National Institute for Health and Care Excellence

Health Technology Evaluation

Enfortumab vedotin with pembrolizumab for first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy ID6332

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Astellas Pharma Ltd	Yes, this is an appropriate topic to refer to NICE for Single Technology Appraisal.	Thank you for your comments. No action needed.
	Merck, Sharp & Dohme	The proposed evaluation route is appropriate.	Thank you for your comments. No action needed.
	British Uro-Oncology Group	The British Uro-Oncology Group believes that evaluating pembrolizumab with enfortumab vedotin is not only appropriate but essential due to the significant unmet needs in the treatment of urothelial cancer. We recommend that NICE consider the characteristics and potential impact of this technology on patients with urothelial cancer to determine the most suitable evaluation route, ensuring that the chosen path facilitates a timely assessment.	Thank you for your comments. The committee will consider all evidence available to them during the appraisal.

Section	Stakeholder	Comments [sic]	Action
			No action needed.
	ABC UK	This topic is highly appropriate for evaluation for a technology appraisal. Treatment options for locally advanced or metastatic bladder cancer are very limited; a large percentage of this patient group are not eligible for current treatment options due to other conditions or comorbidities; other existing treatments can show high levels of lack of tolerability and adversely affect quality of life. It is of particular appropriateness given the trial results for Pembrolizumab plus enfortumab vedotin therapy which demonstrate improved survival versus the current most common treatment available for this patient group.	Thank you for your comments. The committee will consider all evidence available to them during the appraisal. No action needed.
	Fight Bladder Cancer	We emphasise the necessity of evaluating pembrolizumab with enfortumab vedotin for urothelial cancer due to significant unmet needs. We urge NICE to assess its impact and characteristics carefully to select the most appropriate evaluation route for timely assessment.	Thank you for your comments. No action needed.
Wording	Astellas Pharma Ltd	Yes, the remit broadly reflects the clinical and cost effectiveness of pembrolizumab with enfortumab vedotin for untreated metastatic urothelial cancer	Thank you for your comments. No action needed.
	Merck, Sharp & Dohme	The remit is appropriate	Thank you for your comments. No action needed.

Section	Stakeholder	Comments [sic]	Action
	ABC UK	**There is a variance in how the target patient group for this treatment is referred to throughout, including in the title of this remit; is it ?** Pembrolizumab with enfortumab vedotin for **untreated metastatic** urothelial cancer **or** Pembrolizumab with enfortumab vedotin for **locally advanced or metastatic** urothelial cancer **See also comments** in Background regarding issues relating to currently available treatment options.	Thank you for your comments. The population has been updated throughout the scope.
	Fight Bladder Cancer	Yes	Thank you for your comments. No action needed.
Timing issues	Astellas Pharma Ltd	There is a high unmet need for patients with previously untreated La/mUC. Enfortumab vedotin in combination with pembrolizumab (EV+p) EV+P significantly improved outcomes in patients with previously untreated la/mUC, nearly doubling the median PFS and OS compared to platinum-based chemotherapy [T.B. Powles, B. Perez Valderrama, S. Gupta et al. Annals of Oncology (2023) 34 (suppl_2): S1254-S1335. 10.1016/annonc/annonc1358]. These results support EV+P as a new SOC for 1L la/mUC and urgency of this appraisal.	Thank you for your comments. No action needed.
	Merck, Sharp & Dohme	The provisional scheduling for this topic is appropriate.	Thank you for your comments. No action needed.

