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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

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

NIHRIO ID	28446	**NICE ID**	10331
Developer/Company	Roche Products Ltd	**UKPS ID**	645026

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

SUMMARY

Atezolizumab is in clinical development, in combination with platinum-based chemotherapy, for the treatment of patients with locally advanced or metastatic urothelial cancer, who have received no prior systemic therapy (a drug which travels through the bloodstream and affects the whole body). Urothelial cancer, a subset of bladder 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. Metastatic urothelial cancer occurs when the cancer has spread to other parts of the body, such as the liver or bones.

Atezolizumab, administered by intravenous infusion, is designed to stimulate the body's own immune system to fight cancer cells. If licensed, atezolizumab will provide an additional option for the first-line treatment of locally advanced or metastatic urothelial cancer in patients who are both eligible and ineligible for cisplatin chemotherapy.

PROPOSED INDICATION

Atezolizumab (Tecentriq) in combination with platinum-based chemotherapy, for the first-line treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC). [1,2]

TECHNOLOGY

DESCRIPTION

Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody immune checkpoint inhibitor, which binds directly to programmed death ligand 1 (PD-L1) on tumour cells and tumour infiltrating immune cells in the tumour microenvironment (TME). Atezolizumab binds PD-L1 and blocks the interaction with programmed death 1 (PD-1) and B7.1 receptors.[3,4]

PD-L1 is an immune checkpoint protein overexpressed on tumour cells and tumour infiltrating cells, which through binding to PD-1 and B7.1 receptors on T cells, deactivates the T cells cytotoxic activity. Binding of atezolizumab to PD-1 releases the PD-L1/PD-1 mediated inhibition of the immune response, reactivating the anti-tumour immune response without inducing antibody-dependent cellular cytotoxicity. Additionally, atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist, maintaining normal immune homeostasis in healthy tissues.[5]

Atezolizumab in combination with platinum-based chemotherapy is in clinical development for the treatment of patients with untreated locally advanced (T4b, any N; any T, N2-3) or metastatic (M1, stage IV) UC. In the phase III clinical trial (NCT02807636, IMvigor130) patients receive atezolizumab at a fixed dose of 1200 milligrams (mg) by intravenous (IV) infusion on day 1 of each 21-day cycle.[1]

INNOVATION AND/OR ADVANTAGES

Atezolizumab in combination with platinum-based chemotherapy is a novel treatment for advanced or metastatic. UC Results from the phase III clinical trial (IMvigor130; NCT02807636) concluded that adding atezolizumab to platinum-based chemotherapy for first-line treatment of metastatic urothelial cancer prolonged progression free survival compared to placebo alone.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab is currently indicated in the UK for the following:[5]

- As a monotherapy for the treatment of adult patients with locally advanced or metastatic UC; after prior platinum-containing chemotherapy, or for patients who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression $\geqslant$ 5%.
- In combination with bevacizumab, paclitaxel and carboplatinfor the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with epidermal growth factor recepetor (EGFR) mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.
- As monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-

positive NSCLC should also have received targeted therapies before receiving atezolizumab.
- In combination with nab-paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.
- In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

The most common side effects with atezolizumab when used on its own (which may affect more than 1 in 10 people) are tiredness, reduced appetite, nausea (feeling sick), vomiting, cough, difficulty breathing, diarrhoea, rash, fever, pain in the back, joints, muscles and bones, weakness, itching and urinary tract infection (infection of the structures that carry urine).[7]

Atezolizumab is currently in clinical development for the following cancer indications:

- In phase II for anal cancer, bladder cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, head & neck cancer, kidney cancer, leukaemia, lung cancer, lymphoma, melanoma, multiple myeloma, ovarian cancer, pancreatic cancer, penile cancer, prostate cancer, rectal cancer, soft tissue sarcoma, solid tumours and urothelial cancer.

- In phase III for bladder cancer, breast cancer, cervical cancer, hepatocellular carcinoma, lung cancer, melanoma, ovarian cancer, prostate cancer, renal cell carcinoma, urinary tract cancer, urothelial carcinoma.

