NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendation

1.1 Enfortumab vedotin with pembrolizumab can be used, within its marketing authorisation, as an option for untreated unresectable or metastatic urothelial cancer in adults when platinum-based chemotherapy is suitable.

They can only be used if the companies provide them according to the commercial arrangement (see section 2).

What this means in practice

Enfortumab vedotin with pembrolizumab must be funded in the NHS in England for the condition and population in the recommendation, if it is considered the most suitable treatment option. It must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that enfortumab vedotin with pembrolizumab provides benefits and value for money, so it can be used routinely across the NHS in this population.

Issue date: August 2025

Why the committee made this recommendation

For untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable, usual treatment is platinum-based chemotherapies (carboplatin or cisplatin, both with gemcitabine). This is followed by avelumab as maintenance treatment 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.

Despite some uncertainties in the economic evidence, when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, enfortumab vedotin with pembrolizumab can 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 August 2025). The price of

pembrolizumab is £2,630 per 100 mg in a 4-ml vial (excluding VAT; BNF online accessed August 2025).

2.4 Astellas has a commercial arrangement (patient access scheme) for enfortumab vedotin. This makes enfortumab vedotin available to the NHS with a discount. The size of the discount is commercial in confidence.

2.5 MSD has a commercial arrangement (commercial access agreement) for pembrolizumab. This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.6 Information on the Carbon Reduction Plan for UK carbon emissions for Astellas will be included here when guidance is published.

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

Impact on quality of life

3.1 Urothelial cancer affects cells that form the inner lining of the bladder, urethra, ureter or renal pelvis. Locally advanced urothelial cancer refers to cancer that has spread to the pelvic or nearby lymph nodes, or the walls of the pelvis or abdomen, or both. It is considered metastatic when the cancer has spread outside the pelvis. Unresectable cancer cannot be completely removed by surgery. The patient experts explained that living with metastatic urothelial cancer can be intensely challenging and emotionally exhausting for the person, and their family and carers, affecting all aspects of their lives, including their finances. The impact on daily life can be substantial, with people often struggling to work, travel or maintain physical activity. They described the stress of uncertainty when

realising that the aim of treatment is to extend life rather than to cure the condition. They also described feelings of fear, anxiety, hopelessness and sadness. These can have a profound impact on both the person's and their carer's psychological and mental wellbeing. The clinical experts highlighted the poor prognosis for people diagnosed with symptomatic urothelial cancer because survival can be only about 3 to 4 months. One clinical expert highlighted that survival outcomes are usually worse for women. The committee acknowledged that unresectable or metastatic urothelial cancer can have a negative impact on the person with the condition, and on their family and carers.

Clinical management

Treatment options

3.2 First-line treatment for unresectable or metastatic urothelial cancer includes platinum-based chemotherapy such as cisplatin with gemcitabine, carboplatin with gemcitabine, and methotrexate, vinblastine, doxorubicin and cisplatin (MVAC). The company highlighted that around 90% of people would be eligible for platinum-based chemotherapy. Eligibility for cisplatin is based on fitness according to the Galsky criteria (Galsky et al. 2011). People for whom cisplatin is unsuitable 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). There were differences in views about the proportion of people who would be eligible for cisplatin in the NHS. The EAG's clinical experts suggested that around two-thirds of people eligible for platinum-based chemotherapy would have cisplatin. This was compared with 50% estimated by the clinical experts at the committee meeting, with the remaining 50% having carboplatin. After a response to platinum-based chemotherapy, people may be offered avelumab maintenance treatment (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, 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 patient experts highlighted the limited first-line treatment options available for unresectable or metastatic urothelial cancer. They also highlighted that, for many people, chemotherapy may not be well tolerated because of side effects that also impact on quality of life. The clinical experts highlighted that, in about 12% of people on platinum-based chemotherapy, there is improvement in their condition. They reiterated that there is a high unmet need for effective treatments with durable control of urothelial cancer. The committee concluded that people with the condition and their families would welcome safe and effective alternative treatments to chemotherapy that offer a durable response and are well tolerated.

