NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using enfortumab vedotin with pembrolizumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using enfortumab vedotin with pembrolizumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: Tuesday 29 April 2025
- Second evaluation committee meeting: To be confirmed
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Enfortumab vedotin with pembrolizumab should not be used for untreated unresectable or metastatic urothelial cancer in adults who can have platinum-based chemotherapy.

1.2 This recommendation is not intended to affect treatment with enfortumab vedotin with pembrolizumab 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 healthcare professional consider it appropriate to stop.

What this means in practice

Enfortumab vedotin with pembrolizumab is not required to be funded in the NHS in England for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable. So, it should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that enfortumab vedotin with pembrolizumab is value for money.

Why the committee made these recommendations

For unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable, usual treatment is first-line carboplatin or cisplatin (both platinum-based chemotherapies) plus gemcitabine, and then maintenance avelumab if the cancer has not got worse.

Clinical trial evidence shows that enfortumab vedotin with pembrolizumab increases how long people have before their cancer gets worse and how long they live compared with usual treatment.

But, there are uncertainties in the economic evidence. This is because people in the clinical trial had subsequent treatments that are not currently recommended in the NHS and this was not adjusted for in the economic model. It is also unclear how best to estimate how long people have avelumab maintenance treatment for in the NHS.

The cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources. So, enfortumab vedotin with pembrolizumab should not be used.

2 Information about enfortumab vedotin with pembrolizumab

Marketing authorisation indication

2.1 Enfortumab vedotin (Padcev, Astellas) with pembrolizumab (Keytruda, MSD) is indicated for 'the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy'.

Dosage in the marketing authorisation

2.2 The dosage schedules are available in the summary of product characteristics for enfortumab vedotin and summary of product characteristics for pembrolizumab.

Price

2.3 The price of enfortumab vedotin is £578 per 20-mg vial or £867 per 30-mg vial (excluding VAT; BNF online accessed March 2025). The price of pembrolizumab is £2,630 per 100 mg in a 4-ml vial (excluding VAT; BNF online accessed March 2025).

2.4 Astellas has a commercial arrangement for enfortumab vedotin. This makes enfortumab vedotin available to the NHS with a discount and it would have also applied to this indication if

enfortumab vedotin with pembrolizumab had been recommended. The size of the discount is commercial in confidence.

2.5 MSD has a commercial arrangement for pembrolizumab. This makes pembrolizumab available to the NHS with a discount and it would have also applied to this indication if enfortumab vedotin with pembrolizumab had been recommended. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Astellas, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition and effects on quality of life

3.1 Urothelial cancer affects cells that form the inner lining of the bladder, urethra, ureter or renal pelvis. Unresectable or locally advanced urothelial cancer refers to disease that has spread to the pelvic or nearby lymph nodes, or the walls of the pelvis or abdomen, or both. Metastatic urothelial cancer refers to cancer that has spread outside the pelvis. Patient experts explained that the burden of the disease on people with urothelial cancer and their carers was substantial. Patient experts also explained that current first-line treatments for urothelial cancer, such as chemotherapy, cause side effects that impact people's quality of life. So, there is an unmet need for effective first-line treatments with more tolerable side effects. The clinical experts noted that there is an unmet need for effective treatments with durable control of urothelial cancer. The committee concluded that there is an unmet need for effective treatments for unresectable or locally advanced urothelial cancer.

Clinical management

Treatment options

3.2 First-line treatment for unresectable or locally advanced urothelial cancer includes platinum-based chemotherapy such as cisplatin with gemcitabine, carboplatin with gemcitabine, and methotrexate, vinblastine, doxorubicin and cisplatin (MVAC). The company noted that most people (around 90%) are eligible for platinum-based chemotherapy. The EAG's clinical experts estimated that around two-thirds of people eligible for platinum-based treatment would have cisplatin. The clinical experts at the committee meeting estimated that around half of the people eligible for platinum-based treatment would have cisplatin and the other half would have carboplatin. Eligibility for cisplatin is based on fitness according to the Galsky criteria. People unable to have cisplatin are offered either carboplatin with gemcitabine or atezolizumab (see NICE's technology appraisal guidance on atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable). Enfortumab vedotin with pembrolizumab was considered by the company as an alternative first-line treatment option. The committee understood that avelumab maintenance treatment is offered after a response to platinum-based chemotherapy (see NICE's technology appraisal guidance on avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy, from here TA778). After disease progression, further treatment options include platinum-based chemotherapy rechallenge, paclitaxel, and atezolizumab (see NICE's technology appraisal guidance on atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy). The committee concluded that enfortumab vedotin

with pembrolizumab would be used as a first-line treatment for unresectable or locally advanced urothelial cancer.