PATIENT GROUP

DISEASE BACKGROUND

Urothelial cancer (transitional cell carcinoma) occurs on the urothelium (the lining on the inside of the bladder, ureters and urethra and the renal pelvis) and is a subset of bladder cancer. Urothelial cancer accounts for around 90% of bladder cancers in the UK.[8]

Cancer stage (referring to the extent of the cancer) can described using the TNM staging system:[9]

- T (TX-T4) refers to the size and extent of the main tumour. The higher the number after T, the larger the tumour or the more it has grown into nearby tissues.
- N (NX-N4) refers to the number of nearby lymph nodes that have cancer. The higher the number after the N, the more lymph nodes that contain cancer.
- M (MX-M1) refers to whether the cancer has metastasized. M0 indicates no metastases, while M1 indicates metastases has occurred.

Atezolizumab is indicated for locally advanced, metastatic urothelial carcinoma. Locally advanced (T4b, any N; or any T, N2-3) indicates the cancer has spread to the wall of the pelvis or abdomen, or there are cancer cells in more than one lymph node in, or just outside, the pelvis.[10] Metastatic (M1, Stage IV) indicates that the cancer has spread outside the pelvis to other parts of the body, such as the bones, lungs and liver.[10]

About 60% of new cases of UC are in people aged 75 and over. It is more common in men than women, however this may be due to the fact that more men have smoked or been exposed to chemicals at work in recent decades.[8] 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.[11]

The main symptom for UC is blood in the urine. Other symptoms include: increased frequency/urgency/pain of urine passing, weight loss, back/lower tummy/bone pain, fatigue and illness.[12]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016, bladder cancer was the 10th most common cancer in the UK, accounting for 3% of all new cancer cases.[13] In England in 2017, there were 8,686 new registrations for malignant neoplasm of bladder (ICD-10 code C67) and the direct age standardised rate per 100,000 population was 27.6 among males and 8.2 among females.[14] Using the 2018/19 England mid-year population estimates, this equates to 5,945 new cases in adult males and 1,843 new cases in adult females.[15]

The European-standardised incidence rate of bladder cancer in the UK is projected to decrease by 2035 from 20.44 per 100,000 in 2014 (equating to 10,057 observed cases) to 13.43 per 100,000 (equating to 10,386.38 projected cases).[16]

In England in 2018-2019, there were 73,789 finished consultant episodes (FCEs) for malignant neoplasm of the bladder as primary diagnosis (ICD-10 code C67) and 69,198 admissions resulting in 100,777 bed days and 41,236 day cases. Approximately 75% of these consultant episodes were for male patients.[17]

In 2017 in England and Wales, there were 5,014 deaths (3,441 male and 1,573 female) recorded with malignant neoplasm of bladder as the cause (ICD-10 code C67).[18] Between 2013 and 2017 in England, the one-year age-standardised net cancer survival for stage IV bladder cancer in adults was 35.7%, with no data recorded for the 5-year survival of stage IV bladder cancer.[19]

The European-standardised mortality rate of bladder cancer in the UK is projected to decrease by 2035 from 10.91 per 100,000 in 2014 (equating to 5,369 observed cases) to 9.39 per 100,000 (equating to 7,771 projected deaths).[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment options for urothelial cancer depend on how advanced the cancer is. A team of specialists composing of; urologists, pathologists, radiologists and a clinical nurse, is normally employed throughout the treatment.[21]

For locally advanced urothelial cancer, treatment aims to control the spread of the cancer and help to reduce any associated symptoms.[22] Treatment options include cystectomy (removing the bladder or lymph nodes), radiotherapy on the bladder and lymph nodes or immunotherapy.[23] Surgery is often followed by chemotherapy.[21,23] If the cancer is too advanced, palliative care may be offered to manage pain.[21]

CURRENT TREATMENT OPTIONS

Current first-line treatment options for locally advanced or metastatic bladder cancer include according to the NICE treatment pathway;[24]

- Chemotherapy (cisplatin or carboplatin based regimes) or,
- If treatment with cisplatin is unsuitable and the tumour is PD-L1 positive: pembrolizumab or atezolizumab (via the Cancer Drugs Fund)

