chair, that the appraisal committee looked at the estimates from real-world data and clinical expert opinion for the target population and there was no evidence of a lack of generalisability of data from the JAVELIN bladder 100 trial.

72. In response to questioning from the panel chair about "what was in the minds of our masters" about how the word "normally" should be interpreted when the end of life criteria were introduced, Giles Monnickendam stated that as a health economist he understood this to refer to usual mean survival.

73. Helen Knight, on behalf of NICE, stated that she understood the term "normally" was to allow appraisal committees discretion and flexibility around the 24-month timeframe. She stated that it was not unreasonable to use the mean. In response to questioning from the panel chair she stated that flexibility could allow an appraisal committee to use the median.

74. Anthony Eccleston, for Merck Serono Ltd, stated that the life expectancy of a population should be assessed to see if a modifier needs to be applied prior to economic analysis. He stated that the median tells us that the majority survive less than 12 months. He stated

that the ERG felt an estimate of 35 months for the modelled mean was likely to be an overestimate and therefore used 27 months.

75. Simon Crabb, for Merck Serono Ltd, stated that the LaMB study had a median survival of 12 months before immunotherapy was introduced as second line therapy for disease progression. He stated that the atezolizumab trial was a negative study in terms of increasing life expectancy and pembrolizumab only increased life expectancy by three months. He stated that whilst he accepted the LaMB study was an old trial, immunotherapy at most increased life expectancy for participants in that trial by three months. He stated that choice of the estimate of survival should be different for the cost effectiveness analysis and the assessment of whether an intervention fulfils NICE end of life criteria, and this does not undermine the consistency.

76. Alison Birtle, on behalf of the British Uro-Oncology Group, stated that only 30% of patients in LaMB went on to have immunotherapy and only one quarter responded to therapy. She continued that the outcomes following introduction of immunotherapy would not have significantly changed from the LaMB trial. She stated the community could not understand how NICE could have failed to apply the end of life criteria in this appraisal.

77. Anne MacDowell on behalf of Fight Bladder Cancer, stated as a lay person “normally” should mean what the majority of people experience and consequently the median should be the estimate of survival used. She stated that averaging out survival between all patients does not seem right to a lay person.

78. Ross Dent, on behalf of NICE, stated that this is not a new issue. He stated that this has been a subject of previous appeals against NICE appraisals. He stated that in previous appeals, on these grounds the appeal panel had found that the decision to use the modelled mean was not unreasonable.

79. Adela Williams on behalf of Merck Serono Ltd, stated that every appraisal is different and because an appeal panel has previously found that it was reasonable to use the modelled mean did not necessarily mean that it was reasonable to use the modelled mean in the case of avelumab.

80. The appeal panel concluded as follows:

81. The appeal panel recognise that there was consensus between the appellants and the appraisal committee that improvement in survival was in the order of seven months, significantly in excess of the three months mandated for application of end of life criteria in technology appraisals.

82. The appeal panel similarly recognise that there was consensus between the appellants and the appraisal committee that median survival was significantly less than 24 months. The appeal panel note however that the modelled mean survival was slightly larger than 24 months which is entirely consistent with the median survival being less than 24 months.

83. The NICE end of life criteria is applied when, “The treatment is indicated for patients with a short life expectancy, normally less than 24 months”. The appeal panel note that there is no guidance in the NICE Guide to the Methods of Technology Appraisal or from the NICE Decision Support Unit on how the word “normally” should be interpreted and the appeal panel note that historically both the mean and median have been used.

84. The appeal panel note that the NICE end of life criteria are founded on the principles in the NICE guide to the use of Social Value Judgements and the outcomes of the Citizens Council meeting in November 2008.

85. Consequently, the panel feel that the paramount consideration should be what the key stakeholders of NICE: the general public, patients,

clinicians, policy makers and industry would consider a reasonable interpretation of the word “normally”.

86. The appeal panel, therefore, do not accept the argument advanced by the appraisal committee that the mean survival of 24 months must be used as the threshold for application of end of life criteria to maintain consistency with the methodology used to calculate the incremental cost-effectiveness ratio. The appeal panel note that there are a number of other circumstances when policy consideration and social value judgements are incorporated into the technology appraisal framework.

87. The appeal panel felt that the key stakeholders of NICE would consider it unreasonable to state that life-expectancy was not “normally less than 24 months”, even if the mean life expectancy was greater than 24 months, if 65% of patients, the significant majority, in the modelled cohort had died prior to 24 months.

88. The appeal panel agreed that a totality of the data and analysis have to be looked at when considering if life expectancy is “normally less than 24 months”. It does not wish to suggest there is a general rule that median is preferable to mean or vice versa. The question is it reasonable to conclude that life expectancy is below 24 months, and the mean, the median, and clinical opinion all inform that judgement. Taken in the round the panel did not feel it would be possible to explain to patients or clinicians why it was said these patients would have a life expectancy in excess of 24 months, and therefore this conclusion was unreasonable.

89. The panel understood the concern about using means in one context and medians in another, but the end of life criteria are a stand-alone test that have to be considered on their own terms. If they apply, an appraisal committee still has a discretion as to what level of cost effectiveness it considered acceptable.

90. The panel also agreed that “normally” allowed a committee a discretion to apply end of life criteria even if it felt on some measures of life expectancy might be somewhat over 24 months. Even if it had been correct to use the mean as the main driver of a decision in this case, given that the median and clinical expert opinion was all significantly below 24 months, and the mean was not substantially above 24 months, this was a case where that discretion would have needed to have been discussed.