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	British Uro-Oncology Group	Urgent to allow access for patients with poor outcomes	Thank you for your comments. No action needed.
	ABC UK	The availability of effective treatment options for this patient group is of pressing need, thus has an urgency for the NHS.	Thank you for your comments. No action needed.
	Fight Bladder Cancer	The urgency cannot be overstated, highlighting an acute need for prompt and thorough assessment to ensure the healthcare system can rapidly integrate and utilise essential medical advancements for bladder cancer patient care.	Thank you for your comments. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Astellas Pharma Ltd	Astellas Pharma Ltd considers the background to be accurate and complete, However, the section on relevant NICE TAs would need to be updated. The only TAs relating to untreated (1L) patients are: Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable (TA739) - 27 October 2021 Pembrolizumab for untreated PD-L1-positive, locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (terminated appraisal) (TA674) TA 272 (vinfunine) is not relevant as it relates to previously platinum treated La/mUC patients.	Thank you for your comments. The related NICE recommendations have been updated to include all relevant published technology appraisals related to this topic.

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	Merck, Sharp & Dohme	MSD suggest expanding the background information by adding avelumab maintenance treatment option for patients who have not progressed after platinum-based chemotherapy (includes both cisplatin-eligible and cisplatin-ineligible patients) as per TA788 recommendation.	Thank you for your comments. The scope is intended to summarise the background information for untreated metastatic urothelial cancer briefly. No action needed.
	ABC UK	We would question the background information given regarding the incidence of bladder cancer, particularly when citing Cancer Research UK statistics. These statistics do not include the early stage bladder cancer as defined in histology by Ta/CIS which gives an annual total of over 20,300 pa (total from cancer data codes C67, D090 and D414, rather than just C67). There is no reference to the high level of recurrence in bladder cancer, with accompanying risk of progression. There is no reference to the quality of life for patients with existing recommended common treatment (chemotherapy), or the percentage of treatment-related adverse effects with chemotherapy and the impact on quality of life for this patient group as well as survival. Needs to be an expansion of text relating to current treatments available for this patient group, and the issues – see below:	Thank you for your comment. The scope is intended to summarise the background information for untreated metastatic urothelial cancer briefly. The number of new diagnosed bladder cancer diagnosed in England has been updated.

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		• A significant percentage of patients with locally advanced or metastatic urothelial cancer (c50%) are ineligible for first-line cisplatin-based chemotherapy because of other comorbidities or impaired renal function etc. • Gemcitabine plus Carboplatin can be used to treat cisplatin-ineligible patients, but has shown lower activity and poor tolerability for the patient. • In addition, of the cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who receive first-line treatment, a significant percentage do not receive a second-line treatment. • This underlines the need for, and gives a greater urgency to, effective and tolerable first-line therapies. • Other treatment options are limited, or are not available to this patient group via the NHS. The **NICE Guideline NG2** is referenced, we feel obliged to reference, and also feel this is a matter which should be considered within any scoping or review of available evidence regarding the treatment of bladder cancer, that this Guideline was published in 2015 (9 years ago), has had no substantial update since then and is thus out of date in many key areas particularly regarding treatments or treatment methods and the care pathway as recommended within this Guideline. This necessary update of the Guideline is currently being advocated for strongly by patient organisations and clinical experts with NICE and an evidence surveillance review is currently in progress.	

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	Fight Bladder Cancer	The scope says "In 2020, 8,752 new bladder cancers were diagnosed in England". It should say "In 2020, 16,547 new bladder cancers were diagnosed in England" (https://www.cancerdata.nhs.uk/getdataout/bladder)	Thank you for your comment. The number of new bladder cancer diagnosed in England has been updated.
Population	Astellas Pharma Ltd	The population is defined appropriately	Thank you for your comments. No action needed.
	Merck, Sharp & Dohme	The population is defined appropriately.	Thank you for your comments. No action needed.
	British Uro-Oncology Group	In 2020, 8,752 new bladder cancers were diagnosed in England". It should be "In 2020, 16,547 new bladder cancers were diagnosed in England" Reference: https://www.cancerdata.nhs.uk/getdataout/bladder	Thank you for your comment. The number of new bladder cancer diagnosed in England has been updated
	ABC UK	Yes, for this appraisal. NOTE: see earlier comment about variance in how the target patient group is referred to throughout this remit ie: is it untreated metastatic (as in the title), or untreated locally advanced and metastatic as used in some places within the text?	Thank you for your comments. The population has been updated throughout the scope.

