

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using avelumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using avelumab in the NHS in England.

For further details, see [NICE's guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 27 May 2021

Second appraisal committee meeting: 17 June 2021

Details of membership of the appraisal committee are given in section 4

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. This is because it is uncertain how long people in the NHS who would be eligible for avelumab live for. 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.

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 committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see table 1 in the ERG report) and took these into account in its decision making. It considered the following issues (issues 1, 3, 4, 5, 6 and 7), which needed further discussion after the technical engagement stage.

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 after first-line platinum-based chemotherapy. People were randomised to have 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 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 who were randomised and people with PD-L1-positive tumours. The committee noted there was a statistically significant improvement in overall survival for the 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.

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 with 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. But these results were not statistically significant when comparing avelumab with best supportive care (median 3.0 months; 95% CI 2.0 to 3.7 months) with 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 with 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 data

3.6 In the economic model, the company used parametric distributions to extrapolate data on overall and progression-free survival from JAVELIN Bladder 100. The company originally selected the generalised gamma curve to extrapolate both avelumab and watchful waiting overall survival in its base case. However, 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. Overall survival at 5 years is expected to be between 5% to 15% and 10-year overall survival between 2% to 7%. Although 5-year and 10-year overall survival estimates for avelumab were unknown, the ERG preferred the log-normal curve 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 noted that there may be 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). As mean life years changed by a similar proportion in each arm, this has little effect on the cost-effectiveness results. It concluded both models should be considered as 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 this would 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. It noted that, 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 the 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. The model captured the benefits these people had from continued 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 experts stated they would accept a similar stopping rule if this would enable access to avelumab. The committee was aware that the company had not provided a scenario analysis when all patients stopped 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 immunotherapies for urothelial cancer have preferred no stopping rules. It concluded that there was no evidence to support a stopping rule since neither JAVELIN Bladder 100 nor the summary of product characteristics included one, and that it should not be in the model. 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 would therefore like to see 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.

It is not appropriate to include a lifetime treatment effect for people stopping avelumab before disease progression

3.9 Related to the assumptions about stopping treatment, the company 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 has been applied when a stopping rule had been applied. The committee concluded that a lifetime treatment effect is implausible for people stopping avelumab before disease progression.

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, which showed the proportion of people in UK clinical practice who have a second-line therapy after first-line platinum-based chemotherapy was 41.9%. 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 recent NICE recommendations which 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 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. Using treatment-specific utilities slightly increases the ICER. The clinical experts stated it would be reasonable to include health state utilities from each arm of the trial. The committee agreed 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 this criteria for end of life because it increases overall survival by more than 3 months.

It is unclear whether life expectancy for people with urothelial cancer who have not had avelumab is less than 24 months

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 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 economic model was based on the results from JAVELIN Bladder 100, which 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. For immunotherapies, the mean is often higher than the median, because of a long tail of a 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. So it is important for the committee to consider the mean survival. The committee also understood that median overall survival was taken from the time of randomisation. However, randomisation happened if people had progression-free disease 4 to 10 weeks after the last cycle of chemotherapy. 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. 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. The committee was unsure if the overall survival values from existing clinical trials and estimates provided by the clinical experts accurately reflect people who are eligible

for maintenance treatment. It considered that these estimates might include people whose cancer had not responded well to chemotherapy and so have a short prognosis but would not be eligible for maintenance treatment. It would be useful if estimates could be provided for the eligible population of people who have responded well to chemotherapy. The committee concluded it is unclear whether avelumab meets the short life expectancy criterion and so it did not accept that the end of life criteria had been met.

Cost-effectiveness estimates

The ICER using the committee's preferred assumptions is substantially higher than £20,000 per QALY gained

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 some of the assumptions in the company's base-case model were implausible. The committee agreed that its preferred assumptions included:

- progression assessed by blinded independent central review (see section 3.6)
- proportion of people having treatment after treatment based on JAVELIN Bladder 100 (see section 3.9)

- including costs of immunotherapies for people having avelumab whose disease had progressed (see section 3.10)
- time to stopping treatment following survival curves fitted to Kaplan–Meier data with no additional treatment stopping at 2 or 5 years (see section 3.7)
- health state utilities before and after disease progression based on each arm of JAVELIN Bladder 100 (see section 3.11).

Avelumab is not recommended for routine use in the NHS

The committee also agreed that it would prefer to see analyses based on extrapolating overall survival using both the generalised gamma and log-normal distributions (see section 3.5). 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 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 key clinical 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. However the benefits of this innovation, related to improvements in length and quality of life, have already been incorporated into the model. Also, avelumab is not a novel compound because it is available as a treatment option for other types of cancer. The committee 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.

Proposed date for review of guidance

3.19 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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

April 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

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