Comparators

3.3 The company considered platinum-based chemotherapy as the only relevant comparator for enfortumab vedotin with pembrolizumab. But NICE's final scope also included MVAC and atezolizumab (see section 3.2) for people who are cisplatin-eligible and -ineligible, respectively. The company noted that these treatments are only used by a small proportion of people eligible for platinum-based treatments (2% to 3%), which is the relevant population for enfortumab vedotin with pembrolizumab. Clinical advice to the EAG was that it was reasonable to exclude MVAC and atezolizumab as comparators. This is because MVAC can cause substantial side effects. They also noted that healthcare professionals prefer to offer carboplatin-based chemotherapy as first-line treatment instead of atezolizumab, for people eligible for platinum-based treatment but unable to have cisplatin. No further evidence was presented to the committee to refute the company's and EAG's perspectives on the comparator. So, the committee concluded that the relevant comparator is platinum-based chemotherapy with gemcitabine followed by avelumab maintenance for people whose disease did not progress.

Clinical effectiveness

Data sources

3.4 The key clinical-effectiveness evidence used in the company's submission was from a trial called EV-302. This was an open-label, phase 3, randomised trial that included people aged 18 and over with untreated locally advanced or metastatic urothelial cancer. The trial compared the efficacy of enfortumab vedotin plus pembrolizumab against platinum-based chemotherapy (cisplatin or

carboplatin) plus gemcitabine. People whose disease did not progress following platinum-based chemotherapy could have avelumab maintenance treatment after a washout period. The company's updated submission used results from the latest data cut-off in August 2024, which are the results discussed from here on unless otherwise stated. The primary outcomes in EV-302 were progression-free survival and overall survival. The results from EV-302 showed that enfortumab vedotin with pembrolizumab offered statistically significantly better overall survival compared with platinum-based chemotherapy (hazard ratio [HR] 0.513, 95% confidence interval [CI] 0.428 to 0.614). Enfortumab vedotin with pembrolizumab also statistically significantly improved progression-free survival compared with platinum-based chemotherapy (HR 0.481, 95% CI, 0.407 to 0.570). The results suggest that the treatment was effective for both cisplatin-eligible and -ineligible subgroups but the trial was not statistically powered for this subgroup analysis. The committee concluded that enfortumab vedotin with pembrolizumab significantly improved overall and progression-free survival.

Impact of enfortumab vedotin with pembrolizumab

3.5 The patient expert explained to the committee that people with unresectable and metastatic urothelial cancer feel that enfortumab vedotin with pembrolizumab is a breakthrough treatment. They explained that the treatment offered the potential for better quality of life and is a considerable step forward compared with current standard care. The clinical experts noted that 30% of people in the trial experienced a complete response, which represents an important improvement in the treatment pathway. They explained that the trial results suggest that a proportion of people may be considered clinically cured. The clinical experts also noted that a proportion of people had durable response in the trial because they

were progression-free beyond 2 to 3 years, which is another considerable improvement. But the clinical experts explained that there are some side effects associated with using enfortumab vedotin that healthcare professionals would need to be aware of. These side effects included rash and peripheral neuropathy. They explained that a period of learning to identify and manage side effects is not unusual for healthcare professionals when offering new treatments entering the NHS. Similar concerns were raised by healthcare professionals when treatments such as atezolizumab and pembrolizumab (in other indications) were first introduced, but these treatments are now routinely used and well managed. The clinical experts explained that a combination of dose reduction and delay would be used to manage the side effects of enfortumab vedotin with pembrolizumab. They thought that the tolerability of enfortumab vedotin with pembrolizumab is at least as good as or better than platinum-based chemotherapy. The patient expert explained that people having treatment are aware that there could be some side effects. But they would prefer to have the option of having access to a treatment that can extend survival compared with standard care. The committee agreed that healthcare professionals and people who have enfortumab vedotin with pembrolizumab should be aware of the potential side effects. It concluded that the treatment represented considerable improvement in the treatment pathway for unresectable and metastatic urothelial cancer.