Positioning of enfortumab vedotin with pembrolizumab

3.3 For this evaluation, the company positioned enfortumab vedotin with pembrolizumab as a first-line treatment option for unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable. This is in line with the marketing authorisation. The company explained that the only relevant comparator is cisplatin with gemcitabine or carboplatin with gemcitabine, both followed by avelumab maintenance treatment if the cancer has not progressed (see section 3.2). It explained that only a small proportion of people eligible for platinum-based chemotherapy would have MVAC (less than 2%) or atezolizumab (about 3%). The EAG's clinical experts highlighted that healthcare professionals prefer to offer carboplatin rather than atezolizumab, and that MVAC may cause substantial side effects. The clinical experts at the committee meeting explained that, for the company's target population, its choice of comparators was in line with NHS practice. The committee agreed with

the company's positioning of enfortumab vedotin with pembrolizumab in line with its full marketing authorisation. It concluded that the relevant comparator is cisplatin with gemcitabine or carboplatin with gemcitabine, both followed by avelumab maintenance treatment if there is no disease progression.

Clinical effectiveness

Key clinical evidence for enfortumab vedotin with pembrolizumab

3.4 The key clinical-effectiveness evidence used in the company's submission and economic model came from EV-302. This was a phase 3, multinational, open-label, randomised trial that compared enfortumab vedotin plus pembrolizumab with cisplatin or carboplatin, both with gemcitabine (from here referred to as platinum-based chemotherapy). People whose condition had not progressed after platinum-based chemotherapy could have avelumab maintenance treatment after a washout period. The trial included 886 adults (18 years and over) with untreated unresectable locally advanced or metastatic urothelial cancer. Randomisation was stratified based on cisplatin eligibility, PD-L1 expression and the presence of liver metastases. The primary endpoints were progression-free survival (PFS) assessed by a blinded independent central review and overall survival (OS). The company presented results from the latest data cut in August 2024. The results from EV-302 showed that enfortumab vedotin with pembrolizumab offered statistically significantly better PFS (hazard ratio [HR] 0.481, 95% confidence interval [CI] 0.407 to 0.570) and OS (HR 0.513, 95% CI 0.428 to 0.614) compared with platinum-based chemotherapy. Subgroup analyses based on cisplatin eligibility showed similar results, but the trial was not statistically powered for this analysis. The committee concluded that enfortumab vedotin with pembrolizumab statistically significantly improved PFS and OS in people with untreated unresectable locally advanced or metastatic urothelial cancer compared with platinum-based chemotherapy.

Impact of enfortumab vedotin with pembrolizumab

3.5 The patient and clinical experts suggested that enfortumab vedotin with pembrolizumab represented a breakthrough treatment and a 'step change' in the management of urothelial cancer. This was because about 30% of people on enfortumab vedotin with pembrolizumab in EV-302 had a complete response. The clinical experts explained that some people may be considered clinically cured because they showed a durable response and were progression-free beyond 2 to 3 years. The patient and clinical experts acknowledged that there are some potential side effects with enfortumab vedotin, including skin reactions and peripheral neuropathy. The patient experts explained that these side effects may be easier to tolerate than the side effects from chemotherapy. The clinical experts explained that identifying and learning to manage side effects is not unusual for healthcare professionals when offering new treatments entering the NHS. They highlighted that similar concerns were raised by healthcare professionals when treatments such as atezolizumab and pembrolizumab (in other indications) were first introduced. But they added that these treatments are now routinely used and well managed. The committee thought that the side effects of enfortumab vedotin with pembrolizumab should be fully captured in the economic analysis. But it acknowledged that it is not unusual for healthcare professionals to learn to better manage these side effects in clinical practice when their use increases. The committee acknowledged that, in addition to the observed improvement in PFS and OS (see section 3.4), enfortumab vedotin with pembrolizumab showed the potential to have a durable response. It concluded that enfortumab vedotin with pembrolizumab represented a considerable improvement in the treatment pathway for unresectable or metastatic urothelial cancer.

Economic model

Company's modelling approach

3.6 To compare enfortumab vedotin plus pembrolizumab with platinum-based chemotherapy in untreated unresectable or metastatic urothelial cancer, the company used a partitioned survival model. This had 3 health states (pre-progression, post-progression and death), a 1-week cycle with half-cycle correction and a 30-year time horizon (starting age 67.9 years). In response to the draft guidance consultation, the company applied discounted costs and quality-adjusted life years (QALYs) at a rate of 3.5% from the start of year 1. The committee concluded that the company's model was suitable for decision making.

