NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Avelumab is recommended as an option for maintenance treatment of locally advanced or metastatic urothelial cancer that has not progressed after platinum-based chemotherapy in adults, only if:

- avelumab is stopped at 5 years of uninterrupted treatment or earlier if the disease progresses and
- the company provides avelumab according to the commercial arrangement.

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 meets NICE's criteria to be considered a life-extending treatment at the end of life. This is because although there are different ways to estimate life expectancy, overall, it is likely that most people who would have been eligible for treatment with avelumab would live on average less than 24 months. The most likely cost-effectiveness estimates are within what NICE usually considers an acceptable use of NHS resources for end of life treatments. So avelumab is recommended, if it is stopped at 5 years or earlier if the disease progreses.

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 for avelumab.

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 February 2022).

2.4 The company has a commercial arrangement. This makes avelumab available to the NHS with a discount. 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: everyone 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 that 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 that 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 (before the appeal)

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 that 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 original assumptions about stopping avelumab treatment could not be implemented in the NHS. But 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, if the alternative was for avelumab to be not recommended in the NHS. This was confirmed by 2 patient organisations in response to consultation. 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. The committee considered this issue further after the appeal (see section 3.18).

Waning of treatment effect should not be included in the model (before the appeal)

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 that 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 that 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. This was 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 that 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 that 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 that 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 that in that appraisal the same treatments were available to people in both study groups whose disease progressed. The company also suggested that 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 that 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. It concluded that, on balance, it was not appropriate to pool health-state utilities across treatment arms.

End of life (before the appeal)

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 that 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. The committee considered this issue further after the appeal (see section 3.19).

Cost-effectiveness estimates (before the appeal)

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 (see NICE's webpage on managed access). 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.

After the appeal

The committee has considered the appeal points upheld by the appeal panel and the company's revised patient access scheme

3.17 At the third appraisal committee meeting, the committee considered the appeal panel's decision to uphold 2 appeal points and refer these back to the appraisal committee for further consideration. These were:

- The committee should either consider the application of a stopping rule for avelumab or should explicitly detail the rationale for why a stopping rule is either methodologically problematic or practically difficult (in contrast to NICE technology appraisal guidance on 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]).
- The committee should appraise the technology on the basis that the NICE end of life criteria applies.

The committee considered these points and updated analyses including a revised patient access scheme.

The population and setting in this appraisal are different from TA525 and TA692

3.18 The committee reconsidered its decision that a 2-year stopping rule should not be included in the model (see section 3.9). The appeal panel had said that there was no obligation for the committee to apply a stopping rule but that the committee should fully explain its rationale for not doing so. The committee recalled that TA525 and TA692, where stopping rules had been applied, were in the second-line setting. It was also aware that there was a stopping rule in the key pembrolizumab trial (TA692), but not the atezolizumab trial (TA525). The committee recognised that the initial guidance recommending pembrolizumab for use in the Cancer Drugs Fund with a stopping rule was issued before the

appraisal of atezolizumab. Given the overlapping populations, settings and mode of action of the technologies, the committee appraising atezolizumab found the proposed 2-year stopping rule acceptable. In addition, that committee recorded in its considerations that it "also recognised that NICE guidance for other immunotherapies for metastatic urothelial carcinoma and other cancers include 2-year stopping rules". The committee considered that there were key differences between those appraisals and the appraisal of avelumab:

- The setting for this appraisal is maintenance treatment, when platinum-based chemotherapy has controlled the disease, rather than when there has been disease progression as for pembrolizumab and atezolizumab.
- The population in this appraisal includes people whose cancer has responded well to platinum-based chemotherapy, whereas the second-line population would include some people with cancer that had not responded to chemotherapy or had progressed very quickly. The population in this appraisal may have cancer that also responds differently to immunotherapy.
- In JAVELIN Bladder 100, a substantially higher proportion of people were having treatment at 2 years (the exact figures are considered confidential by the company, so cannot be reported). Just under 10% of people were still on pembrolizumab and atezolizumab treatment at 2 years, irrespective of whether the trials included a stopping rule. So a stopping rule for avelumab would potentially affect a higher proportion of people.
- There is more experience now of using immunotherapies beyond 2 years in clinical practice than at the time of the appraisals of pembrolizumab and atezolizumab. TA525 notes clinical concern about using immunotherapies beyond 2 years, but clinical experts suggest that these concerns have reduced.

  For these reasons, the committee considered that stopping treatment at 2 years for people whose disease has responded to chemotherapy and is continuing to respond to maintenance treatment was distinct from stopping treatment at 2 years in the second-line setting. The committee concluded that the population and setting in this appraisal are different from TA525 and TA692.

