National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Atezolizumab in combination with platinum-based chemotherapy for untreated locally advanced or metastatic urothelial cancer

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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	Roche	The anticipated licence is as follows: [redacted] We recommend the remit is updated to reflect this. Further, we recommend that the technology appraisal and scope titles are updated to reflect this for transparency to the clinical and patient community. We suggest it is updated to: [redacted]	Thank you for your comments. The remit and titles have been amended to reflect the locally advanced or metastatic population.
	Janssen	No comment	Thank you for your response.

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Timing Issues	Roche	We encourage this appraisal to continue in line with usual NICE scheduling to ensure there is no delay to patient access. [redacted]	Thank you for your comments. The appraisal committee will consider the clinical and cost effectiveness evidence during the development of the appraisal. No changes have been made.
	Fight Bladder Cancer	Metastatic and locally advanced urothelial cancer has a very poor prognosis. Chemotherapy can often have quite serious side effects that significantly reduce the quality of life for the final months. For carers, it is a period of ultimate worry and exhaustion as you care for your loved one as the patient and their medical team fight to preserve life for as long as possible. There is a substantial unmet need for treatment options that can meaningfully improve survival and quality of life in patients with advanced bladder cancer. Urothelial cancer has come at the bottom of the annual NHS cancer patient experience survey since its launch. The high risk of recurrence and progression has led to this cancer seeing one of the highest associated suicide rates for cancer patients due to the emotional strains of the treatment and quality of life issues. At the moment, in order to access immunotherapy, patients must be either ineligible for chemotherapy or have already tried chemotherapy.	Thank you, your comments have been noted. The appraisal will consider the health benefits and adverse effects that are important to patients and/or their carers. Consultees can expand on the unmet need and patient experience in their evidence submissions and it will be considered fully by the appraisal committee.

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	Janssen	No comment	Thank you for your response.

Comment 2: the draft scope

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Background information	Roche	The first sentence of the second paragraph should read as follows: In 2017, 8,686 new bladder cancers were diagnosed in England.[1] The first three sentences of the third paragraph should be replaced by: Up to 50% of patients are considered to be ineligible or "unfit" to receive cisplatin-based regimens.[2] Patients who are ineligible to receive treatment with 1L cisplatin-based regimens constitute a heterogeneous population. This includes patients who are frail due to pre-existing co-morbidities such as renal impairment, myelosuppression or hearing impairment, as well as those with a history of an allergy to cisplatin or other platinum-containing regimens. A consensus working group has defined cisplatin-ineligibility under specific criteria,[3] including PS, renal function, hearing loss and peripheral neuropathy history, and cardiac function.	Thank you for your comments. The prevalence of bladder cancer noted in the scope has been updated. The scope includes the current treatment pathway as recommended in NICE guidelines. No changes have been made.

[1] Office for National Statistics (2019) Cancer Registration Statistics, England: 2017. Accessed December 2019.
[2] De Santis, M., & Bachner, M. (2007). New developments in first-and second-line chemotherapy for transitional cell, squamous cell and adenocarcinoma of the bladder. Current opinion in urology, 17(5), 363-368.
[3] Galsky, M. D., Hahn, N. M., Rosenberg, J., Sonpavde, G., Hutson, T., Oh, W. K., ... & Bellmunt, J. (2011). Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. Journal of clinical oncology, 29(17), 2432-2438.