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Subgroups	Astellas Pharma Ltd	There are no groups that should be considered separately. EV+P significantly improved outcomes in patients with previously untreated la/mUC regardless of characteristics such as PD-1 expression or cisplatin eligibility in the EV-302 phase III study.	Thank you for your comments. Based on consultation comments received NICE agrees that people for whom cisplatin containing chemotherapy is unsuitable and people whose tumours express PD-L1 are both potentially relevant subgroups for this appraisal. These have been included in the final scope.
	Merck, Sharp & Dohme	Subgroup data based on PD-L1 status is expected to be available. Cisplatin eligible and ineligible subgroups are considered to be relevant for this appraisal.	Thank you for your comments. These subgroups have been included in the final scope.
	British Uro-Oncology Group	Patients not suitable for cisplatin based chemotherapy are usually treated with carboplatin based combinations in England. The use of immunotherapy (atezolizumab) is reserved for patients who have PDL-1 positive tumours and usually chemotherapy is used in preference unless the patient is unsuitable for both cisplatin and carboplatin.	Thank you for your comments. NICE considers These subgroups have been included in the final scope.

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	Fight Bladder Cancer	In the UK, patients unsuitable for cisplatin-based chemotherapy typically receive carboplatin-based combinations, with immunotherapy (atezolizumab) designated for those with PD-L1 positive tumours, preferring chemotherapy unless the patient is unsuitable for both cisplatin and carboplatin. Subgroup analyses by PD-L1 expression in the EV-302 trial indicate that pembrolizumab with enfortumab vedotin benefits extend across various levels of PD-L1 expression, advocating for its use in a wide patient demographic, irrespective of PD-L1 status. This efficacy of enfortumab vedotin and pembrolizumab across all subgroups, regardless of PD-L1 expression, as presented at ASCO GU 2024, suggests that the choice of enfortumab vedotin + pembrolizumab in the treatment regimen for cisplatin-ineligible patients should not be confined by PD-L1 expression, with potential comparators being either carboplatin-based chemotherapy (followed by avelumab immunotherapy maintenance therapy in chemotherapy responders) or atezolizumab.	Thank you for your comments. These subgroups have been included in the final scope.
Comparators	Astellas Pharma Ltd	Platinum-based therapy, i.e., cis-platin or carboplatin with gemcitabine, is the most relevant comparator in clinical practice in England. According to real world data from 2021 analysed by Astellas, MVAC is rarely used in UK clinical practice according with only 2% of treated 1L patients receiving MVAC in UK centres. Astellas therefore do not believe that MVAC should be considered a relevant comparator. Best supportive care is not a relevant comparator for enfortumab vedotin with pembrolizumab as patients receiving this option would be eligible to receive platinum-based (cisplatin or carboplatin) therapy and would therefore be offered active therapy in clinical practice and not palliative supportive care only. In addition, Astellas Pharma Ltd is not aware of evidence evaluating the efficacy and safety of best supportive care in a relevant patient population, which makes forming robust indirect treatment comparisons difficult.	Thank you for your comments. NICE agrees that best supportive care is not an appropriate comparator for those eligible to receive platinum-based therapy and has been removed from the comparator list.

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	Merck, Sharp & Dohme	MSD suggests amending the comparators list to reflect the current standard of care in England which includes avelumab maintenance for patients who have not progressed after platinum-based chemotherapy (includes both cisplatin-eligible and cisplatin-ineligible patients) regardless of PD-L1 status, as per TA788 recommendation. MSD also notes that for people to whom cisplatin-based chemotherapy is unsuitable, atezolizumab is recommended only in patients whose tumours express PD-L1 at a level of 5% or more, as per TA739 recommendation. Furthermore, MSD does not consider best supportive care to be a relevant comparator for patients who are eligible for pembrolizumab with enfortumab vedotin. Patients who are eligible for pembrolizumab with enfortumab vedotin would be fit enough to receive active treatment if cisplatin-based chemotherapy is suitable or unsuitable. Overall, MSD suggests amending the comparators list to the following: • For people whom cisplatin-based chemotherapy is suitable: o Gemcitabine plus cisplatin with or without avelumab maintenance treatment o Methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] plus granulocyte stimulating factor [G-CSF]) with or without avelumab maintenance treatment • For people whom cisplatin-based chemotherapy is unsuitable: o Gemcitabine plus carboplatin with or without avelumab maintenance o Atezolizumab in people whose tumours express PD-L1 at a level of 5% or more	Thank you for your comments. NICE considers that avelumab is not a relevant comparator for this appraisal. NICE agrees that best supportive care is not an appropriate comparator for those eligible to receive platinum-based therapy and has been removed from the comparator list.