OS extrapolation

3.7 The company extrapolated the long-term effects of enfortumab vedotin with pembrolizumab and platinum-based chemotherapy on OS in people with unresectable or metastatic urothelial cancer. To do this, it fitted independent models to survival data from EV-302 for both treatment arms. The company selected the log-logistic model for both treatment arms, based on statistical fit and clinical expert opinion on the plausibility of survival estimates. It highlighted that applying the generalised gamma model for the platinum-based chemotherapy arm also provided plausible OS estimates. The clinical experts at the committee meeting highlighted that the 10-year OS estimate of 5%, generated using the log-logistic model for the platinum-based chemotherapy arm, was likely to be optimistic. They thought that the estimate from the generalised gamma model (3%) was more plausible. The EAG agreed with the company's selected distributions for its base case and also applied independently fitted log-logistic models for both treatment arms in its base case. The committee was aware that the choice of OS model for the platinum-based chemotherapy arm affected the severity weighting calculation (see section 3.15). It preferred to use the log-logistic model for both treatment arms in the base case. But it concluded that it would also consider the generalised gamma model for the platinum-based chemotherapy arm in its decision making (see section 3.15).

PFS extrapolation

3.8 The company extrapolated the long-term effects of enfortumab vedotin with pembrolizumab and platinum-based chemotherapy on PFS in people with unresectable or metastatic urothelial cancer. To do this, it fitted independent models to survival data from EV-302 for both treatment arms. It noted that the hazards data from EV-302 showed a pattern of initially increasing hazards that then decreased for both arms. So, it preferred to use spline models, which are more flexible, for its base case. The EAG explained that the company applied constraints to its spline model for enfortumab vedotin with pembrolizumab because PFS was estimated to be higher than OS at about 8 years. The EAG preferred to use standard parametric models that did not need such constraints. It noted that the log-logistic model also followed a similar pattern of initially increasing hazards that then decreased. So, it preferred to apply the log-logistic model for both treatment arms in its base case. The committee noted that the choice of PFS models had a minor impact on the cost-effectiveness estimates. But it was concerned that the spline model for the enfortumab vedotin with pembrolizumab arm provided implausible results. In response to the draft guidance consultation, the company applied the log-logistic model to both treatment arms in its revised base case. The committee concluded that the company's revised base case, which applied the log-logistic models to extrapolate PFS for both treatment arms, was acceptable for decision making.

Time on pembrolizumab

3.9 In EV-302, people could have enfortumab vedotin until disease progression or unacceptable toxicity. But, pembrolizumab could only be used for a maximum of 35 3-week treatment cycles. The company applied the time-on-treatment Kaplan–Meier curve for pembrolizumab from EV-302 directly in its model. The NHS England Cancer Drugs Fund lead (from here, Cancer Drugs Fund lead) explained that although pembrolizumab should be stopped after 35 3-week treatment cycles, this

could occur over more than 24 months. At the first committee meeting, the committee noted that the Kaplan–Meier curve for pembrolizumab had not been properly applied in the company's model. This was because time on pembrolizumab was restricted to 24 months. It thought that the full Kaplan–Meier curve for pembrolizumab from EV-302 should have been used and properly implemented in the model to reflect the 35 3-week treatment cycles stopping rule. In response to the draft guidance consultation, the company corrected its modelling of time on pembrolizumab. This was to reflect the time on treatment seen in EV-302, in which people stopped after 35 completed cycles, which could happen after 24 months. The EAG agreed with the company's revised approach to modelling time on pembrolizumab. But the manufacturer of pembrolizumab, in its response to the draft guidance consultation, suggested that excluding the 24-month stopping rule in the model could result in delayed doses being double counted. The committee noted these concerns. But it was satisfied that the company's revised modelling reflected pembrolizumab time on treatment seen in EV-302. It concluded that the company's revised modelling of time on pembrolizumab was acceptable for decision making.