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		Historically, the cisplatin-ineligible patient population has had limited treatment options that varied according to different guidelines, underlying patient characteristics, and physician discretion. Carboplatin-based regimens are feasible in these patients, but studies suggest they are less effective than cisplatin-based regimens.[4] The last two sentences of the third paragraph should be replaced by: Platinum-based chemotherapy is the standard of care in previously untreated patients with mUC and is associated with an OS of around 9-15 months.[5,6,7] Cisplatin-based chemotherapy has remained the preferred 1L regimen for decades; however, only 50% of patients actually receive cisplatin-based 1L chemotherapy. Common co-morbidities such as chronic kidney disease, peripheral neuropathy, hearing loss and heart failure restrict the number of patients eligible to receive cisplatin. These patients generally receive inferior carboplatin-based 1L regimens.2 Approved programmed death-ligand 1 (PD-L1) and programmed death 1 (PD-1) inhibitors are the first new systemic therapies for mUC, both for 1L treatment of cisplatin-ineligible patients whom tumors are PD-L1 positive and for patients experiencing disease progression despite platinum-based	

[4] Dogliotti, L., Cartenì, G., Siena, S., Bertetto, O., Martoni, A., Bono, A., ... & Marini, L. (2007). Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. European urology, 52(1), 134-141.
[5] Loehrer Sr, P. J., Einhorn, L. H., Elson, P. J., Crawford, E. D., Kuebler, P., Tannock, I., ... & Blumenstein, B. (1992). A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol, 10(7), 1066-73.
[6] von der Maase, H., Sengelov, L., Roberts, J. T., Ricci, S., Dogliotti, L., Oliver, T., ... & Arning, M. (2005). Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. Journal of clinical oncology, 23(21), 4602-4608.
[7] De Santis, M., Bellmunt, J., Mead, G., Kerst, J. M., Leahy, M. G., Daugaard, G., ... & Sylvester, R. (2010). Randomized phase II/III trial comparing gemcitabine/carboplatin (GC) and methotrexate/carboplatin/vinblastine (M-CAVI) in patients (pts) with advanced urothelial cancer (UC) unfit for cisplatin-based chemotherapy (CHT): Phase III results of EORTC study 30986. Journal of Clinical Oncology, 28(18_suppl), LBA4519-LBA4519.

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		chemotherapy. However, there are still no new approved treatments for patients who are treatment naïve in the metastatic setting and can tolerate cisplatin-based therapy.	
	Fight Bladder Cancer	"In 2016, 8,500 new bladder cancers were diagnosed in England. Bladder cancer accounts for around 1 in every 30 new cancer diagnoses each year in the UK, with an overall incidence of around 17 per 100,000." should be changed to: "In 2013, 18,000 new muscle-invasive (ICD-10 CD67) and non-muscle-invasive bladder cancers (ICD-10 D09.0 and D41.4) were diagnosed in England (Roger Kockelbergh, Luke Hounsome, and Erik Mayer. 2017 Journal of Clinical Urology, Vol. 10(1S) 3–8). Advanced bladder cancer accounts for around 1 in every 30 new cancer diagnoses each year in the UK, with an overall incidence of around 17 per 100,000"	Thank you for your comments. The prevalence of bladder cancer noted in the scope has been updated.
	Janssen	No comment	Thank you for your response.
The technology/ intervention	Roche	The description of the technology is accurate. However, the intervention wording needs to be updated to reflect the anticipated licence: [redacted]	Thank you for your comments. The description of the technology has been updated.
	Janssen	Please clarify if only the combination of atezolizumab with gemcitabine and carboplatin is being appraised or if the combination of atezolizumab with gemcitabine and cisplatin is also being considered.	Thank you for your comments. The description of the

