National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Enfortumab vedotin for treating locally advanced or metastatic urothelial cancer platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor

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

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Astellas Pharma Ltd	Astellas Pharma Ltd propose a minor amendment to the name of the appraisal from: "Enfortumab vedotin for treating locally advanced or metastatic urothelial cancer after 2 therapies" To: "Enfortumab vedotin for treating locally advanced or metastatic urothelial cancer after a platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor"	Comment noted, has been changed to 'Enfortumab vedotin for treating locally advanced or metastatic urothelial cancer after platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor'.
	British Uro-oncology Group	Yes *(in response to: 'Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?')*	Comment noted.

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Timing Issues	Astellas Pharma Ltd	There is a high unmet need for this patient population and therefore urgency of this appraisal. As set out in the draft remit "there are currently no routinely recommended drug treatments in the NHS for people with locally advanced or metastatic urothelial cancer, who have experienced progression or relapse of their cancer" We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval	Comment noted.
	British Uro-oncology Group	As this is an area of unmet need this appraisal should be prioritised	Comment noted.

Comment 2: the draft scope

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Background information	Astellas Pharma Ltd	Astellas Pharma Ltd considers the background to be accurate and complete	Comment noted.
	British Uro-oncology Group	The draft scope covers it well. As an update- pembrolizumab is now not available through CDF	Comment noted. This has been addressed in the updated scope.
	Fight Bladder Cancer	You state "There are around 10,000 new bladder cancer cases in the UK each year". However this number only counts muscle-invasive bladder cancer (ICD-10 C67). Fight Bladder Cancer have published more accurate statistics - 20,507 cases of bladder cancer per year in the UK, which includes ICD-10 C67 (Malignant neoplasm of bladder) and also ICD-10 D09.0 (Carcinoma in situ of bladder) & D41.4 (Bladder neoplasm of uncertain or unknown behaviour, and other bladder cancer). See	Comment noted. Figures on all bladder cancers have been included in the scope, and the text has been amended to make it clear when figures are

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		https://fightbladdercancer.co.uk/sites/default/files/downloads/My-diagnosis-counts.pdf You state “Approximately 8,700 people are diagnosed with bladder cancer each year in England”. Once again this number only counts muscle-invasive bladder cancer (ICD-10 C67). Fight Bladder Cancer have published more accurate statistics - 17,921 cases of bladder cancer per year in England, which includes 8,066 cases of ICD-10 C67 (Malignant neoplasm of bladder) and 9,855 cases of ICD-10 D09.0 (Carcinoma in situ of bladder) & D41.4 (Bladder neoplasm of uncertain or unknown behaviour, and other bladder cancer). See https://fightbladdercancer.co.uk/sites/default/files/downloads/My-diagnosis-counts.pdf Technology appraisal guidance [TA522] (Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable) has been updated and replaced by NICE technology appraisal guidance 674: “NICE is unable to make a recommendation on pembrolizumab (Keytruda) for untreated PD-L1-positive, locally advanced or metastatic urothelial cancer when cisplatin is unsuitable in adults.” On 4 February 2021, Avelumab was granted a marketing authorisation by the Medicines and Healthcare products Regulatory Agency for the treatment of bladder cancer.	related specifically to muscle-invasive cancer. The scope has been changed after TA674 replacement of TA522. Avelumab has been included under appraisals in development in the scope. It has not been included in the background section, as NICE guidance for avelumab in this indication has not been published.
The technology/ intervention	Astellas Pharma Ltd	Astellas Pharma Ltd considers the description of the technology to be accurate	Comment noted.
	British Uro-oncology Group	Yes	Comment noted.