Economic model

Company's modelling approach

3.6 The company submitted a partitioned survival model with 3 mutually exclusive health states: pre-progression, post-progression and death. The company’s base case model used data from the intention-to-treat population from EV-302 (see section 3.4)

and assumed people start treatment at age 67.9 years. The model also assumed a lifetime horizon (maximum 30 years), a weekly cycle length and discounted costs and quality-adjusted life years (QALYs) at a rate of 3.5%. The EAG noted that the company had applied discounting from year 2 onwards. It preferred costs and QALYs to be discounted from the start of the model. The committee thought that the EAG's approach was acceptable. It concluded that the model was suitable for decision making.

Overall-survival extrapolation

3.7 The company estimated long-term overall survival in its base case by applying independently fitted models to survival data from EV-302 for both treatment arms. It did so because it thought that the proportional hazards assumption may not hold and that this would be clearer if the trial data was more mature. It also noted that there was a difference in the mechanisms of action between the treatment arms and that the proportional hazards assumption did not hold for progression-free survival (see section 3.8). The company selected the log-logistic model for both treatment arms, based on statistical fit and how well the survival estimates aligned with the clinical expert opinion it had received. The EAG agreed with the company and applied independently fitted log-logistic models for both treatment arms in its base case. The committee heard from the company that applying the generalised gamma model for the platinum-based chemotherapy with gemcitabine arm was also plausible. This is because the generalised gamma model provided overall-survival estimates within the range suggested by the clinical expert opinion received by the company. The clinical experts present during the committee meeting thought that the 10-year overall-survival estimate of 5% generated using the log-logistic model for the platinum-based chemotherapy with gemcitabine arm was likely to be optimistic. They noted that the

results of the generalised gamma model (3%) was more plausible. The EAG explained that the generalised gamma model was plausible but it is more methodologically appropriate to apply the same type of model for both treatment arms. It noted that using the generalised gamma model for both arms would increase the company's cost-effectiveness estimates. The committee was aware that the choice of overall-survival model impacts the severity weighting calculation (see section 3.14). It concluded that both the log-logistic and generalised gamma models were plausible and it would consider both in its decision making (see section 3.14).

Progression-free survival extrapolation

3.8 The company considered that the proportional hazards assumption was not met for progression-free survival. So, to extrapolate progression-free survival it fitted independent models for both treatment arms. It noted that hazards data from the clinical trial showed a pattern of initially increasing hazards that then decreased. It considered that standard parametric models did not appropriately capture the changing hazards and could overestimate observed hazards (people whose disease progress). So it preferred to use spline models, which are more flexible, for its base case. The company modelled transformed versions of its survival data, that is, log cumulative hazard and log cumulative odds. Specifically, it applied a spline model to hazard with 2 knots for the enfortumab vedotin with pembrolizumab arm and a spline model to odds with 3 knots for the platinum-based chemotherapy with gemcitabine arm. The EAG noted that with the company's approach, progression-free survival becomes higher than overall survival in the enfortumab vedotin with pembrolizumab arm at about 8 years. So, the company had to apply constraints in the model to adjust this. The EAG preferred parametric models that did not require similar constraints. The EAG noted that the log-logistic model also

followed a similar pattern of initially increasing hazards that then decreased. So, it preferred to apply log-logistic models for both treatment arms in its base case. The committee highlighted that the choice of progression-free survival models had a minor impact on the cost-effectiveness estimates. But it was concerned that the spline model resulted in progression-free survival being greater than overall survival in the enfortumab vedotin with pembrolizumab arm and that this was not plausible. So it concluded that applying the log-logistic models for both treatment arms was reasonable.