Proportion of people having avelumab

3.10 Based on EV-302 data, the company assumed in its base case that 30% of people on platinum-based chemotherapy would have avelumab maintenance treatment. The EAG also used this estimate in its base case. At the first committee meeting, the clinical experts suggested that around 60% to 70% of people would be eligible to have avelumab, but that about 33% would choose not to have it. The clinical experts and Cancer Drugs Fund lead highlighted that there is variation across the NHS on the proportion of people having avelumab. The clinical experts explained that the OS estimates for people on platinum-based chemotherapy would likely be lower in practice if fewer people have avelumab in the NHS than the 30% seen in EV-302. The committee noted that the proportion of people having avelumab affected the clinical outcomes and the total costs

in the comparator arm. So, it also affected the cost-effectiveness estimates. The committee thought that the proportion of people on avelumab from EV-302 (30%) was plausible and suitable for decision making but it would value further evidence relevant to the NHS. In response to the draft guidance consultation, the company and NICE independently did analyses using real-world data from the National Disease Registration Service (NDRS) Systemic Anti-Cancer Therapy (SACT) dataset. The SACT data included adults in the NHS diagnosed with metastatic urothelial cancer between 2020 and 2022. NICE shared its analyses with the company, who also applied the data in its model and economic analyses. The EAG highlighted that the selection criteria applied to the SACT dataset by NICE and the company were generally similar. But the company included stage 4 (metastatic) disease only and multiple tumours (bladder, renal pelvis, ureter) at diagnosis. The company also placed time restrictions on the start of avelumab maintenance treatment to avoid off-label use, and on the start of platinum-based chemotherapy. NICE's cohorts comprised 793 people in total (median age 68 years and 71% male):

- Cohort 1: people who had platinum-based chemotherapy only and no subsequent avelumab maintenance treatment (n=642).
- Cohort 2: people who had platinum-based chemotherapy and subsequent avelumab maintenance treatment (n=151).

The company's cohorts comprised 771 people in total (median age 71 years and 67% male):

- Cohort A: people who had platinum-based chemotherapy before the publication of TA788 from 1 April 2021 to 30 April 2022 (n=431).
- Cohort B: people who had platinum-based chemotherapy after the publication of TA788 from 2 May 2022 to 31 July 2024 (n=340).

The committee noted that TA788 was published on 11 May 2022. The EAG highlighted that NICE's and the company's SACT cohorts were

similar in age and sex. But it highlighted several differences between the company's SACT cohorts and EV-302. People in EV-302 were younger (median age 69 years) and fitter (2.5% with an Eastern Cooperative Oncology Group Performance Status of 2 compared with 9.0% to 11.8% in the company SACT cohorts). EV-302 also had fewer people from a White background (65.3% compared with 83.2% to 87.0% in the company SACT cohorts). The EAG explained that the company had done naive indirect comparisons of the SACT dataset with EV-302 because it had not adjusted for these differences in baseline characteristics. The Cancer Drugs Fund lead highlighted that, according to Blueteq data, between May 2022 and July 2024, 942 people started avelumab maintenance treatment compared with 340 people in the company's SACT cohort B.

The company explained that it did not have direct access to the SACT data and could not explore details of diagnosis and disease progression. It explained that the difference was likely because the company used metastatic stage rather than disease progression status to identify people in cohort B. This was because progression was not defined in the NDRS. In the NICE SACT analysis, 19% of people had avelumab (151 out of 793 people). The company's SACT analysis had a similar proportion of 20% of people who had avelumab (68 out of 340 people). The Cancer Drugs Fund lead highlighted that, based on Blueteq data, about 425 of the 1,400 people starting platinum-based chemotherapy in the NHS begin with avelumab maintenance treatment. This is about 30%, which aligns with estimates from EV-302. The committee acknowledged the company's and NICE's analyses of real-world data to provide evidence of avelumab use in the NHS. But it noted the limitations of the SACT data analyses. It concluded that the proportion of people on avelumab from EV-302 (30%) was plausible, as confirmed by Blueteq data, and should be used in the base case.