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	British Uro-Oncology Group	The use of best supportive care as an alternative for patients for whom cisplatin based chemotherapy is suitable is not an appropriate comparison- it would be an appropriate comparison only for patients not suitable for any form of systemic therapy. In addition, patients who achieve either a complete response, partial response or stable disease after first line cisplatin or carboplatin based combination chemotherapy, receive maintenance treatment with avelumab immunotherapy and it is this combination that is the accurate first line treatment in the group of chemotherapy responders, as per previous NICE consultation. The use of atezolizumab immunotherapy is only an appropriate comparator in the PDL-1 positive population as per licensing. It should be noted that the EV302 study has shown comparable benefit for EV+Pembro in all subgroups including both cisplatin and carboplatin eligible, visceral metastases and PDL-1 positive and negative patients groups.(ASCO GU24) Please note that pembrolizumab did have approval within the UK for first line treatment in metastatic/advanced urothelial cancer in patients who were PDL 1 positive and unsuitable for cisplatin based chemotherapy. There was a period of managed access within the UK to allow further collection of overall survival data in evidence submission. The report analysed real world data for patients treated with pembrolizumab for urothelial cancer in the CDF. This should provide additional data for comparison in an appropriate population, for patients who are PDL-1 positive and unsuitable for cisplatin based	Thank you for your comments. NICE agrees that best supportive care is not an appropriate comparator for those eligible to receive platinum-based therapy and has been removed from the comparator list.

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		chemotherapy. (Public Health England Review on Pembrolizumab for treating urothelial cancer Feb 2021).The final NICE review (TA674) Feb 2021 was terminated due to incomplete data set from the manufacturer. Nevertheless, this additional review provides survival data for comparison with pembrolizumab monotherapy in an appropriate population comparator. It should be noted that Pembrolizumab in first line in this indication for PDL1 positive cisplatin ineligible patients is in EAU and ESMO guidelines and it is only the English patients that have this unavailable with preference for atezolizumab due to financial negations on cost price at time of NICE approval.	
	Fight Bladder Cancer	The initial scope, focusing on traditional chemotherapy and best supportive care as comparators, needs updating to reflect the comprehensive efficacy of pembrolizumab with enfortumab vedotin across patient subgroups. It's crucial to compare this combination to both existing cisplatin-based therapies and novel treatments, considering their impact on efficacy, side effects, and quality of life. The scope should include emerging therapies showing significant benefits and not limit comparisons to best supportive care for patients unsuitable for systemic therapy. Maintenance treatment with avelumab following chemotherapy response and atezolizumab's use in PD-L1 positive cases highlight the need for nuanced comparator choices. EV-302 study results, showing benefits for various subgroups, and additional data on pembrolizumab's real-world use in specific populations, should guide accurate treatment comparisons, ensuring the scope aligns with the evolving treatment landscape.	Thank you for your comments. No action needed.
Outcomes	Astellas Pharma Ltd	The outcomes listed are appropriate.	Thank you for your comments. No action needed.