91. Consequently, the appeal panel concluded that in this case it would be unreasonable to conclude that this end of life criterion was not met.

92. The appeal panel therefore upheld the appeal on these points.

Conclusion and effect of the appeal panel decision

93. The appeal panel therefore upholds the appeal of Merck Serono Ltd on points 1a.1 and 2.1, the appeal of Action Bladder Cancer UK on points 1a.1 and 2.1, the appeal of Fight Bladder Cancer on point 2.1, the appeal of the Association of Cancer Physicians on points 1a.1 and 2.1, and the appeal of the British Uro-Oncology Group on points 1a.2 and 2.1.

94. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to address the following issues:

    a. The appraisal committee should either consider the application of a stopping rule for avelumab or should explicitly detail the rationale for why in contrast to TA525 and TA692 a stopping rule is either methodologically problematic or practically difficult (Merck Serono Ltd point 1a.1, Action Bladder Cancer UK point 1a.1, the Association of Cancer Physicians point 1a.1, and the British Uro-Oncology Group points 1a.2).

    b. The appraisal committee should appraise the technology on the basis that the NICE end of life criteria applies (Merck Serono Ltd

point 2.1, Action Bladder Cancer UK point 2.1, Fight Bladder Cancer point 2.1, the Association of Cancer Physicians point 2.1, and the British Uro-Oncology Group 2.1).

Whether in light of these recommendations the recommendation will be amended will be a matter for the appraisal committee to consider.

95. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.

From: Alan Silman <[redacted]>
Date: Tuesday, 9 November 2021 at 11:56
To: Mark Chakravarty <[redacted]>, Alan Silman <[redacted]>
Cc: Elaine Inglesby <[redacted]>, Christopher Rao <[redacted]>, Alan M Thomas <[redacted]>
Subject: Re: Appeal decision avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Dear Mark,

Thank you for your email requesting clarification of our judgement on the avelumab appeal, which I have discussed with the Appeal Panel

We feel that we should not change the wording of our decision but that the opinion below can be published alongside as a clarification

The panel were very clear that this decision not to invoke the end of life (EoL) criteria was unreasonable and we gave our reasons for this. We accept that we cannot absolutely direct, as oppose to advise, an appraisal committee (AC). Conceptually it will be open for the AC, having reconsidered the question with an open mind, to come again to the view that the EoL criteria are not met. There would be a very high bar for the AC to persist in that view. They need to be left in no doubt of this, which was the intent of our wording.

Best wishes

Alan

Alan Silman
[redacted]

Telephone (PA) +44 (0)[redacted]

From: Mark Chakravarty <[redacted]>
Sent: 07 November 2021 10:41
To: Alan Silman <[redacted]>
Cc: Hocking, Stephen <[redacted]>; David Coombs <[redacted]>
Subject: Appeal decision avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

Dear Alan

Many thanks for the work that you and you panel have put in on the Avelumab appeal.

Based on the outcome of the appeal, the Institute is in process of remitting the evaluation to the appraisal committee. In order to avoid any possibility of misunderstanding of the appeal panel's findings I would like to clarify one point.

At paragraphs 82-94 of your decision, the panel gives its reasons for finding that the committee's conclusion that NICE's End of Life criteria did not apply were unreasonable. In those paragraphs the panel examine the judgements the committee has to make and the discretion they exercise.

At paragraph 96 of the letter you set out the consequences for the committee, and say:

> *"The evaluation is remitted to the appraisal committee who must now take all reasonable steps to address the following issues:*
> *(a)…*
> *(b) The appraisal committee should appraise the technology on the basis that the NICE end of life criteria applies"*

The clarification being sought is how the discussion at paragraphs 82-94 and the reference to all reasonable steps interacts with the apparently mandatory wording at paragraph 96(b). Specifically, is the panel's view that having found it unreasonable to reject end of life criteria, based on the totality of the evidence available to the panel:

- The consideration for the application of end of life criteria is now fundamentally binary and that the only option for any reasonable committee, given the facts your panel heard in this appeal, would be limited to moving on to deciding the impact of the criteria.

Or

- The consideration for the application of end of life criteria still has the potential for deliberation and judgement by a committee based on the evidence.

There is some concern that stakeholders should not think that an appeal panel can direct a committee on specific assumptions it must adopt. For my part, I can see that if an appeal panel has reached the conclusion on a binary question that only one possible answer can be reasonable, it should say so. The consequence must be that any reappraisal that did not adopt the same conclusion would again be unreasonable and it is sensible to make that clear. On the other hand, even if an appeal panel has reached a firm view that a conclusion is unreasonable, if it considers there may be a chance, even if very limited, that a similar outcome could be reached reasonably then the correct outcome would be to refer the issue back to the committee and allow them to retake the decision taking account of the observations of the appeal panel. Their subsequent decision may again be subject to appeal.

Could I ask you to consult with your colleagues and indicate whether your conclusion was that the only reasonable view on end of life was that the criteria applied, or whether your view was that the committee should revisit that question in the light of the reasoning in your letter and the strong indication that gives?

For absolute clarity, you are not being asked to revisit your decision that the committee's position on end of life was unreasonable. That decision has been taken. It is simply whether the committee are to be allowed to look at the question themselves again or not.

Yours sincerely

Dr Mark Chakravarty

Lead non executive director for appeals

National Institute for Health and Care Excellence