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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Durvalumab in combination with tremelimumab and chemotherapy for unresectable, locally advanced or metastatic urothelial cancer

NIHRIO ID	26780	**NICE ID**	10301
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Durvalumab in combination with tremelimumab is in clinical development for patients with unresectable, locally advanced or metastatic urothelial cancer (UC). UC, a subset of bladder cancer, occurs on the lining of the renal pelvis, ureter, bladder and urethra, and other parts of the urinary system and the most common symptom is blood in the urine. Metastatic UC occurs when the cancer has spread to other parts of the body, such as the liver or bones. Despite chemotherapy, most patients with metastatic bladder cancer experience disease progression and therefore additional treatment with immunotherapy may improve clinical outcomes.

Durvalumab and tremelimumab are immunotherapies, meaning they target the immune system. Durvalumab binds to a protein called PD-L1 to prevent it from binding its target (PD-1). In doing so, durvalumab allows immune cells, called T cells, to be activated so that they can destroy the cancer cells. Tremelimumab binds a protein called CTLA4 on T-cells, activating them and allowing them to kill cancer cells. Durvalumab and tremelimumab are administered intravenously. If licensed, durvalumab in combination with tremelimumab and chemotherapy will offer an additional treatment option for patients with unresectable, locally advanced or metastatic UC.

PROPOSED INDICATION

Unresectable, locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal, pelvis, ureters, urinary bladder and urethra).[1]

TECHNOLOGY

DESCRIPTION

Durvalumab is an Fc optimised monoclonal antibody directed against programmed cell death-1 ligand 1 (PD-L1), with potential immune checkpoint inhibitory and antineoplastic activities. Upon intravenous administration, durvalumab binds to PD-L1, thereby blocking its binding to and activation of its receptor programmed death 1 (PD-1) expressed on activated T cells. This may reverse T-cell inactivation and activate the immune system to exert a cytotoxic T-lymphocyte (CTL) response against PD-L1-expressing tumour cells. PD-L1, a member of the B7 protein superfamily, is overexpressed on certain tumour cell types and on various tumour-infiltrating immune cells. PD-L1 binding to PD-1 on T cells suppresses the immune system and results in increased immune evasion. The Fc region of durvalumab is modified in such a way that it does not induce either antibody-dependent cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).[2,3]

Tremelimumab is a human immunoglobulin (Ig) G2 monoclonal antibody directed against the human T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA4), with potential immune checkpoint inhibitory and antineoplastic activities. Tremelimumab binds to CTLA4 on activated T-lymphocytes and blocks the binding of the antigen-presenting cell ligands B7-1 (CD80) and B7-2 (CD86) to CTLA4, resulting in inhibition of CTLA4-mediated downregulation of T-cell activation. This promotes the interaction of B7-1 and B7-2 with another T-cell surface receptor protein CD28, and results in a B7-CD28-mediated T-cell activation that is unopposed by CTLA4-mediated inhibition. This leads to a cytotoxic T-lymphocyte (CTL)-mediated immune response against cancer cells. CTLA4, an inhibitory receptor and member of the immunoglobulin superfamily, plays a key role in the downregulation of the immune system.[4]

In the phase III trial, NILE (NCT03682068), durvalumab and tremelimumab will be administered every three weeks in concurrence with chemotherapy, followed by durvalumab monotherapy every four weeks. Tremelimumab will be provided for 4 cycles. All patients will receive one of the following standard of care chemotherapy regimens every 3 weeks for 6 cycles: cisplatin + gemcitabine, or if the patient is cisplatin-ineligible, carboplatin + gemcitabine.[1]

INNOVATION AND/OR ADVANTAGES

Durvalumab is currently not licensed in combination in the EU/UK for any indication;[5] tremelimumab is not currently licensed in the EU/UK for any indication. Therefore, offering durvalumab in combination with tremelimumab and chemotherapy for urothelial cancer, would be a new indication for both drugs, as well as offering a novel combination.

Despite high response rates to standard care for locally advanced or metastatic urothelial cancer chemotherapy (gemcitabine +cisplatin or gemcitabine + carboplatin for patients who are cisplatin-ineligible) most patients experience disease progression. Novel strategies like combining chemotherapy and immunotherapy offer hope for improving clinical outcomes. Durvalumab is a selective, high affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. Tremelimumab is a human IgG2 mAb directed against CTLA-4. The mechanisms of action of PD-1 and CTLA-4 are non-redundant, so targeting both checkpoint pathways may have additive or synergistic efficacy compared to monotherapy.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Durvalumab in combination with tremelimumab and chemotherapy does not currently have marketing authorisation in the EU/UK for any indication.