Time-on-avelumab maintenance treatment

3.11 To model time-on-avelumab maintenance treatment in the platinum-based chemotherapy arm, the company extrapolated time on avelumab from EV-302 using standard parametric distributions. It also applied a 60-month stopping rule for avelumab in line with TA788. Based on statistical fit and comparison of extrapolations with estimates from other sources, such as TA788, the company preferred the Weibull distribution with 16.9 months estimated mean time on avelumab. The EAG's clinical expert suggested that avelumab is usually used for less than 1 year (about 9 months) in the UK. So, the EAG preferred to apply the exponential model, which estimated the lowest mean time on avelumab to be 13.9 months. The clinical experts at the first committee meeting explained that they could not suggest which of the models (Weibull or exponential) provided the most plausible time on avelumab estimates. This was because there is limited clinical experience and less than the maximum recommended 5-year treatment duration has elapsed since TA788 was published in 2022. The committee thought that it had not been presented with enough evidence to determine whether the company's or the EAG's distributions for time on avelumab best reflected NHS clinical practice.

In response to the draft guidance consultation, the company used generalised gamma distributions for the SACT data (see section 3.9). This gave mean times on avelumab of 8.2 months for cohort B and 14.9 months for cohort 2. NICE independently did analyses using the area under the observed curve without extrapolation. It estimated a mean time of 11.1 months on avelumab for cohort 2. The EAG agreed with the company's preferred generalised gamma models. But it explained that, using SACT data to model time-on-avelumab maintenance treatment, affected the total costs but not the number of QALYs gained in the platinum-based chemotherapy arm. It agreed with the company that it was not appropriate to adjust time on avelumab for costs only. So, it preferred to use the estimated time-on-avelumab maintenance treatment from EV-302. The company highlighted that data from EV-302 and SACT show

that people may stay on avelumab maintenance treatment for extended periods of time. There are also observed plateaus, suggesting that hazards for stopping treatment reduce over time. So, it thought that the exponential distribution was not appropriate and preferred the Weibull distribution. The EAG acknowledged that the hazards for the exponential curve do not predict an avelumab treatment stopping rate that reduces over time. But it maintained its position that the Weibull overestimates the time on avelumab. So, it preferred to use the exponential distribution that estimates the shortest time-on-avelumab maintenance treatment in its base case.

The committee recalled the limitations of the SACT datasets (see section 3.9). It thought that the true time-on-avelumab maintenance treatment was uncertain because of its limited use in the NHS since TA788 was published. It noted that the Weibull distribution best fitted the trends seen in avelumab use in EV-302 and the SACT data. So, it concluded that the Weibull distribution using EV-302 extrapolations for time on avelumab should be used in the base case.

Treatment effect waning

3.12 In its base case, the company did not model a treatment-effect-waning assumption. It assumed that treatment-effect waning had been incorporated into the OS extrapolations for enfortumab vedotin with pembrolizumab and platinum-based chemotherapy arms (see section 3.7). The EAG agreed with the company and highlighted that the OS extrapolations for both arms gradually converged over the 30-year time horizon. It cited Taylor et al. (2024), which suggested that, if independently fitted hazard models gradually converge, treatment-effect waning might already be accounted for in the model. The EAG highlighted that, although pembrolizumab was stopped after 2 years, it was unclear whether this would lead to treatment-effect waning. It presented a range of scenario analyses that applied a treatment-effect-waning assumption for pembrolizumab. But it explained that these scenarios may have

overestimated the impact of the treatment-effect waning for enfortumab vedotin with pembrolizumab. This was because people would still be having enfortumab vedotin, which may still provide benefit. The clinical experts explained that both treatments work synergistically to produce long-term immunological change in the body. They explained that there is some evidence showing a long-term effect with pembrolizumab in people who stop taking it because of toxicity after about 10 months of initial treatment.

In response to the draft guidance consultation, the company maintained its position that it was not appropriate to apply additional treatment-effect waning in the model. It cited 5-year follow-up results from EV-103. This was a multicohort, non-randomised, open-label, phase 1b and 2 trial of first-line enfortumab vedotin with pembrolizumab in people with locally advanced or metastatic urothelial cancer. It explained that EV-103 showed a sustained plateau in PFS and OS beyond 3 years. The committee recalled that a proportion of people in EV-302 who had enfortumab vedotin with pembrolizumab remained progression-free beyond 24 months (see section 3.5). 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 about inherent treatment-effect waning in the model. It concluded that there was uncertainty around applying a treatment-effect-waning assumption for pembrolizumab in this case.