PLACE OF TECHNOLOGY

If licensed atezolizumab, in combination with chemotherapy will offer an additional first-line treatment option for locally advanced or metastatic urothelial cancer.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**IMvigor130; NCT02807636; A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti–PD-L1 Antibody) as Monotherapy and in Combination With Platinum-Based Chemotherapy in Patients With Untreated Locally Advanced or Metastatic Urothelial Carcinoma.** **Phase III** **Locations(s): US, Canada, EU (including UK), and other countries.**
Trial design	Randomised, parallel assignment, double blinded (participant and investigator)
Population	N=1,200; Subjects with untreated locally advanced or metastatic urothelial carcinoma; aged 18 years and older.
Intervention(s)	• Atezolizumab IV infusion monotherapy • Atezolizumab IV infusion + platinum-based chemotherapy (Gemcitabine IV infusion + Carboplatin/Cisplatin IV infusion)
Comparator(s)	Placebo comparator: Placebo + platinum-based chemotherapy (Gemcitabine IV infusion + Carboplatin/Cisplatin IV infusion)
Outcome(s)	• **Progression-Free Survival (PFS)** Assessed by Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in Participants Treated with Atezolizumab Combination Therapy Compared With Placebo Arm [Time Frame: Baseline up to disease progression, death, or loss of follow-up, whichever occurs first (assessed at baseline, every 9 weeks for 54 weeks and every 12 weeks thereafter up to 44 months)] • **Overall Survival (OS)** [Time Frame: Baseline until death due to any cause (up to 44 months)] • **Percentage of Participants with Adverse Events (AEs)** Assessed Using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [Time Frame: Baseline up to 44 months]
Results (efficacy)	Results from IMvigor130 were presented at EMSO 2019. IMvigor130 met its co-primary objective of demonstrating a statistically significant and clinically meaningful improvement in INV-PFS investigator-assessed progression free survival (PFS) (assessed per RECIST v1.1) in the Atezolizumab + Chemotherapy arm relative to Placebo +

	Chemotherapy in the intention to treat (ITT) population (stratified Hazard Ratio (HR): 0.82; 95% CI: 0.70, 0.96; one-sided p-value=0.007<0.01). The result for the co-primary endpoint of OS in the ITT population suggests a clinically meaningful improvement in the Atezolizumab + Chemotherapy arm vs. Placebo + Chemotherapy arm, however, did not cross the pre-specified one-sided interim efficacy analysis boundary of α=0.007 (stratified HR: 0.83; 95% CI: 0.69,1.00; one-sided p-value=0.027). At the time of the clinical cut-off date (CCOD), the median duration of survival follow-up was 11.8 months. In the ITT population, overall response rate (ORR) (95% CI) was 47% in the Atezolizumab + Chemotherapy arm and 44% in the Placebo + Chemo arm, with higher complete response (CR) rates in the Atezolizumab + Chemothrapy arm (12.5% vs. 6.8%, respectively). The median duration of response (DOR) (95% CI) was 8.5 months (7.2, 10.4) vs. 7.6 months (6.3, 8.5) in the Atezolizumab + Chemothrapy arm vs. Placebo+Chemotherapy, respectively.[6]
Results (safety)	The overall toxicity profile of each arm was consistent with the toxicity profile of each tested drug. Both the atezolizumab + chemotherapy arm and the placebo + chemotherapy arm exhibited similar safety profiles, with 34% of adverse events leading to treatment discontinuation in both arms.[25]

ESTIMATED COST

Atezolizumab is already marketed in the UK. The NHS indicative price for atezolizumab solution for infusion is as follows:[26]

- Tecentriq 1200mg/20ml concentrate for solution for infusion (1 vial) costs £3,807.69
- Tecentriq 840mg/14ml concentrate for solution for infusion (1 vial) costs £2,665.38.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Atezolizumab with gemcitabine and carboplatin for treating metastatic urothelial bladder cancer (GID-TA10202). Expected publication date to be confirmed.
- NICE technology appraisal in development. Durvalumab for untreated PD-L1 positive metastatic urothelial bladder cancer (GID-TA10324). Expected publication date to be confirmed.
- NICE technology appraisal in development. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (GID-TA10466). Expected publication date: April 2020.

- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA522). July 2018.
- NICE technology appraisal. Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy (TA530). July 2018.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA525). June 2018.
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- NICE clinical guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS106). December 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). N15/S/a.
- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. 16033/P. 2016

OTHER GUIDANCE

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ADDITIONAL INFORMATION

At the time of writing, the information within the UKPS was not representative of the proposed indication and licensing plans.

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