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		The study this appraisal is based on -IMVigor130- explores atezolizumab+gemcitabine+carbo/cisplatin vs placebo+ gemcitabine+carbo/cisplatin.	technology has been updated.
Population	Roche	No comment	Thank you for your response.
	Janssen	No comment	Thank you for your response.
Comparators	Roche	The draft scope includes the following comparators: • People for whom cisplatin-based chemotherapy is suitable: o Gemcitabine plus cisplatin o Accelerated methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) plus granulocyte-colony stimulating factor (G-CSF) • People for whom cisplatin-based chemotherapy is unsuitable: o Gemcitabine plus carboplatin o Best supportive care (BSC). With regards to MVAC plus G-CSF, although this is currently recommended in NICE guidelines, in practice this is rarely used. Therefore this is not considered standard of care and should not be considered as a comparator. With regards to BSC, given the availability of other treatments, it is assumed BSC alone is not an established treatment option for patients who can tolerate, or are willing to have, pharmacological intervention. It is assumed that only patients who are can tolerate, or are willing to have pharmacological intervention will be eligible for atezolizumab, hence, BSC is not an appropriate comparator for atezolizumab. Therefore MVAC plus G-CSF and	Thank you for your comments. The comparators listed are examples of treatments that may be used in clinical practice. Consultees can submit further information as part of their evidence submissions which will be considered by the appraisal committee. Pembrolizumab monotherapy (TA522) and atezolizumab monotherapy (TA492) are recommended as treatment options within the Cancer Drugs Fund (CDF). These have

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		BSC are not relevant comparators and should be removed from the final scope. Further, in some instances, the current standard of care is that some patients who are considered eligible for cisplatin may still receive gemcitabine plus carboplatin due to local capacity restraints. Therefore, we recommend the comparators to include in the analysis should consist of: • For people for whom cisplatin-based chemotherapy is suitable: o Gemcitabine plus cisplatin o Gemcitabine plus carboplatin • For people for whom cisplatin-based chemotherapy is unsuitable: o Gemcitabine plus carboplatin	been added to the scope as they may become standard clinical practice during the process of this appraisal.
	Janssen	Pembrolizumab monotherapy for front-line cisplatin-ineligible (TA522) is due to be reappraised from the CDF imminently. Depending on the results of the appraisal it might be a pertinent comparator within the cisplatin-ineligible cohort.	Thank you for your comments. The comparators listed are examples of treatments that may be used in clinical practice. Consultees can submit further information as part of their evidence submissions which will be considered by the appraisal committee.

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			Pembrolizumab monotherapy (TA522) and atezolizumab monotherapy (TA492) are recommended as treatment options within the Cancer Drugs Fund (CDF). These have been added to the scope as they may become standard clinical practice during the process of this appraisal.
Outcomes	Roche	Yes, the listed outcomes capture the most important health-related benefits and harms.	Thank you for your comment. No changes have been made.
	Fight Bladder Cancer	Health-related quality of life is of particular importance to this patient population.	Thank you for your comment. No changes have been made.
	Janssen	No comment	Thank you for your response.
Economic analysis	Roche	Atezolizumab with platinum-based chemotherapy has demonstrated considerable benefit over chemotherapy, thus a cost-effectiveness analysis is the most appropriate economic analysis. This will be expressed in terms of incremental cost per quality-adjusted life-year.	Thank you, your comments have been noted.

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		The time horizon should be sufficient to capture all health related benefits and costs of treatment. A lifetime horizon that captures the full expected overall survival of patients is the appropriate time horizon. The draft scope includes the cost of diagnostic testing for PD-L1. As outlined in comment in the other considerations section, [redacted]	
	Fight Bladder Cancer	More evidence is needed to examine whether PD-L1 should be used as a biomarker to identify a population that is more likely to respond to immunotherapy, or whether it is merely a prognostic marker that is associated with higher survival rates overall (J. Bellmunt, S. A. Mullane, L. Werner, A. P. Fay, M. Callea, J. J. Leow, M. E. Taplin, T. K. Choueiri, F. S. Hodi, G. J. Freeman, S. Signoretti, Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma, Annals of Oncology, Volume 26, Issue 4, April 2015, Pages 812–817)	Thank you, your comments have been noted.
	Janssen	No comment	Thank you for your response.
Equality and Diversity	Roche	No equality issues have been identified	Thank you, your comment has been noted.
	Fight Bladder Cancer	Women with bladder cancer 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	Thank you for your comment. The equalities issues raised are addressed in the