A 5-year stopping rule is acceptable in this appraisal

3.19 The committee was also not confident that a 2-year stopping rule could be applied without risking significant harm to people. The clinical and patient experts stated that people would accept a stopping rule if it was explained to them at the start of treatment and if the mechanism of action of immunotherapies was also explained. But the committee was concerned what effect stopping treatment would have on these people. It queried whether there was any evidence that stopping treatment in a maintenance setting would not result in increasing numbers of people whose disease relapses. The company stated that there was no evidence in the maintenance setting, but there was evidence in other settings and indications. This has showed that there is a continued benefit from immunotherapy after treatment is stopped. The committee was aware of a trial in people with non-small-cell lung cancer that showed that stopping treatment with immunotherapy after 1 year resulted in worse outcomes compared with people who stayed on treatment. It was also aware of emerging long-term follow up from pembrolizumab trials showing a significant proportion of people whose cancer relapsed after stopping treatment at 2 years. Although the clinical expert broadly agreed with the company, they noted that the optimal length of treatment was still uncertain. As such, trials were planned to look at different treatment durations. The committee noted that accepting a stopping rule would increase the uncertainty in the model and would need additional assumptions, on how long reduced risk of disease progression would continue after stopping avelumab and how treatment effect waning should be applied. However, it accepted that it had been possible to adapt the models in other appraisals, so these challenges did not prevent a stopping rule. In response to the committee's concerns, the company presented a scenario which modelled stopping treatment at 5 years. The extrapolation suggested that the proportion of people still on avelumab treatment at 5 years would be less than 10%. The committee noted that this was similar to the proportion of people on treatment at 2 years in the atezolizumab and pembrolizumab trials in TA525 and TA692. The company also argued that the proportion of people on treatment at 5 years in clinical practice is likely to be lower than that in the extrapolation data. The clinical expert agreed that they would expect few people to be on treatment at 5 years. The committee accepted that a 5-year stopping rule would address some of its concerns regarding a 2-year stopping rule since most people would have stopped treatment by this time. The committee concluded that it is acceptable to include a 5-year stopping

rule in this appraisal.

A treatment effect cap at 1 year should be included in the model

3.20 Having accepted the inclusion of a 5-year stopping rule, the committee discussed at what point any treatment benefit would stop. The company had originally proposed a lifetime treatment benefit, which the committee agreed was implausible (see section 3.9). After the appeal, the company provided scenario analyses varying the duration of continued benefit from 1 to 3 years after stopping avelumab. The committee considered that there was no evidence that a treatment benefit would continue for 3 years after stopping treatment. However, it agreed that the benefits of avelumab would not end immediately on stopping treatment. So it considered a treatment effect cap at 1 year was plausible, despite a lack of evidence to support this. The committee concluded that, although the treatment effect duration was uncertain, a treatment effect cap at 1 year after stopping avelumab should be included in the model.

Avelumab meets the short life expectancy criterion and is a life-extending treatment at the end of life

3.21 The committee reconsidered its decision that avelumab does not meet the short life expectancy criterion (see section 3.14). It firmly believed that the best estimate of life expectancy came from the mean survival for the eligible patient population, based on the decision model submitted by the company. This is because the model should reflect all relevant, quality-assessed evidence on the costs and effects of the different comparator treatments. Also, the mean is the most suitable statistic reflecting the totality of evidence, whereas the median does not take into account the outcomes of 50% of people. Using mean survival is also consistent with cost-effectiveness results, which are based on mean quality-adjusted life years and costs. However, the committee accepted that the NICE methods guide does not specifically state how this criterion should be assessed. It noted that the appeal panel had a different interpretation of the NICE methods guide and considered that the model and the decision about usual life expectancy are standalone considerations. The appeal panel concluded that the totality of evidence should be considered when assessing whether avelumab

meets the short life expectancy criterion, including mean and median survival estimates and clinical opinion. The panel concluded that NICE stakeholders would consider it unreasonable to state that life expectancy for this population was normally more than 24 months, given that the modelled mean life expectancy indicated that most people (65%) did not survive after 24 months. At the committee meeting after the appeal, the clinical expert reiterated that that overall survival for people whose disease responds to chemotherapy was less than 24 months. The committee accepted the appeal panel's conclusion that the short life expectancy criterion was met. The committee therefore concluded that avelumab meets the criteria to be considered a life-extending treatment at the end of life.

The ICER with a 5 year stopping rule and 1 year treatment effect cap is within the range usually considered cost effective for end of life treatments

3.22 After the appeal, the company revised its patient access scheme and submitted revised cost-effectiveness estimates. The company accepted the committee's preferred assumptions (see section 3.15), except around a stopping rule. The company's base case with a 2-year stopping rule and treatment effect cap at 3 years resulted in an ICER of less than £50,000 per QALY gained. The committee also considered the company's analyses including a 5-year stopping rule and a treatment effect cap at 1 year. The ICER for this scenario, including the revised patient access scheme and the confidential discounts for subsequent treatments was within the range usually considered a cost-effective use of NHS resources for end of life treatments. The committee therefore recommended avelumab for routine use in the NHS for the maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy. It is only recommended only if treatment is stopped at 5 years of uninterrupted treatment or earlier if the disease progresses.

Innovation

The treatment benefit from avelumab has been adequately

incorporated into the model

3.23 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

3.24 No equality or social value judgement issues were identified.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Because avelumab has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has locally advanced or metastatic urothelial cancer that has not progressed after platinum-based chemotherapy and the doctor responsible for their care thinks that avelumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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 and Anita Sangha
Technical leads

Sally Doss
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