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	Merck, Sharp & Dohme	MSD considers that the outcome measures listed are appropriate. However, it is known that the response to immunotherapies (immuno-oncology drugs) may have a later onset but once triggered, is likely to be durable, bringing unquantifiable long-term survival benefit for a subset of patients. This benefit is not captured by the outcome measures listed; thus, MSD suggests the inclusion of “Duration of Response” as an additional outcome measure.	Thank you for your comments. The list of outcomes specified in the scope is not exhaustive and any relevant outcomes will be considered by the committee. Response rates is included in the list of outcomes. So, no action needed.
	British Uro-Oncology Group	The EV-103 study results indicate that first-line enfortumab vedotin alone or with pembrolizumab significantly improves Quality of Life, emotional functioning, pain, and symptoms in cisplatin-ineligible patients with locally advanced/metastatic urothelial carcinoma, as evidenced by maintained or improved scores in EORTC QLQ-C30 and BPI-SF measures. Final QoL data for EV302 is currently awaited, however, for EV-103 (first-line (1L) enfortumab vedotin (EV) alone or with pembrolizumab (P) on QOL/functioning/symptoms in patients with la/mUC who were cisplatin-ineligible), these were the results: "Of 149 patients treated, 65 (EV + P) and 63 (EV mono) comprised the PRO analysis set. For EV + P, EORTC QLQ-C30 QOL was maintained through week 24 with improvements in emotional functioning, pain, and insomnia. Clinically meaningful improvements were seen in EORTC QLQ-C30 pain after EV + P at weeks 12 (–14.41 [3.14]) and 24 (–14.99 [3.56]) and BPI-SF worst pain at week 24 (–2.07 [0.37]). For EV mono, EORTC QLQ-C30 QOL remained stable with clinically meaningful improvements in EORTC QLQ-C30 pain (–12.55 [4.27]), insomnia (–14.46 [4.69]), and constipation (–10.09 [4.35]) at week 24. There were small-to-moderate improvements in BPI-SF worst pain at week 24	Thank you for your comments. No action needed.

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	ABC UK	As always, we would advocate that adverse effects of comparator treatments and the benefits of health-related quality of life for this patient group, as well as improved survival, are given sufficient and equal weight within any scoping and appraisal.	Thank you for your comments. No action needed.
	Fight Bladder Cancer	The results from the EV-103 study show that using enfortumab vedotin by itself or combined with pembrolizumab as a first treatment option significantly enhances the quality of life, emotional well-being, pain management, and overall symptoms for patients who cannot receive cisplatin and are battling locally advanced or metastatic urothelial carcinoma. This improvement is clearly demonstrated through sustained or better scores in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and the Brief Pain Inventory-Short Form assessments, highlighting a positive impact on patients' lives.	Thank you for your comments. No action needed.
Equality	Astellas Pharma Ltd	Astellas Pharma Ltd do not believe that there are any issues with regards to Equality in the proposed remit and scope.	Thank you for your comments. No action needed.
	Merck, Sharp & Dohme	No equality issues are anticipated.	Thank you for your comments. No action needed.
	British Uro-Oncology Group	The British Uro-Oncology Group recognises that people residing in remote or rural areas encounter barriers in accessing healthcare facilities that offer treatments like pembrolizumab with enfortumab vedotin. Given the necessity for frequent visits to treatment centres, it's imperative to adapt our healthcare infrastructure to ensure that these therapies are accessible to all, irrespective of geographic location.	Thank you for your comments. The committee will consider evidence on equality issues raised

