NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pembrolizumab with chemotherapy for treating advanced or metastatic urothelial cancer

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab with chemotherapy within its marketing authorisation for treating advanced or 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 approximately 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, and is the 10th most common cancer in the UK[3]. The majority of new cases are in those over the age of 75 but can also affect young people too. 72% of bladder cancer cases in the UK are in males, and 28% are in females[4]. Smoking is a major factor in the cause of bladder cancer.

People with muscle invasive urothelial cancer may have surgery and/or radiotherapy. Chemotherapy may be given before (neoadjuvant) 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

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology. It is administered intravenously.

Pembrolizumab does not currently have a marketing authorisation in the UK with platinum-based combination chemotherapy for treating advanced or metastatic urothelial cancer. It has been studied in clinical trials alone and in combination with gemcitabine and cisplatin or carboplatin in people with advanced or metastatic urothelial cancer that has not been treated with chemotherapy.

Pembrolizumab as monotherapy has marketing authorisation for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy, and for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Intervention(s)	Pembrolizumab with platinum-based combination chemotherapy
Population(s)	People with advanced or 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, comparator and subsequent treatment technologies will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered: • people who have not had previous treatment • people who have had previous treatment. 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 PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (2017). NICE Technology Appraisal 492. Review date: December 2020. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (2018). NICE Technology Appraisal 525. Review date: June 2021. Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy (2018). NICE Technology Appraisal 530. Review date: July 2021. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (2018). NICE Technology Appraisal 522. Review date: November 2019. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (2018). NICE Technology Appraisal 519.

	Review date to be confirmed. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (2013). NICE Technology Appraisal 272. Transferred to the static list November 2015. **Appraisals in development (including suspended appraisals):** Erdafitinib for treating metastatic or unresectable FGFR-positive urothelial cancer. NICE technology appraisals guidance [ID1333]. Publication expected: July 2020. Durvalumab for treating metastatic urothelial bladder cancer after chemotherapy. Suspended NICE technology appraisals guidance [ID1172]. Durvalumab for untreated PD-L1 positive metastatic urothelial bladder cancer. NICE technology appraisals guidance [ID1169]. Publication date to be confirmed. Durvalumab with tremelimumab for untreated PD-L1-positive urothelial bladder cancer. NICE technology appraisals guidance [ID1335]. Publication date to be confirmed. **Related Guidelines:** Bladder cancer: diagnosis and management (2015) NICE guideline NG2. Improving outcomes in urological cancers (2002) NICE cancer service guidance. Published September 2002. **Related Interventional Procedures:** Laparoscopic cystectomy NICE interventional procedure guidance 287. Published February 2009. Electrically-stimulated intravesical chemotherapy for superficial bladder cancer NICE interventional procedure guidance 277. Published November 2008 Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer NICE interventional procedure guidance 235. Published October 2007. **Related Quality Standards:** Bladder cancer NICE quality standard. Published December 2015. **Related NICE Pathways:** Bladder cancer (2019) NICE Pathway.
Related National	NHS England (2019) Specialised kidney, bladder and

Policy	prostate cancer services (adults) The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 1. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for pembrolizumab with platinum-based combination chemotherapy been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for urothelial cancer?

Should best supportive care be included as a comparator? If so, how should best supportive care be defined? Do any patients receive best supportive care in clinical practice?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' (people who have and have not had previous treatment) appropriate? Is clinical and cost effectiveness likely to differ based on previous treatment?

Are there any other subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider pembrolizumab with platinum-based combination chemotherapy will fit into the existing NICE pathway '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 pembrolizumab with platinum-based combination chemotherapy 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 pembrolizumab with platinum-based combination chemotherapy 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 pembrolizumab with platinum-based combination chemotherapy 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 (2018) Types of bladder cancer. Accessed March 2019.

2. Office for National Statistics (2018) Cancer Registration Statistics, England: 2016. Accessed March 2019.

3. Cancer Research UK (2018) Bladder cancer statistics. Accessed March 2019.

4. Cancer Research UK (2018) Bladder cancer incidence statistics. Accessed March 2019.