Durvalumab as a monotherapy is licensed in the EU/UK for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥1 of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.[5]

Common or very common side effects include: cough; diarrhoea; dysphonia; dysuria; fever; flank pain; gastrointestinal discomfort; gastrointestinal disorders; hyperthyroidism; hypothyroidism; increased risk of infection; infusion related reaction; myalgia; night sweats; peripheral oedema; respiratory disorders; skin reactions; thyroiditis.[2]

Durvalumab is currently in 359 phase II/III studies. Examples include the treatment of:[7]

- Stage III NSCLC
- Non-muscle-invasive bladder cancer
- Hepatocellular carcinoma
- Squamous cell carcinoma of the head and neck
- Solid tumours

Tremelimumab is not currently licensed in the UK.

Durvalumab in combination with tremelimumab and chemotherapy is currently in 42 phase II/III studies. Examples include the treatment of:[8]

- Ovarian cancer
- Lung cancer
- Biliary tract cancer
- NSCLC

PATIENT GROUP

DISEASE BACKGROUND

Urothelial cancer (UC), also called transitional cell carcinoma (TCC), begins in the transitional cells that line the renal pelvis, ureters, bladder and urethra, and some other organs). These cells can change shape and stretch without breaking apart.[9] When the bladder is empty, the transitional cells are all bunched together. As the bladder fills with urine the cells stretch out into a single layer. These cells come into contact with waste products in the urine that may cause cancer, such as chemicals from cigarette smoke.[10] UC accounts for about 90% of all bladder cancers and 13% of kidney cancers (of which 7% begin in the renal pelvis, and 5% in the ureter).[11]

Locally advanced bladder cancer indicates that the cancer has grown through the bladder wall or has spread into lymph nodes.[12] Metastatic cancer is when the cancer has spread from the place where they first formed to another part of the body. In metastasis, cancer cells break away from the original (primary) tumour, travel through the blood or lymph system, and form a new tumour in other organs or tissues of the body.[13]

Levels of PD-L1 expression have been shown to correlate with bladder cancer severity and outcome. It has been found that tumours that express higher levels of PD-L1 (on tumour cells)

are more likely to be considered high-grade, and patients experience higher frequencies of postoperative recurrence and poorer survival in organ-confined disease.[14]

The main risk factors for UC include: smoking, bladder infections, medical conditions such as systemic sclerosis, as well as prior bladder cancer and family history.[15] The most common symptom of UC is blood in the urine, but this may only appear once the cancer grows larger or into the deeper layers of the bladder wall for both men and women. Other symptoms may include increased frequency/urgency/pain when passing urine, weight loss, back/lower tummy/bone pain, fatigue and illness.[16]

CLINICAL NEED AND BURDEN OF DISEASE

UC accounts for about 90% of all bladder cancers and 13% of kidney cancers (of which 7% begin in the renal pelvis, and 5% in the ureter).[11] Between 2015 and 2017, there were around 10,200 new bladder cancer cases and 13,056 new kidney cancer cases in the UK every year. In the UK, about 90% of bladder cancers are urothelial cancer type.[17] Incidence rates for bladder cancer and kidney cancer in the UK were highest in people aged 85 to 89 (2015-2017).[17,18]

In England in 2017, there were 8,686 new registrations for malignant neoplasm of bladder, 692 for malignant neoplasm of renal pelvis (ICD-10 code C65), and 596 for malignant neoplasm of ureter (ICD-10 code C66). The direct age-standardised rates per 100,000 population were 27.6 among males and 8.2 among females for malignant neoplasm of bladder. The direct age standardised rates were low for malignant neoplasm of renal pelvis (1.8 for males and 1.0 for females) and malignant neoplasm of ureter (1.7 for males and 0.7 for females).[19]

In 2018-2019, the finished consultant episodes (FCEs) in England for malignant neoplasm of the bladder as primary diagnosis were 73,789, resulting in 69,198 admissions and 100,777 FCE bed days. There were 1,533 FCEs for malignant neoplasm of renal pelvis (1,386 admissions and 3,219 bed days); and 2,445 FCEs for malignant neoplasm of ureter (2,157 admission and 5,579 bed days).[20]