Utility values

Pre-progression utility values

3.13 In its model, the company used utility values derived from EQ-5D-5L data from EV-302 mapped onto EQ-5D-3L according to the methods described by Hernández Alava et al. (2023) and Dolan (1997). In is base case, the company assumed that the utility values for the pre-progression health state were treatment dependent because covariate analyses had shown

that 'treatment arm' was a statistically significant variable. For the platinum-based chemotherapy arm, the EAG preferred to apply treatment-dependent pre-progression utility only for the first 6 months to reflect the lower quality of life while on treatment. This would be followed by a treatment-independent utility to reflect that quality of life would improve and be similar to people having enfortumab vedotin with pembrolizumab. The EAG highlighted that the utility values for both treatment arms were not statistically significantly different after 5 to 8 months. So, it preferred to apply treatment-independent utility for enfortumab vedotin with pembrolizumab. The committee thought that sufficient justification would be needed for treatment-dependent utility values to be applied in the model. In response to the draft guidance consultation, the company accepted the EAG's approach to modelling pre-progression utilities for both treatment arms in its revised base case. The committee concluded that the company's revised base case was acceptable for decision making. This included the EAG's approach of applying treatment-independent utility for enfortumab vedotin with pembrolizumab, and only applying treatment-dependent utility for the first 6 months for the platinum-based chemotherapy arm.

Costs

Administration costs

3.14 In its base case, the company used an administration cost of £392 for pembrolizumab (SB17Z with service code DCRDN). In response to the draft guidance consultation, the manufacturer of pembrolizumab highlighted that a lower administration cost (£208; SB12Z with service code OP) has been accepted in previous appraisals, such as NICE's technology appraisal guidance on:

- pembrolizumab for relapsed or refractory classical Hodgkin lymphoma
- pembrolizumab for gastric or gastro-oesophageal junction adenocarcinoma

- pembrolizumab for resectable non-small-cell lung cancer.

The Cancer Drugs Fund lead advised that the correct code to use is SB13Z (deliver more complex parenteral chemotherapy at first attendance) for the first cycle (2023/24 price £343). This should be followed by SB15Z (deliver subsequent elements of a chemotherapy cycle) in subsequent cycles (2023/24 price £343). The committee noted that, for platinum-based chemotherapy, the company had used a higher cost code for the first cycle in its base case. Instead of SB13Z, which was used in the intervention arm, it used SB14Z (deliver complex chemotherapy, including prolonged treatment by infusion, at first attendance) at a cost of £485 (2023 to 2024: price £515). The committee thought that the same cost code should have been used for both arms. For avelumab maintenance treatment, the company had applied SB17Z (chemotherapy for regimens not on the national list) at a cost of £392. The committee noted that the manufacturer of avelumab in TA788 had applied SB12Z (deliver simple parenteral chemotherapy at first attendance) in its submission. It thought that the administration cost for avelumab maintenance treatment should have also used the code SB12Z (2023/24 price £172). It concluded that, for enfortumab vedotin with pembrolizumab and platinum-based chemotherapy, the administration codes of SB13Z and SB15Z should be used.

Severity modifier

3.15 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). It 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. These shortfall

estimates were based on log-logistic extrapolated OS data from EV-302 (see section 3.7). The company highlighted that 5 of the 7 OS extrapolation models explored for the platinum-based chemotherapy arm (including the generalised gamma; see section 3.7) estimated proportional QALY shortfall values of between 0.85 and 0.87. The company explained that the OS estimates in people on platinum-based chemotherapy in EV-302 may have been overestimated because people could have subsequent treatments not used in the NHS. Also, the full impact of avelumab availability on OS was uncertain (see section 3.10 and section 3.11). The EAG agreed that the OS for people having platinum-based chemotherapy was likely overestimated in the model, but the magnitude of the difference on the QALYs was uncertain. The committee questioned whether the OS models were interchangeable. The EAG explained that there were different hazard functions underpinning each model, which would need to be considered individually. To reduce the uncertainty, the committee requested additional evidence on the OS of people having standard care treatments that are generalisable to NHS practice. In response to the draft guidance consultation, the company used SACT data (see section 3.10) and estimated proportional QALY shortfalls for people having standard care in the NHS of:

- 0.88 using a combination of cohorts A and B
- 0.90 using cohort 1
- 0.87 using cohort 2.