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		(in response to: 'Is the description of the technology or technologies accurate?')	
Population	Astellas Pharma Ltd	Population is defined appropriately and there are no groups that should be considered separately.	Comment noted.
	British Uro-oncology Group	Yes *(in response to: 'Is the population defined appropriately?')*	Comment noted.
Comparators	Astellas Pharma Ltd	Astellas Pharma Ltd believe that the comparator should be "Taxane Chemotherapy (paclitaxel or docetaxel)" Astellas Pharma Ltd believe that although there will be a group of patients who would receive Best Supportive Care only following platinum-chemotherapy and immunotherapy, these patients would likely be those in poor physical condition or who would be unwilling to receive further active therapy. This group of patients is therefore unlikely to be treated with enfortumab vedotin in clinical practice and as such we do not believe Best Supportive Care would be an appropriate comparator. Similarly, there is a paucity of evidence evaluating the efficacy and safety of Best Supportive Care in a relevant patient population, which makes forming robust indirect treatment comparisons difficult. This view is supported by TA519 and TA525. Astellas Pharma Ltd believe that Palliative Care is not an appropriate comparator and the approval of enfortumab vedotin is not expected to displace the use of Palliative Care in clinical practice. For patients with locally advanced (La) or metastatic urothelial carcinoma (mUC) who have previously failed platinum-chemotherapy and immunotherapy, 'Palliative Care' is used to define a group of treatments for patients as they approach the end of life. Palliative care will be incorporated into the cost-effectiveness model as end of life care.	Comment noted. Other stakeholders have indicated that 'the majority of patients would get best supportive care' (see below), so best supportive care kept as a comparator in the scope. Palliative care removed as a comparator in the scope.

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	British Uro-oncology Group	Majority of the patients would get best supportive care	Comment noted, best supportive care kept as a comparator in the scope.
Outcomes	Astellas Pharma Ltd	Yes. Astellas Pharma Ltd suggests that 'response rate' could be split into 'disease control rate' and 'overall response rate'	Comment noted. If the company intend to split response rate up into 2 components, the evidence submission should explain the justification for this. The ERG and the committee will consider whether this appropriately captures the outcome specified in the scope. No changes to the scope required.
	British Uro-oncology Group	Yes *(in response to: 'Will these outcome measures capture the most important health related benefits (and harms) of the technology?')*	Comment noted.
	Fight Bladder Cancer	For progression-free survival, are you going to use RECIST defined progression (used in clinical trials) or investigator defined progression (used in the real world)?	Comment noted. Outcomes in the scope do not usually specify individual criteria and are generally kept broad. One or both of

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			these progression data types may be provided by the evidence submissions.
Economic analysis	Astellas Pharma Ltd	Astellas Pharma Ltd will conduct a cost utility analysis over an appropriate time horizon to reflect the impact on survival	Comment noted.
	British Uro-oncology Group	As this is an area of unmet need, important to do analysis promptly	Comment noted.
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.	Comment noted.
	British Uro-oncology Group	No concerns	Comment noted.
	Fight Bladder Cancer	Bladder cancer might be more common in men, however women are much less likely to receive a timely diagnosis (Zhou, Y.; Walter, F.M.; Singh, H.; Hamilton, W.; Abel, G.A.; Lyratzopoulos, G. Prolonged Diagnostic Intervals as Marker of Missed Diagnostic Opportunities in Bladder and Kidney Cancer Patients with Alarm Features: A Longitudinal Linked Data Study. Cancers 2021, 13, 156). Women with bladder cancer also have worse outcomes compared to men. Women tend to present with advanced stage, experience differences in quality of life following treatment, and suffer worse cancer-specific mortality (Hart ST, Woods ME, Quek ML. Gender disparities in bladder cancer management. Urology Times, February 20, 2019, Volume: 47, Issue: 2)	Comment noted.
Innovation	Astellas Pharma Ltd	Yes. Astellas Pharma Ltd does consider enfortumab vedotin to be innovative.	Comment noted.~~Noted~~

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		Astellas Pharma Ltd believe that enfortumab vedotin meets the criteria for the MHRA's Promising Innovative Medicine (PIM) designation as enfortumab vedotin is intended for the treatment of a life-threatening or seriously debilitating condition with the potential to address an unmet medical need. Astellas Pharma Ltd has made an application for a PIM designation on this basis. [redacted]	
	British Uro-oncology Group	Yes, it is a step-change and recently presented trial results show a clinically and statistically meaningful improvement in outcomes in this setting.	Comment noted.
	Fight Bladder Cancer	Yes, the technology is innovative. "Enfortumab vedotin significantly prolonged survival as compared with standard chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who had previously received platinum-based treatment and a PD-1 or PD-L1 inhibitor. Overall survival was longer in the enfortumab vedotin group than in the chemotherapy group (median overall survival, 12.88 vs. 8.97 months; hazard ratio for death, 0.70; 95% confidence interval [CI], 0.56 to 0.89; P=0.001). Progression-free survival was also longer in the enfortumab vedotin group than in the chemotherapy group (median progression-free survival, 5.55 vs. 3.71 months; hazard ratio for progression or death, 0.62; 95% CI, 0.51 to 0.75; P<0.001)." Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, Matsubara N, Vulsteke C, Castellano D, Wu C, Campbell M. Enfortumab	Comment noted.

