NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Durvalumab with tremelimumab for untreated metastatic urothelial cancer

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of durvalumab with tremelimumab within its marketing authorisation for untreated metastatic urothelial cancer**.**

Background

Urothelial carcinoma is cancer of the transitional cells which form the inner lining of the bladder, urethra, ureter, or renal pelvis. Urothelial carcinoma is most common in the bladder, and accounts for 90% of bladder cancers[1]. Urothelial carcinomas can be described as non-invasive or invasive depending on how far the carcinomas invade the tissues. Non-invasive urothelial carcinomas can be further split into papillary carcinomas or flat carcinomas. Papillary carcinomas often grow towards the hollow part of the organ (for example bladder and ureter), without going into deeper layers. Flat carcinomas remain in the inner layers. Both papillary and flat carcinomas can become invasive.

In 2016, 8,500 new bladder cancers were diagnosed in England[2]. 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[3]. About a quarter of bladder cancers are diagnosed at a late stage[4].The majority of cases are in those over the age of 60 but can also affect young people too.

People with locally advanced or metastatic urothelial cancer may have surgery and/or radiotherapy. Chemotherapy may be given before (neoadjuvant) or after surgery and/or radiotherapy in an attempt to improve cure rates. If the cancer is too advanced for surgery/radiotherapy or has recurred after these treatments, chemotherapy can be used to improve quality of life and survival. NICE guideline NG2 recommends cisplatin-based regimens (such as gemcitabine plus cisplatin or accelerated [high dose] methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] plus granulocyte stimulating factor [G-CSF]) for untreated disease. Carboplatin plus gemcitabine may be considered for untreated disease if cisplatin is unsuitable. In people for whom cisplatin is unsuitable, and their tumours express PD-L1 at a level of 5% or more, NICE technology appraisal 492 recommends atezolizumab within the Cancer Drugs Fund. Where cisplatin is unsuitable and tumours express PD-L1 with a combined positive score of 10 or more, NICE technology appraisal 522 recommends pembrolizumab within the Cancer Drugs Fund.

The technology

Durvalumab (Imfinzi, AstraZeneca) is a human monoclonal antibody directed against programmed cell death ligand-1 (PD-L1). Durvalumab blocks PD-L1 interaction with both PD-1 and CD80 on T cells, countering the tumour's immune-evading tactics and activating the patient's immune system to attack the cancer. It is administered intravenously.

Tremelimumab (brand name unknown, AstraZeneca) is a human monoclonal antibody directed against cytotoxic T-lymphocyte-associated protein 4 (CTLA4). By blocking the activity of CTLA-4, tremelimumab aim to stimulate and activate the T cell and boosts the immune response against cancer cells. It is administrated intravenously.

Durvalumab with tremelimumab do not currently have a marketing authorisation in the UK for untreated urothelial cancer. It has been studied in a 3-arm clinical trial in people with unresectable stage IV urothelial cancer compared with standard of care and with durvalumab monotherapy.

Intervention(s)	Durvalumab with tremelimumab
Population(s)	People with untreated metastatic urothelial cancer
Comparators	People for whom cisplatin-based chemotherapy is suitable: • Gemcitabine plus cisplatin • Accelerated methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) plus granulocyte-colony stimulating factor (G-CSF) People for whom cisplatin-based chemotherapy is unsuitable: • Gemcitabine plus carboplatin • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention or comparator technologies will be taken into account. The economic modelling should include the costs associated with any diagnostic testing in people with urothelial cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	If the evidence allows, consideration will be given to subgroups based on the biological marker PD-L1. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Atezolizumab for untreated locally advanced or metastatic urothelial carcinoma when cisplatin is unsuitable. NICE technology appraisal guidance 492. Review date December 2020. Pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable. NICE technology appraisal guidance 522. Review date November 2019. **Appraisals in development:** Durvalumab for untreated PD-L1 positive metastatic urothelial cancer' NICE technology appraisals guidance [ID1169]. Publication date to be confirmed 'Erdafitinib for treating metastatic or unresectable FGFR-positive urothelial cancer'. NICE technology appraisal

	guidance [ID1333] Publication date to be confirmed **Related Guidelines:** Bladder cancer: diagnosis and management (2015) NICE guideline 2. Review date 2019. Improving outcomes in urological cancers (2002) NICE cancer service guidance. Review date March 2020. **Related Interventional Procedures:** Electrically-stimulated intravesical chemotherapy for superficial bladder cancer (2008). NICE interventional procedure guidance 277. Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer (2007). NICE interventional procedure guidance 235. **Related Quality Standards:** Bladder cancer (2015) NICE quality standard. **Related NICE Pathways:** Bladder cancer (2018) NICE Pathway
Related National Policy	NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Chapter 105. Specialist cancer services (adults). Department of Health (2016) NHS outcomes framework 2016 to 2017. Department of Health (2014) The national cancer strategy: 4th annual report NHS England (2013) B14/S/a 2013/14 NHS standard contract for cancer: specialised kidney, bladder and prostate cancer services (adult)

Questions for consultation

How would durvalumab with tremelimumab be used in clinical practice in the NHS for urothelial cancer?

- Would it be used only for metastatic disease in line with the clinical trial or would it be used for locally advanced disease too?

Have all relevant comparators for durvalumab with tremelimumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for locally advanced or metastatic urothelial cancer?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom durvalumab with tremelimumab are expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider durvalumab with tremelimumab will fit into the existing NICE Pathway on Bladder cancer?

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. 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 durvalumab with tremelimumab 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.

Do you consider durvalumab with tremelimumab 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)?

Do you consider that the use of durvalumab with tremelimumab 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.

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.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Cancer Research UK (2015) Types of bladder cancer. Accessed August 2018.

2. Office for National Statistics (2018) Cancer Registration Statistics, England: 2016. Accessed August 2018.

3. Cancer Research UK (2016) Bladder cancer incidence statistics. Accessed August 2018.

4. Cancer Research UK (2016) Bladder cancer incidence statistics. Accessed September 2018.