Time on pembrolizumab

3.9 In EV-302 people could have enfortumab until disease progression or unacceptable toxicity, whereas pembrolizumab could only be used for a maximum of 35 3-week treatment cycles. In its original base case the company noted that it had applied a stopping rule of 24 months (which it said approximated 35 treatment cycles) for pembrolizumab. In its revised base case, the company noted that because the time-on-treatment Kaplan–Meier curve for pembrolizumab was complete, it used this directly in its model. It explained that some people may have missed doses, which meant that their permitted maximum number of cycles would occur after month 24. The committee understood that the Kaplan–Meier curve for pembrolizumab was not properly applied in the company's revised model. This was because the 24-month stopping rule from the company's original base case was still functional. The committee was concerned that the Kaplan–Meier curve showed that some people were still having pembrolizumab treatment beyond 24 months. The NHS England Cancer Drugs Fund lead also noted that pembrolizumab had a stopping rule of 35 3-week treatment cycles and that this could be beyond 24 months. The committee concluded that the full Kaplan–Meier curve for pembrolizumab should be used and properly implemented in the

model to reflect the stopping rule for pembrolizumab of 35 3-week treatment cycles.

Time on avelumab maintenance

3.10 People in EV-302 could have 6 cycles of platinum-based chemotherapy with gemcitabine. Then, after a washout period, people whose disease did not progress could have avelumab maintenance treatment. In its base case model the company applied a 4.14-month (approximately 6 cycles) stopping rule for platinum-based chemotherapy with gemcitabine. It also applied a 60-month stopping rule for avelumab in line with TA788. To extrapolate long-term time on treatment for avelumab, it used a Weibull model. The EAG noted that the mean time on treatment estimated using the company's model, and the proportion of people on avelumab treatment at 1 year and 2 years, were higher than estimates from one of its clinical experts. The expert suggested that avelumab is normally used for less than 1 year (about 9 months) in the UK. The EAG preferred to apply the exponential model, which estimated the lowest mean time on treatment, but it acknowledged this was still higher than 12 months. The exact mean time-on-treatment data is considered confidential by the company and cannot be reported here. The clinical experts at the committee meeting explained that they could not confirm which of the extrapolation models (Weibull or exponential) provided the most plausible time-on-treatment estimates. They explained this was because avelumab maintenance had been recommended by NICE, and so available in routine practice, for less than 5 years (the maximum recommended treatment duration). The committee considered that it had not been presented with enough evidence to determine if either the company's or the EAG's models for time on avelumab reflected clinical practice. To reduce the uncertainty, it requested:

- further information on time on treatment for avelumab maintenance in the NHS, including mean time on treatment
- more justification for the choice of time-on-treatment model for avelumab maintenance.

Proportion of people having avelumab

3.11 The company assumed 30% of people who have platinum-based chemotherapy with gemcitabine would have avelumab maintenance treatment. It based this estimate on its clinical trial evidence. The EAG also used the same estimate for its base case. The clinical experts at the committee meeting estimated that around 60% to 70 % of people would be eligible to have avelumab maintenance treatment but that a proportion of these (about one-third) would choose not to have treatment. But they noted that the proportion of people having avelumab maintenance treatment varies across the NHS. The NHS England Cancer Drugs Fund lead noted that around 400 people in England who are eligible for immunotherapy currently have avelumab maintenance treatment. They agreed with the clinical experts that use of avelumab maintenance treatment was currently variable across the NHS. The clinical experts noted that the proportion of people who had avelumab maintenance in the clinical trial likely reflected its availability at the trial sites, not people's willingness to have it. They also explained that the overall-survival estimates would be lower if fewer people were to have avelumab than in the trial. The committee noted that the proportion of people having avelumab maintenance impacts both the clinical outcomes and the total costs in the comparator arm, and therefore the cost-effectiveness estimates. It concluded that the proportion of people on avelumab from the clinical trial (30%) was plausible and suitable for decision making but it would value further evidence relevant to the NHS, where available.