The committee recalled the patient experts' testimony of the substantial burden the condition could have on people with urothelial cancer and their carers (see section 3.1). It recalled the clinical expert's testimony that survival outcomes are worse for women. It noted that the proportion of women in the SACT datasets ranged from 29% to 33% (see section 3.10). This was higher than the 24% in the platinum-based chemotherapy arm of EV-302. This further supported that OS estimates in people on platinum-based chemotherapy in EV-302 may have been

overestimated. The committee concluded that, on balance, the severity weight of 1.2 should apply to the QALYs.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.16 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 in applying a treatment-effect waning assumption for pembrolizumab (see section 3.12). The committee recalled the impact of unresectable or metastatic urothelial cancer on people with the condition and their carers, and the high unmet need for effective treatments (see section 3.1 and section 3.2). 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 PFS and OS (see section 3.4). It acknowledged that the clinical evidence was informed by a randomised trial that included the target population and directly compared enfortumab vedotin plus pembrolizumab with standard treatment available in the NHS. This indicated less uncertainty than if the evaluation 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.

Committee's preferred assumptions

3.17 The committee's preferred assumptions were to:

- consider platinum-based chemotherapy 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 OS for both enfortumab vedotin with pembrolizumab and platinum-based chemotherapy arms, but also consider the generalised gamma model for the platinum-based chemotherapy arm (see section 3.7)
- apply the log-logistic models for extrapolating PFS 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 30% to estimate the proportion of people having avelumab maintenance treatment (see section 3.10)
- apply the Weibull distribution using EV-302 extrapolation for time-on-avelumab maintenance treatment (see section 3.11)
- apply treatment-dependent pre-progression utilities for the first 6 months for platinum-based chemotherapy and then treatment-independent utilities afterwards (see section 3.13)
- apply the administration costs for enfortumab vedotin with pembrolizumab of £343 for initial (SB13Z) and subsequent (SB15Z) administrations (see section 3.14)
- apply the administration costs for platinum-based chemotherapy (SB13Z for the first cycle and SB15Z for subsequent administrations) and SB12Z for avelumab maintenance (see section 3.14)
- apply a severity weighting of 1.2 (see section 3.15).

The committee concluded that the most plausible ICER using its preferred assumptions was within the range normally considered a cost-effective use of NHS resources.

Company and EAG cost-effectiveness estimates

3.18 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 within the range that NICE normally considers an acceptable use of NHS resources when a QALY weighting of 1.2 is applied.

Other factors

Equality

3.19 The committee considered potential equalities issues raised by consultees, commentators and the company, such as:

- the incidence of bladder cancer is higher for people from more socioeconomically deprived backgrounds
- there may be unequal access to treatment across England, and people in rural areas may have difficulty accessing treatments
- bladder cancer outcomes could differ based on people's age and sex (for example, women are often diagnosed at a more advanced disease stage than men)
- there was an under-representation of people from Black backgrounds and other ethnic minorities in EV-302, and about 25% of people were over 75
- 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 noted that its recommendation applies to all people within the marketing authorisation and does not restrict access to treatment for some people over others. The committee considered whether any of the methods or processes used in the evaluation would disadvantage particular populations. It recalled its conclusion that, based on the current evidence and analyses, a severity weight of 1.2 applied to the QALYs was likely to be appropriate (see section 3.15). This included the consideration that survival outcomes are worse for women, and that the proportion of women in the SACT datasets was higher than the proportion in the platinum-based chemotherapy arm of EV-302.

Conclusion

Recommendation

3.20 The most likely cost-effectiveness estimates were within the range considered to be a cost-effective use of NHS resources. So, enfortumab vedotin with pembrolizumab can be used for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable.

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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

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 untreated unresectable or metastatic urothelial cancer and the healthcare professional responsible for their care thinks that enfortumab vedotin with pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

Sharlene Ting and Raphael Egbu
Technical leads

Rachel Williams
Technical adviser

Leena Issa
Project manager

Lorna Dunning
Associate director

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