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		The British Uro-Oncology Group is concerned that women are disproportionately affected, facing higher mortality rates and poorer outcomes than men. It is crucial for health technology assessments involving pembrolizumab with enfortumab vedotin to include a detailed analysis of outcomes by sex. With the National Institute for Health and Care Excellence (NICE) introducing significant methodological changes, including replacing end-of-life criteria with a severity modifier for evaluating new medications, the British Uro-Oncology Group notes the potential implications for older patients with bladder cancer. This demographic is at risk of being disadvantaged if the unique severity of their condition and the associated QALY shortfall are not adequately accounted for in cost-effectiveness assessments	during the course of the appraisal. No action needed.
	Fight Bladder Cancer	People in remote or rural areas might face challenges accessing treatment centres offering pembrolizumab with enfortumab vedotin, especially if frequent hospital visits are required. The scope should consider the availability of the treatment across different healthcare settings to ensure equitable access. We are aware of the disturbing disparities in bladder cancer outcomes between men and women, with research consistently showing that women with this disease experience higher mortality rates and worse outcomes compared to their male counterparts. It is essential that clinical trials and evaluations of this treatment combination rigorously analyse and report data disaggregated by gender. This approach will enable a clear understanding of the efficacy and safety of pembrolizumab with enfortumab vedotin in women compared to men, potentially illuminating pathways to mitigate the observed disparities. Fight Bladder Cancer acknowledges the National Institute for Health and Care Excellence's (NICE) recent methodological updates for health	Thank you for your comments. The committee will consider evidence on equality issues raised during the course of the appraisal. The remit of NICE's single technology appraisal is limited to making recommendations within enfortumab vedotin with pembrolizumab's

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		technology evaluations, notably the shift from end-of-life criteria to the introduction of a severity modifier. This change, intended to refine the assessment of new medications' cost-effectiveness, is a critical development with implications for older people with bladder cancer. This raises concerns about the potential for older people to face indirect disadvantages under the new system. Bladder cancer, predominantly affecting this demographic, could see treatments undervalued if the severity of the condition and the Quality-Adjusted Life Year (QALY) shortfall are not adequately recognised. To mitigate these concerns, the scope and remit should advocate for: • Expanding telehealth services, mobile treatment units, and community-based infusion centres to reduce the need for frequent travel to distant hospitals • Mandate the inclusion and thorough analysis of gender-disaggregated data in clinical trials and health technology evaluations for pembrolizumab with enfortumab vedotin. • Support mechanisms for disabled people or those requiring additional assistance to navigate their treatment options and adhere to their treatment plans. • Recognising the full value of treatments that may offer significant quality of life improvements or extend life for older peopl	anticipated marking authorisation. No action needed.
Questions for consultation	Astellas Pharma Ltd	**Where do you consider pembrolizumab with enfortumab vedotin will fit into the existing care pathway for urothelial cancer?** Enfortumab vedotin with pembrolizumab (EV+P) is expected to replace platinum-based therapy (cis-platin or carboplatin with gemcitabine) as a first-line treatment for adult patients with La/mUC who are eligible for platinum-based therapy. EV+P	Thank you for your comments. No action needed.

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		significantly improved outcomes in patients with previously untreated la/mUC, nearly doubling the median PFS (median PFS, 12.5 months vs 6.3 months, respectively; HR 0.45 [95% CI: 0.38-0.54]; P<0.00001) and OS (median OS, 31.5 months vs 16.1 month, respectively; HR 0.47 [95% CI: 0.38-0.58]; P<0.00001) compared to platinum-based chemotherapy in the phase III EV-302 study [T.B. Powles, B. Perez Valderrama, S. Gupta et al. Annals of Oncology (2023) 34 (suppl_2): S1254-S1335. 10.1016/annonc/annonc1358] **Have all relevant comparators for pembrolizumab with enfortumab vedotin been included in the scope?** There are no additional relevant comparators. See our comments in section 2. **If the evidence allows, should subgroups by PD-L1 expression be considered?** There are no groups that should be considered separately. EV+P significantly improved outcomes in patients with previously untreated la/mUC regardless of PD-1 expression or cisplatin eligibility in the EV-302 phase III study. **Would pembrolizumab with enfortumab vedotin be a candidate for managed access?** It is anticipated that routine commissioning should be achievable for pembrolizumab with enfortumab vedotin and therefore it would not be considered a likely candidate for managed access. **Do you consider that the use of pembrolizumab with enfortumab vedotin can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** The health-related benefits of the use of enfortumab vedotin with pembrolizumab are expected to be included in the QALY calculation.	