Treatment effect waning

3.12 The company's base case model did not include a treatment-effect-waning assumption. The company explained that enfortumab vedotin was given until disease progression or unacceptable toxicity, and that some people are expected to have long-term treatment. It also noted that because independently fitted overall-survival hazard models had been applied for both treatment arms, any treatment effect waning would already be incorporated. The EAG also did not apply a treatment-effect-waning assumption in its base case. It cited Taylor et al. (2024), which suggests that if independently fitted hazard models gradually converge, treatment effect waning might already be accounted for in the model without an explicit treatment-effect-waning assumption being included. The EAG explained that the overall-survival hazard models for enfortumab vedotin with pembrolizumab and platinum-based chemotherapy with gemcitabine gradually converge over the 30-year time horizon. The EAG also noted that although pembrolizumab is stopped after 2 years, it is not clear if this would lead to treatment effect waning. It presented a range of scenario analyses that apply a treatment-effect-waning assumption for pembrolizumab but noted that these scenarios may overestimate the impact of treatment effect waning. That is, the scenarios may be biased against enfortumab vedotin with pembrolizumab. This is because people have treatment as a combination. So the effect of pembrolizumab may wane but people would still be having enfortumab vedotin, which may still provide benefit. The clinical experts explained to the committee that both treatments work synergistically to produce long-term immunological change in the body. They explained that there is some evidence showing long-term effect with pembrolizumab in people who had stopped treatment because of toxicity after about 10 months of initial treatment. The committee recalled that a proportion of people in the

trial who had enfortumab vedotin with pembrolizumab remained progression-free beyond 24 months. It acknowledged the difficulty in plausibly separating a waning assumption for each treatment in a combination. It also took into account the EAG's and company's perspectives regarding inherent treatment waning in the model. It concluded that there is uncertainty in applying a treatment waning assumption for pembrolizumab in this case.

Utility values

Pre-progression utility values

3.13 The model used utility values from the enfortumab vedotin with pembrolizumab clinical trial (EV-302). The trial collected EQ-5D-5L data, which was mapped to EQ-5D-3L according to methods described by Hernández Alava et al. (2023) and Dolan (1997). The company used treatment-dependent utility values for the pre-progression health state in its base case. It explained that it did so because it had done analyses for a number of covariates including cisplatin eligibility, time since randomisation and treatment arm. This had shown that treatment arm was a statistically significant covariate. The EAG preferred to apply treatment-independent utility for enfortumab vedotin with pembrolizumab. It also disagreed with applying treatment-dependent utility for the entirety of the pre-progression health state for platinum-based chemotherapy with gemcitabine. It noted that both enfortumab vedotin with pembrolizumab and platinum-based chemotherapy with gemcitabine would cause side effects that impact quality of life. The EAG explained that people having platinum-based chemotherapy with gemcitabine would be expected to have lower utility values initially, while on treatment for about 4.5 months. But after treatment, the utility for this group would improve and be similar to people having enfortumab vedotin with pembrolizumab. The EAG also noted that the utility values for both treatment arms was not

statistically significantly different after 5 to 8 months. So, it applied treatment-dependent utility for the first 6 months and the treatment-independent value after that for the platinum-based chemotherapy with gemcitabine arm. The committee recalled the clinical and patient experts' view that the side effects of chemotherapy can have a large burden on people's quality of life (see section 3.5). In light of this, it asked the clinical experts why the difference between the treatment-dependent utility values was relatively small. The clinical experts explained that healthcare professionals have become better at managing the side effects of chemotherapy, such as myelosuppression, whereas enfortumab vedotin with pembrolizumab is relatively new. They also highlighted that the difference in reported quality of life could be related to how long people had treatment. People only had platinum-based chemotherapy with gemcitabine for about 4.5 months before switching to other treatments, whereas enfortumab vedotin with pembrolizumab was used for longer. The committee considered that sufficient justification would be needed for treatment-dependent utility values to be applied for the entire duration of the pre-progression health state. It concluded that the EAG's approach of applying treatment-dependent utility only for the first 6 months for the platinum-based chemotherapy with gemcitabine arm and then treatment-independent utility afterwards was reasonable. It also preferred to apply treatment-independent utility for enfortumab vedotin with pembrolizumab.