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		Vedotin in Previously Treated Advanced Urothelial Carcinoma. New England Journal of Medicine. 2021 Feb 12.	
Questions for consultation	Astellas Pharma Ltd	**Does the population defined in the scope reflect the treatments that people with locally advanced or metastatic urothelial cancer have in the NHS?** Yes – the population is defined appropriately. **Have all relevant comparators for enfortumab vedotin been included in the scope?** The relevant comparator for enfortumab vedotin for locally advanced or mUC patients that have been pre-treated with a platinum-based chemotherapy and a checkpoint inhibitor, is Taxane chemotherapy - either paclitaxel or docetaxel. **Are any listed which aren't used in NHS practice for this point in the pathway?** **Which treatments are considered to be established clinical practice in the NHS for urothelial cancer after 2 therapies?** **What chemotherapy regimens would be given at this point in the treatment pathway?** La/mUC patients that have been pre-treated with a platinum-based therapy and a checkpoint inhibitor will have only further single agent taxane chemotherapy (paclitaxel or docetaxel) or clinical trials as a choice and this will depend on how fit the patient is and whether they wish for further treatment. For those patients not fit enough or who choose not to receive a further systemic therapy, they will continue to receive best supportive care with the addition of palliative care at the appropriate time.	Noted, see response regarding comparators above.

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		Whilst our clinical trial EV-301 included vinflunine as a comparator, NICE scientific advice confirmed that vinflunine is not recommended for use in patients with locally advanced or metastatic urothelial carcinoma in the NHS, and hence is not an appropriate comparator for a NICE appraisal of enfortumab vedotin. **How should best supportive care be defined?** Best supportive care is offered to all patients from the point of diagnosis with the objective of managing symptoms and preventing patient quality of life deterioration. At this point in the treatment pathway a switch to best supportive care only could be summarised as “no active treatment” with no curative intent. Best supportive care might include palliative radiotherapy, analgesia, antiemetics, sometimes corticosteroids, access to cancer nurse specialist support etc. **How should palliative care be defined in this particular setting?** ‘Palliative Care’ is used to define a group of treatments for patients as they approach the end of life. Palliative care can be considered as an element of best supportive care. **What differentiates chemotherapy, best supportive care and palliative care in this stage of the treatment pathway?**	

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		At this stage of the treatment pathway, chemotherapy is an active treatment with disease modifying objectives/curative intent. Best supportive care and palliative care should be considered as “no active treatment” **Are the outcomes listed appropriate?** Yes. Astellas Pharma Ltd suggests that ‘response rate’ could be split into ‘disease control rate’ and ‘overall response rate’ **Are there any subgroups of people in whom enfortumab vedotin is expected to be more clinically effective and cost effective or other groups that should be examined separately?** There are no sub-groups in whom enfortumab vedotin is expected to be more clinically effective and cost effective or other groups that should be examined separately. **Where do you consider enfortumab vedotin will fit into the existing NICE pathway, Bladder cancer?** Enfortumab vedotin will fit in the NICE pathway for “Managing locally advanced or metastatic bladder cancer” for the treatment of adult patients with locally advanced (LA) or metastatic urothelial cancer (mUC) who have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and who have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know**	

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		if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which enfortumab vedotin will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** There are no issues identified in relation to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. **Do you consider enfortumab vedotin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes - Astellas Pharma Ltd believe that enfortumab vedotin meets the criteria for the MHRA's Promising Innovative Medicine (PIM) designation as enfortumab vedotin is intended for the treatment of a life-threatening or	

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		seriously debilitating condition with the potential to address an unmet medical need. Astellas Pharma Ltd has made an application for a PIM designation on this basis. [redacted] **Do you consider that the use of enfortumab vedotin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** No additional benefits to be considered **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Astellas Pharma Ltd do not believe that there will be any barriers to adoption of enfortumab vedotin	
Additional comments on the draft scope	Astellas Pharma Ltd	The NICE guidance for “Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy” is missing from the draft scope list of related technology appraisals.	Comment noted. This has been added to the scope.