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		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	
	Merck, Sharp & Dohme	**Where do you consider pembrolizumab with enfortumab vedotin will fit into the existing care pathway for urothelial cancer?** MSD expects that the combination of pembrolizumab with enfortumab vedotin will be used in line with its expected marketing authorisation (for adults with untreated locally advanced or metastatic urothelial cancer). **Have all relevant comparators for pembrolizumab with enfortumab vedotin been included in the scope?** MSD suggests amending comparators list to reflect the current standard of care in England which includes avelumab maintenance for patients who have not progressed after platinum-based chemotherapy (includes cisplatin-eligible and cisplatin-ineligible patients) regardless of PD-L1 status, as per TA788 recommendation. MSD also notes that for people to whom cisplatin-based chemotherapy is unsuitable, atezolizumab is recommended only in patients whose tumours express PD-L1 at a level of 5% or more, as per TA739 recommendation. Furthermore, MSD does not consider best supportive care to be a relevant comparator for patients who are eligible for pembrolizumab with enfortumab vedotin. Patients who are eligible for pembrolizumab with enfortumab vedotin would be fit enough to receive active treatment. Therefore, MSD suggests amending the comparator list accordingly, as detailed in our above response against the section “Comparators”.	Thank you for your comments. NICE consider people with untreated locally advanced or metastatic urothelial cancer whose tumours express PD-L1 and cisplatin-containing chemotherapy is unsuitable as a relevant subgroup. This has been added in the scope. The scope identifies all potentially relevant comparators that are established practice in the NHS. At this stage of the evaluation, identifying comparators should be inclusive. NICE agrees that best supportive care is not an appropriate comparator for those

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		If the evidence allows, should subgroups by PD-L1 expression be considered? The evidence in PD-L1 positive subgroup of cisplatin ineligible patients would be of interest for a comparison with atezolizumab (TA739). **Would pembrolizumab with enfortumab vedotin be a candidate for managed access?** The submission to NICE will be made based on data from an interim analysis of KEYNOTE-A39. Further follow-up data will become available in the future, which may mean it is appropriate to consider this technology as a managed access candidate. **Do you consider that the use of pembrolizumab with enfortumab vedotin can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** MSD does not consider that the use of pembrolizumab in combination with enfortumab vedotin will result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation.	eligible to receive platinum-based therapy and has been removed from the comparator list.
	British Uro-Oncology Group	1. Pembrolizumab with enfortumab vedotin will be a significant step forward for patients with advanced urothelial cancer where survival has not improved over 20 years. Cisplatin or carboplatin combinations have been the mainstay of treatment and this is landmark change in improving overall survival and progression. It will be key to provide education for clinicians who lack previous experience with the combination due to specific toxicities with enfortumab vedotin which	Thank you for your comments. NICE consider people with untreated locally advanced or metastatic urothelial cancer whose tumours express PD-L1

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		are very manageable. This will be the first line choice for patients who are otherwise fit for systemic treatment. It is not a appropriate to compare it with best supportive care unless you include chemotherapy with maintenance avelumab immunotherapy, or first line immunotherapy as part of best supportive care, as they improve symptoms as well as survival. 2. Comparators: please see comments above. 3. Enfortumab vedotin and pembrolizumab shows efficacy across all subgroups irrespective of PDL-1 expression.(ASCO GU 2024) The only difference would be the potential comparator in the cisplatin ineligible patients, where it would be either carboplatin based chemotherapy or atezolizumab. The use of EV +Pembro should not be restricted by PDl-1 expression. 4. Managed access- this would offer collection of “real world data” via bluteq to monitor access and toxicity . 5. HES data is of benefit to look at patient hospital admissions with complications of advanced urothelial cancer such as interventional radiology for nephrostomies/ureteric stent, palliative TURBT, management of haematuria. It is potentially more difficult to capture the burden on palliative care services where this disease can represent a significant challenge to optimise patient symptoms. Palliative radiotherapy may also be used for symptoms such as pain from local or metastatic disease, or haematuria. 6. The burden on care givers in urothelial cancer is significant. To allow an effective treatment to be used in first line treatment would reduce this burden allowing care givers to return to employment and contribute to society.	and cisplatin-containing chemotherapy is unsuitable as a relevant subgroup. This has been added in the scope. The scope identifies all potentially relevant comparators that are established practice in the NHS. At this stage of the evaluation, identifying comparators should be inclusive. NICE agrees that best supportive care is not an appropriate comparator for those eligible to receive platinum-based therapy and has been removed from the comparator list.
	ABC UK	Treatment with the combination of enfortumab vedotin-ejfv (Padcev) and pembrolizumab (Keytruda) led to an improvement in overall survival (OS) and progression-free survival (PFS)	Thank you for your comments.