Severity modifier

3.14 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. For its base case, the company provided absolute (8.18) and

proportional (0.83) QALY shortfall estimates in line with NICE's health technology evaluations manual. The EAG also estimated absolute (7.94) and proportional (0.84) QALY shortfalls for its base case. Both base cases were below the threshold for a QALY weighting for severity (absolute shortfall of 12.0 or proportional shortall of 0.85) to be applied to the QALYs. The committee understood that the shortfall estimates were based on results from EV-302. The company explained that in EV-302 people in the platinum-based chemotherapy with gemcitabine arm could have subsequent treatments (such enfortumab vedotin monotherapy, erdafitinib and sacituzumab) that are not recommended in the NHS. This could have improved their overall survival beyond what would be expected in the NHS. So, this makes the severity modifier calculation uncertain. The company explained that it had not collected sufficient data about when people switched treatment in the clinical trial to allow it to remove the treatment effect of these non-standard treatments from the overall-survival curves. It also considered that using real world evidence such as the Systemic Anti-Cancer Therapy data to inform overall survival for people having platinum-based chemotherapy with gemcitabine would be flawed. It noted that NICE has only recently (in 2022) recommended avelumab maintenance treatment for people whose disease has not progressed after platinum-based chemotherapy. The company said that because of this, the current overall-survival data is not mature enough to include the full impact of avelumab availability in the NHS. The EAG agreed with the company. It noted that overall survival for people having platinum-based chemotherapy with gemcitabine is likely overestimated in the model, but the magnitude of the difference on the QALYs is uncertain. The company reported that it consulted an additional clinical expert. They agreed with the EAG's expert (see section 3.10) that avelumab maintenance is normally given for less than a year in the NHS. The company noted that avelumab was given for longer in the trial. So, the company argued, the overall survival in the trial was likely further overestimated for people having platinum-based chemotherapy with

gemcitabine. The clinical experts at the committee meeting noted that there are now treatment options such as atezolizumab and avelumab maintenance available in the NHS. These treatments make it plausible for people on standard care to have overall survival of around 16 months, as seen in EV-302. The company provided additional data showing that overall survival was lower for people who had subsequent treatments with taxanes (such as paclitaxel) compared with enfortumab vedotin monotherapy. But the data did not include the impact of other subsequent treatments that are relevant to the NHS, such as atezolizumab, sacituzumab and erdafitinib. Finally, the company explained that 5 of the 7 overall-survival extrapolation models explored for the platinum-based chemotherapy with gemcitabine arm estimated proportional QALY shortfall values between 0.85 and 0.87. It argued that this suggests a QALY weighting for severity should be applied. This included the generalised gamma model, which both the company and EAG noted were plausible (see section 3.7). The committee commended the company's transparency in selecting its base case overall-survival model regardless of the resulting severity weighting. But the committee understood that the company's model included a round up function. This meant that its proportional QALY shortfall estimate using the generalised gamma curve was slightly below the 0.85 threshold. But, proportional QALY shortfall values of 0.85 to 0.87 were estimated in the EAG's base case model for 5 of the 7 overall-survival models for the platinum-based chemotherapy with gemcitabine arm, regardless of rounding up. The committee questioned the interchangeability of the overall-survival models. It heard from the EAG that there are different hazard functions underpinning each model, which would need to be considered individually. But the EAG reiterated that the generalised gamma model was plausible (see section 3.7). The clinical experts also reiterated that that the 10-year overall-survival estimate predicted using the generalised gamma curve (3%) was plausible (see section 3.7). The committee recalled that a substantial burden of disease on people with urothelial cancer and their carers was

reported by the patient experts (see section 3.1). The committee noted that the point estimates of proportional QALY shortfall showed that a QALY weighting of either 1 or 1.2 may be plausible. This was because extrapolating overall survival with either log-logistic or generalised gamma models was reasonable (see section 3.7). To reduce the uncertainty, the committee requested additional evidence on the overall survival of people having standard care treatments that are generalisable to NHS practice. This should include the impact of avelumab maintenance treatment. But, where unavailable, additional evidence on overall survival for people having platinum-based chemotherapy without avelumab maintenance may also be considered to better understand the potential impact of modelling avelumab maintenance on the severity modifier.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.15 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per 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. But it will also take into account other aspects including uncaptured health benefits. The committee noted the unresolved uncertainty, including in:

- extrapolating time on avelumab maintenance treatment (see section 3.10)
- applying a treatment effect waning for pembrolizumab (see section 3.12)
- applying a severity weighting (see section 3.14).

