

**EVIDENCE BRIEFING
SEPTEMBER 2018**

**Pembrolizumab in addition to chemotherapy for
advanced or metastatic urothelial cancer - first
line**

NIHRIO ID	24238	NICE ID	10033
Developer/Company	Merck Sharp & Dohme Ltd (MSD)	UKPS ID	647714

Licensing and market availability plans	Currently in phase III clinical trials.
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SUMMARY

Pembrolizumab, in addition to chemotherapy, is in clinical development for adults with urothelial cancer that is advanced or metastatic. Urothelial cancer occurs on the lining of the bladder and other parts of the urinary system. In advanced urothelial cancer, the cancer has grown into deeper layers including connective tissue or muscle. In metastatic urothelial cancer, the cancer has spread to other parts of the body, such as the liver or bones. Urothelial cancer usually occurs in patients aged 60 years and older, and many patients have other medical conditions, or are not fit enough to be given certain treatments.

Pembrolizumab is a drug administered by intravenous infusion which stimulates the body's own immune system to fight cancer cells. If licensed, pembrolizumab in addition to chemotherapy could provide an additional or alternative treatment option to patients who currently have limited treatment options.

PROPOSED INDICATION

Advanced or metastatic urothelial cancer in adults - first line¹

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.²

In the phase III trial of participants with advanced or metastatic urothelial carcinoma (MK-3475-361/KEYNOTE-361; NCT02853305), pembrolizumab is administered by intravenous infusion (IV) at 200mg on day 1 of each 3-week cycle in addition to one of two chemotherapy regimens: 1) cisplatin 70 mg/m² IV on day 1 (or day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine IV infusion at 1,000 mg/m² on day 1 and day 8 of each 3-week cycle, or 2) carboplatin area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) IV on day 1 (or day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine IV infusion at 1,000 mg/m² on day 1 and day 8 of each 3-week cycle. Duration of treatment is for a maximum of 35 doses.¹

INNOVATION AND/OR ADVANTAGES

The phase III trial KEYNOTE-361 (NCT02853305) compares pembrolizumab monotherapy with pembrolizumab in addition to chemotherapy and with chemotherapy alone. Results from this trial may determine if pembrolizumab in addition to chemotherapy is effective in treating PD-L1 negative urothelial tumours, or tumours with low levels of PD-L1. This would be an advantage over pembrolizumab monotherapy, which is currently recommended only for tumours with high levels of PD-L1.³ Only 5%-15% of patients with advanced bladder cancer attain long-term survival with standard first-line cisplatin-based chemotherapy. Programmed death 1 (PD-1)/PD-L1 inhibitors have proven effective in recurrent, advanced urothelial cancer. Emerging data suggest these agents may also be useful in the first-line setting.⁴

Cisplatin-based combination chemotherapy is the standard of care first line treatment for metastatic urothelial cancer. Although response rates to these regimens are high, they are rarely durable, and median overall survival is only 12 to 15 months. Treatment options for patients unfit for cisplatin due to poor performance status, impaired renal function or comorbidities have been quite limited. As most people who have urothelial cancer are over 60 years old, a significant number of patients are deemed cisplatin-unfit.⁵ Pembrolizumab in addition to carboplatin-based chemotherapy may provide another treatment option for patients who are cisplatin-unfit.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is licensed in the EU/UK as a monotherapy for the treatment of:²

- advanced (unresectable or metastatic) melanoma in adults
- metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a $\geq 50\%$ tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations – first line
- locally advanced or metastatic NSCLC in adults whose tumour express PD-L1 with a $\geq 1\%$ TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.
- adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- 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

The most common side effects of pembrolizumab (affecting more than one in ten people) include diarrhoea, nausea, rash, pruritus and fatigue.²

The combination of pembrolizumab and chemotherapy is also in development for:

- Non-small-cell lung cancer (squamous and non-squamous)
- Head and neck cancer
- Sarcoma
- Oesophageal cancer
- Triple-negative breast cancer
- Gastric cancer and gastro-oesophageal junction cancer
- Cervical cancer