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		(Hart ST, Woods ME, Quek ML. Gender disparities in bladder cancer management. Urology Times, February 20, 2019, Volume: 47, Issue: 2)	Equalities Impact Assessment.
	Janssen	No comment	Thank you for your response.
Other considerations	Roche	The draft scope outlines that consideration will be given to subgroups based on the biological marker PD-L1. [redacted]	Thank you for your comment. The committee will consider the evidence base submitted by the company and will appraise to technology in line with the marketing authorisation. No changes have been made.
	Janssen	No comment	Thank you for your response.
Innovation	Roche	[redacted]	Thank you, your comment has been noted. During the development of the appraisal, the committee will consider the degree to which atezolizumab in combination with

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			platinum-based chemotherapy is an innovative technology when making its recommendations. No changes have been made.
	Fight Bladder Cancer	The data on first-line atezolizumab in combination with chemotherapy for advanced bladder cancer that have been presented publicly so far are not practice changing. More information is needed regarding the overall survival benefit and progression free survival (IMvigor130: Efficacy and safety from a Phase 3 study of atezolizumab (atezo) as monotherapy or combined with platinum-based chemotherapy (PBC) vs placebo + PBC in previously untreated locally advanced or metastatic urothelial carcinoma (mUC). Annals of Oncology, Volume 30, Supplement 5, October 2019).	Thank you, your comment has been noted. During the development of the appraisal, the committee will consider the degree to which atezolizumab in combination with platinum-based chemotherapy is an innovative technology when making its recommendations. No changes have been made.
	Janssen	No comment	Thank you for your response.
	Roche	Have all relevant comparators for atezolizumab with gemcitabine and carboplatin been included in the scope? Which treatments are considered to	Thank you for your responses to the

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Questions for consultation		be established clinical practice in the NHS for locally advanced or metastatic urothelial cancer? • See comment in the comparators section How should best supportive care be defined? • No comment – see comment in the comparators section for rationale on why BSC not considered appropriate in this treatment setting Are the outcomes listed appropriate? • Yes, see comment in the outcomes section Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom atezolizumab with gemcitabine and carboplatin is expected to be more clinically effective and cost effective or other groups that should be examined separately? • Please note, this appraisal will explore atezolizumab in combination with platinum chemotherapy (not just atezolizumab with gemcitabine and carboplatin [redacted] Where do you consider atezolizumab with gemcitabine and carboplatin will fit into the existing NICE pathway on bladder cancer? • Atezolizumab in combination with platinum-based chemotherapy will be used in the first-line setting for treatment of adult patients with locally advanced or metastatic UC 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 if you think that the proposed remit and scope may need changing in order to meet these aims.	questions for consultation. Please see the responses in the comparator section above. Please see the responses in the outcomes section above. The committee will consider the evidence base submitted by the company and will appraise to technology in line with the marketing authorisation. The committee will consider relevant subgroups, if evidence allows. No changes have been made.

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		• No equality issues have been identified Do you consider atezolizumab with gemcitabine and carboplatin 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)? • Atezolizumab with platinum-based chemotherapy is considered a step-change in the management of the condition as outlined in comment in the innovation section Do you consider that the use of atezolizumab with gemcitabine and carboplatin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? • No comment Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. [redacted] 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. • No barriers to adoption are expected Would it be appropriate to use the cost comparison methodology for this topic? • Cost effectiveness analysis is the most appropriate method for this appraisal Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?	Your comment on the pathway has been noted. Your comment on equality issues has been noted. Please see the responses in the innovation section above. Thank you for your response. The committee will consider the evidence base submitted by the company.

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		• As outlined in comment in the innovation section, atezolizumab is clinically superior to the comparators which represent the current standard of care • It is anticipated that the resource use for atezolizumab will be similar to the comparators Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? • Yes Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? • [redacted]	Thank you for your response. Thank you for your response. The committee will consider the evidence base submitted by the company. Thank you for your response. Please see the responses in the timing section above.
	Janssen	No comment	Thank you for your response.

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