The committee recalled the unmet need for effective treatments for unresectable or locally advanced urothelial cancer (see section 3.1). It also recalled the considerable impact of enfortumab vedotin with pembrolizumab on the treatment pathway (see section 3.5), including statistically significant improvements in both progression-free survival and overall survival (see section 3.4). And it noted that the clinical evidence was informed by a randomised trial that included the population and treatment comparison of interest, indicating less uncertainty than if the appraisal had been based on indirect evidence (see section 3.4). So, the committee concluded that an acceptable ICER would be around £30,000 per QALY gained.

Company and EAG cost-effectiveness estimates

3.16 The exact cost-effectiveness estimates cannot be reported here because there are confidential discounts for enfortumab vedotin, pembrolizumab, avelumab and atezolizumab. Both the company's and EAG's base case ICERs were above the range that NICE normally considers an acceptable use of NHS resources, even if a QALY weighting of 1.2 is applied.

Preferred assumptions

3.17 The committee's preferred assumptions were to:

- consider platinum-based chemotherapy with gemcitabine as the comparator (see section 3.3)
- apply discounting from the start of the model (see section 3.6)
- apply the log-logistic models for extrapolating progression-free survival in both treatment arms (see section 3.8)
- use the full Kaplan–Meier curve for modelling pembrolizumab time on treatment (see section 3.9)
- use the clinical trial data (30%) to estimate the proportion of people having avelumab maintenance treatment (see section 3.11).

- apply treatment-dependent pre-progression utilities for the first 6 months for platinum-based chemotherapy with gemcitabine and then treatment-independent utility afterwards (see section 3.13)

Additional analyses requested

3.18 With the committee's preferred assumptions, ICERs for scenarios with and without the QALY severity weighting applied remained above the range that NICE normally considers an acceptable use of NHS resources. The committee considered further data is needed to resolve the uncertainty in evidence required for decision making. It requested the following analyses:

- further information on time on treatment for avelumab maintenance in the NHS, including mean time on treatment and justification for the choice of time-on-treatment model for avelumab, as well as the proportion of people having avelumab maintenance in the NHS, where available (see sections 3.10 and 3.11)
- additional evidence on the overall survival of people having standard care treatments that are generalisable to NHS practice, including the impact of avelumab maintenance treatment (where unavailable, additional evidence on overall survival for people having platinum-based chemotherapy without avelumab maintenance treatment may also be considered [see section 3.14]).

Other factors

Equality

3.19 The committee considered equalities issues raised by consultees, commentators and the company. It was noted that the incidence of bladder cancer is higher for people from more socioeconomically deprived backgrounds. It was also noted that there may be unequal access to treatment across England and that people in rural areas may have difficulty accessing treatments. Consultees also noted that blader cancer

outcomes could differ based on people's age and sex. They noted that women are often diagnosed at a more advanced disease stage than men. Consultees also noted that there was an underrepresentation of black people in the EV-302 trial and that around a quarter of people were over 75. It was noted that the severity modifier may not fully capture the unmet need in older people. Age, sex and race are protected under the Equality Act 2010. The committee acknowledged these equality concerns but it noted that they could not be addressed in a technology appraisal.

Conclusion

Recommendation

3.20 The committee took into account:

- its preferred assumptions
- the range of most plausible cost-effectiveness estimates
- key uncertainties around modelling time on maintenance treatment and
- the appropriateness of applying a QALY weighting for severity.

It requested further evidence to resolve the uncertainty. It concluded that enfortumab vedotin with pembrolizumab did not currently represent a cost-effective use of NHS resources. So enfortumab vedotin with pembrolizumab should not be used for untreated unresectable or metastatic urothelial cancer.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C. Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a

conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

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

Raphael Egbu

Technical lead

Rachel Williams

Technical adviser

Leena Issa

Project manager

Lorna Dunning

Associate director

ISBN: [to be added at publication]