PATIENT GROUP

DISEASE BACKGROUND

Urothelial cancer (also called transitional cell carcinoma) occurs on the urothelium (the lining on the inside of the bladder, ureters and urethra and the renal pelvis).⁶ Around 90% of bladder cancers in the UK are urothelial cancer.⁷ Early urothelial cancer (non-muscle-invasive) affects only the lining of the urothelium, but in advanced urothelial cancer the cancer has grown into deeper layers including connective tissue or muscle. Metastatic urothelial cancer occurs when the cancer has spread to other parts of the body, such as the liver or bones.⁸

Urothelial cancer usually takes a long time to develop, and is most common in people over 60 years old. It is also more common in men than women, but this may be because more men have smoked or been exposed to chemicals at work in recent decades.⁹ The main symptom of urothelial cancer is blood in the urine, but symptoms may only appear once the cancer grows larger or into the deeper layers of the bladder wall.⁶ Other symptoms may include urinary frequency or urgency, whilst symptoms of metastatic urothelial cancer include loss of appetite, weight loss or change in bowel habits.⁶

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2016 there were 8,437 registrations of newly-diagnosed bladder cancer (ICD-10 C67).¹⁰ Statistics from Cancer Research UK report that in UK in 2014 there were 10,057 observed cases of bladder cancer, an age-standardised rate of 20.44 per 100,000, and predict that the number of cases will increase to 10,386 cases in 2035, with a decrease in the age-standardised rate to 13.43 per 100,000.¹¹

In England and Wales in 2017 there were 5,014 deaths with malignant neoplasm of the bladder (ICD-10 code C67) recorded as the underlying cause.¹² The latest published survival statistics for bladder cancer in England (2016, patients diagnosed in 2011-2015) report 1-year survival rate of 75.0% and 5-year survival rate of 56.4% (age-standardised).¹³ Figures reported by Cancer Research UK suggest that 5-year survival rates for advanced cancer (stage 3) are around 30% for men and 15% for women, and for metastatic cancer (stage 4) the 5-year survival rate is around 10%.¹⁴

In England in 2016/2017 there were 70,649 hospital admissions with a primary diagnosis of malignant neoplasm of bladder (ICD-10 code C67), resulting in 109,718 bed days and 40,727 day cases.¹⁵

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

For most people with advanced urothelial cancer, the treatment aims to slow the cancer and reduce the symptoms.¹⁶ Treatments for locally advanced urothelial cancer are surgery (cystectomy) or radiotherapy on the bladder and lymph nodes.¹⁷ Chemotherapy may be given before or after surgery, before radiotherapy or during radiotherapy (chemoradiotherapy).¹⁸

For advanced or metastatic urothelial cancer, treatment may include chemotherapy to shrink the cancer or keep it under control. Older people who are less fit might find the side effects of intensive chemotherapy too severe, but it is possible to have less intensive chemotherapy.¹⁹ Radiotherapy may be offered if the cancer is causing symptoms such as pain; it will not cure the cancer but can improve the quality of life and help to keep the cancer under control in the area of the body that has been treated.²⁰ Surgery may be offered to remove the cancer from the bladder if it is causing symptoms (TURBT operation), or if the cancer is blocking the ureters or kidneys.

CURRENT TREATMENT OPTIONS

NICE recommends the following as first line chemotherapy for patients with locally advanced or metastatic bladder cancer:

- Cisplatin-based chemotherapy regimen such as cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) in combination with granulocyte-colony stimulating factor (G-CSF) for people who are otherwise physically fit (have an ECOG performance status of 0 or 1) and have adequate renal function.²¹
- Carboplatin in combination with gemcitabine if a cisplatin-based chemotherapy regimen is unsuitable, for example because of poor ECOG performance status, inadequate renal function or comorbidity.

Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial cancer in adults when cisplatin-containing chemotherapy is unsuitable only if:

- their tumours express PD-L1 with a combined positive score of 10 or more
- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses, and
- the conditions of the managed access agreement for pembrolizumab are followed.³

Atezolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial cancer in adults when cisplatin-containing chemotherapy is unsuitable, only if:

- their tumours express PD-L1 at a level of 5% or more, and
- the conditions of the managed access agreement for atezolizumab are followed.²²

PLACE OF TECHNOLOGY

If licenced, pembrolizumab in addition to chemotherapy may offer an additional first line treatment option for patients with advanced or metastatic urothelial cancer.

CLINICAL TRIAL INFORMATION

Trial	MK-3475-361/KEYNOTE-361, NCT02853305 , EudraCT 2015-005731-41; pembrolizumab vs pembrolizumab + chemotherapy vs chemotherapy; phase III
Sponsor	Merck Sharp & Dohme Ltd (MSD)
Status	Ongoing
Source of Information	Trial registry ¹ , search portal ²³
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled
Participants	n=990 (planned); aged 18 yrs and older; urothelial cancer; advanced/unresectable or metastatic; no prior systemic chemotherapy (neoadjuvant platinum-based chemotherapy with recurrence > 12 months after completion is allowed; adjuvant platinum-based chemotherapy following radical cystectomy with recurrence >12 months from completion of therapy is permitted) ⁴
Schedule	Randomised to: <ul style="list-style-type: none"> • Arm 1: pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-wk cycle • Arm 2: pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-wk cycle plus either 1) cisplatin 70 mg/m² IV on day 1 (or day 2 if required per local guidelines) of each 3-wk cycle plus gemcitabine IV infusion at 1,000 mg/m² on day 1 and day 8 of each 3-wk cycle, or 2) carboplatin area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) IV on day 1 (or day 2 if required per local guidelines)

	<p>of each 3-wk cycle plus gemcitabine IV infusion at 1,000 mg/m² on day 1 and day 8 of each 3-wk cycle.</p> <ul style="list-style-type: none"> • Arm 3: either 1) cisplatin 70 mg/m² IV on day 1 (or day 2 if required per local guidelines) of each 3-wk cycle plus gemcitabine IV infusion at 1,000 mg/m² on day 1 and day 8 of each 3-wk cycle, or 2) carboplatin AUC 5 (or AUC 4.5 if required per local guidelines) IV on day 1 (or day 2 if required per local guidelines) of each 3-wk cycle plus gemcitabine IV infusion at 1,000 mg/m² on day 1 and day 8 of each 3-wk cycle.
Follow-up	Active treatment up to a maximum of 35 doses, follow-up 24 mths
Primary Outcomes	Progression-free survival (PFS) [Time Frame: up to approx 24 mths] Overall survival [Time Frame: up to approx 24 mths]
Secondary Outcomes	<ul style="list-style-type: none"> • Number of participants who experience an adverse event (AE) [Time Frame: up to approx 27 mths] • Number of participants who discontinue study drug due to AE [Time Frame: up to approx 24 mths] • Objective response rate using RECIST 1.1 [Time Frame: up to approx 24 mths] • Disease control rate using RECIST 1.1 [Time Frame: up to approx 24 mths] • PFS using RECIST 1.1 at milestone timepoints [Time Frame: at 6, 12, 18 and 24 mths] • Duration of response using RECIST 1.1 [Time Frame: up to approx 24 mths] • Change from baseline in health-related Quality of Life score on the EORTC QLQ-30 [Time Frame: Baseline and 24 mths]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as May 2020

ESTIMATED COST

Pembrolizumab is already marketed in the UK; a 100mg/4ml concentrate for solution for infusion vial (25mg/ml) costs £2,630, and 50mg powder for concentrate for solution for infusion vial costs £1,315.²⁴

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA522). Updated July 2018.
- NICE technology appraisal guidance. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA492). Updated July 2018.
- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS06). December 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

OTHER GUIDANCE

- European Association of Urology. Muscle-invasive and Metastatic Bladder Cancer. 2018.²⁵
- European Society for Medical Oncology (ESMO). Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. 2014.²⁶

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