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		Substantial improvement in OS – impact of patients having more time with their loved ones and of progression free survival.	No action needed.
	Fight Bladder Cancer	**Where do you consider pembrolizumab with enfortumab vedotin will fit into the existing care pathway for urothelial cancer?** The recent FDA approval of pembrolizumab combined with enfortumab vedotin marks a pivotal advancement in the treatment landscape for locally advanced or metastatic urothelial carcinoma, positioning this combination as a potential new standard of care. Given the compelling evidence from the EV-302 trial, which demonstrates significant improvements in both progression-free survival and overall survival compared to traditional platinum-based chemotherapy, it's clear that this combination should be considered for first-line treatment. For over two decades, the survival rates for advanced urothelial cancer have remained stagnant, with cisplatin or carboplatin combinations being the primary treatment options. It will be essential to educate clinicians on managing specific toxicities associated with enfortumab vedotin, which are manageable with proper care. This combination should ideally be the first choice for patients fit for systemic treatment. **Would pembrolizumab with enfortumab vedotin be a candidate for managed access?** Given the significant improvement in outcomes demonstrated by the EV-302 trial, pembrolizumab with enfortumab vedotin is a strong candidate for managed access. This approach would allow people to benefit from this	Thank you for your comments. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		promising treatment while ongoing data collection and analysis continue to confirm its long-term efficacy and safety profile across the broader patient population. Managed access could also facilitate a more rapid adoption of this treatment in clinical practice, ensuring people receive the most advanced care available. **Do you consider that the use of pembrolizumab with enfortumab vedotin can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Although Quality-Adjusted Life Year (QALY) calculations do consider several aspects of health-related quality of life, they often overlook patient-reported outcomes. These outcomes include the psychological advantages of accessing innovative treatments, a reduction in treatment-related burdens, and fewer hospital visits or interventions due to side effects. The impact on caregivers and family members, who bear a significant burden in managing urothelial cancer, must also be acknowledged. Utilising effective treatments as the first line of defence could alleviate some of this strain, enabling caregivers to resume their professional lives and societal contributions. From the Personal Social Services' viewpoint, therapies that enhance life quality and promote patient independence could lead to a decrease in long-term care expenses. Effective treatments could help individuals maintain greater levels of functionality and independence, offering substantial benefits both to the patient's welfare and economically.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Examining Hospital Episode Statistics data can reveal insights into hospital admissions due to complications from advanced urothelial cancer, such as the need for interventional radiology procedures like nephrostomies or ureteric stents, palliative Transurethral Resection of the Bladder Tumour (TURBT), and management of haematuria. Palliative radiotherapy is often employed to alleviate symptoms like pain from local or metastatic disease or haematuria, underlining the comprehensive burden of this condition.	
Additional comments on the draft scope	ABC UK	**Re The Related NICE recommendations: this list requires updating:** **TA492**: Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (December 2017) This guidance has been updated and **replaced by NICE technology appraisal guidance 739 below** **TA739**: Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable. (27 October 2021) **TA522:** Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (June 2018) **replaced by TA674** **TA674**: Pembrolizumab for untreated PD-L1-positive, locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (terminated appraisal February 2021)	Thank you for your comments. The related NICE recommendations have been updated to include all relevant published technology appraisals related to this topic.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Roche (comparator)