The European age-standardised mortality rate in the UK is projected to decrease by 2035 to 9.39 per 100,000 (7,771 projected deaths) for bladder cancer and 7.61 per 100,000 (5,739 projected deaths) for kidney cancer.[21] Between 2015 and 2017, there were around 4,500 kidney cancer deaths in the UK every year.[18] In 2019, there were 5,014 deaths (3,441 male and 1,573 female) in England and Wales recorded with malignant neoplasm of bladder as the cause (ICD-10 code C67).[22] The one-year age-standardised net cancer survival for stage IV bladder cancer in adults was 35.7% (2013-2017). The one-year age-standardised net cancer survival for stage IV kidney cancer was 38.7% and 5-year age-standardised survival was 12.4%.[23]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment options for urothelial cancer depends on how advanced the cancer is. A specialist urology multidisciplinary team (composing of urologists, pathologists, radiologists and a specialist clinical nurse) is normally employed throughout the treatment.[24]

For locally advanced or metastatic urothelial cancer, treatment may include chemotherapy, immunotherapy or treatment to relieve cancer symptoms. If the cancer is too advanced, palliative care may be offered to manage pain.[24] The role of first-line chemotherapy should be discussed with patients who have locally advanced or metastatic bladder cancer. For people having first-line chemotherapy for locally advanced or metastatic bladder cancer: regular

clinical and radiological monitoring ought to be carried out, symptoms of disease and treatment-related toxicity need to be actively managed and chemotherapy needs to be stopped if excessive toxicity or disease progression.[25]

CURRENT TREATMENT OPTIONS

According to the current NICE treatment pathway, current first-line treatment options for locally advanced or metastatic bladder cancer include:[26]

- Cisplatin-based chemotherapy regimen
- Carboplatin in combination with gemcitabine chemotherapy if cisplatin-based chemotherapy is unsuitable

For PD-L1 positive locally advanced or metastatic UC the following are also recommended:[26]

- Pembrolizumab
- Atezolizumab

PLACE OF TECHNOLOGY

If licensed, durvalumab in combination with tremelimumab will offer an additional treatment option for adult patients with unresectable, locally advanced or metastatic UC.[1]

CLINICAL TRIAL INFORMATION

Trial	**NILE** (NCT03682068), A Phase III, Randomized, Open-Label, Controlled, Multi-Center, Global Study of First-Line Durvalumab in Combination With Standard of Care Chemotherapy and Durvalumab in Combination With Tremelimumab and Standard of Care Chemotherapy Versus Standard of Care Chemotherapy Alone in Patients With Unresectable Locally Advanced or Metastatic Urothelial Cancer. **Phase III** - recruiting **Location(s):** Europe (not UK), Canada, USA and other countries **Estimated primary completion date:** April 2023
Trial design	Randomised, parallel assignment, open label
Population	N = 1434 (planned); adults aged 18 to 130 years old; unresectable, locally advanced or metastatic transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra); not been previously treated with first-line chemotherapy.
Intervention(s)	- Durvalumab every 3 weeks in concurrence with chemotherapy, followed by durvalumab monotherapy every 4 weeks. All patients will receive one of the following standard of care chemotherapy regimens every 3 weeks for 6 cycles: cisplatin + gemcitabine OR carboplatin + gemcitabine - Durvalumab and Tremelimumab every 3 weeks in concurrence with chemotherapy, followed by durvalumab monotherapy every 4 weeks. Tremelimumab will be provided for 4 cycles. All

	patients will receive one of the following standard of care chemotherapy regimens every 3 weeks for 6 cycles: cisplatin + gemcitabine OR carboplatin + gemcitabine
Comparator(s)	Cisplatin + gemcitabine OR carboplatin + gemcitabine
Outcome(s)	Overall Survival [Time frame: approximately 5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of durvalumab in combination with tremelimumab is not yet known.

Durvalumab at 120mg/2.4mL concentrate costs £592.00 (list price); 500mg/10mL concentrate costs £2466.00 (list price).[2]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Atezolizumab with gemcitabine and carboplatin for treating metastatic urothelial bladder cancer (ID1206). Expected July 2021.
- NICE technology appraisal guidance. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing therapy (TA525). June 2018.
- NICE technology appraisal guidance. Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA492). July 2018.
- NICE technology appraisal guidance. Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy (TA530). July 2018
- NICE technology appraisal guidance. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA522). July 2018.
- NICE technology appraisal guidance. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing therapy (TA519). April 2018.
- NICE technology appraisal guidance. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272). January 2013.
- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS106). December 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Specialised kidney, bladder and prostate cancer services (Adults). Service Specification (170114S). February 2019.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- European Association of Urology. Guidelines on muscle-invasive and metastatic bladder cancer. 2020.[27]
- ESMO bladder cancer practice guidelines for diagnosis, treatment and follow-up. 2014.[28]

ADDITIONAL INFORMATION

AstraZeneca did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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