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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Atezolizumab for muscle-invasive urothelial carcinoma –adjuvant

NIHRIO ID	12759	**NICE ID**	9574
Developer/Company	Roche Products Ltd	**UKPS ID**	645031

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

SUMMARY

Atezolizumab is currently in clinical development for the treatment of patients muscle-invasive urothelial cancer (MIUC) including muscle-invasive bladder cancer (MIBC) and upper tract urothelial cancer (UTUC) patients who are at high risk following resection. MIBC is a cancer that spreads into the thick muscle deep in the bladder wall. MIBC starts in the inner bladder layer and then grows in the deep muscle. While UTUC can arise along any part of the urinary tract lined with urothelium with the majority of cases in the lower tract and rest in the upper tract. Over time the tumour may grow outside the bladder into tissues close by and then may spread to lymph nodes, the lungs, the liver and other parts of the body. The current standard care of treatment includes a surgery which might not be adequate and some patients might be at high risk for recurrence.

Atezolizumab is a cancer medicine that is designed to recognise and attach to a protein called PD-L1, which is present in many cells. By attaching to PD-L1 and reducing its effects, atezolizumab increases the ability of the immune system to attack the cancer cells and thereby slow down progression of the disease. If licensed, atezolizumab will offer an adjuvant treatment for muscle-invasive urothelial carcinoma (MIUC) patients who are at high-risk for recurrence following resection.

PROPOSED INDICATION

Adjuvant treatment of the patients with muscle-invasive urothelial carcinoma (MIUC) who are at high-risk of recurrence following resection.[a]

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1) and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the anti-tumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen-presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.[1]

Atezolizumab is in clinical development for the adjuvant treatment of patients with MIUC who are at high risk of recurrence following resection. In the phase III clinical trial (NCT02450331), atezolizumab will be administered to patients at a dose of 1,200 mg via intravenous (IV) infusion on day 1 of each 21-day cycle for 16 cycles (up to 1 year).[2]

INNOVATION AND/OR ADVANTAGES

MIBC has high metastatic potential at diagnosis but is still often curable with aggressive management, which may give patients the best chances for a favourable clinical outcome. Despite improvements in surgical approaches and an excellent 5-year local control rate, the 5-year survival rate for high risk MIBC after radical cystectomy remains very low (between 50-70%). Because of the high risk of relapse with surgery alone, pre- and post-surgery (neo/adjuvant chemotherapy) treatments have been used in conjunction with radical cystectomy. Neoadjuvant chemotherapy has been shown to provide a small but statistically significant overall survival advantage. However, there is currently no standard treatment for those patients in the adjuvant setting, after cystectomy.[3]

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity with advanced cancers and most related toxicities observed are mild and transient in nature. It is anticipated that adjuvant treatment with atezolizumab will have a manageable safety profile and acceptable benefit risk assessment.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab is indicated in the UK:

- As monotherapy, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression $\geqslant$ 5%.[1]
- In combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in

[a] Information provided by Roche Products Ltd

combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.[1]
- 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.[1]
- In combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.[1]
- In combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.[4]
- In combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).[1]

Very common (≥ 10%) adverse events associated with atezolizumab monotherapy include: decreased appetite, cough, dyspnoea, nausea, vomiting, diarrhoea, urinary tract infections, rash, pruritus, arthralgia, back pain, musculoskeletal pain, pyrexia, fatigue, and asthenia.[1]

PATIENT GROUP

DISEASE BACKGROUND

Bladder cancer starts in inner lining of the bladder (urothelium).[5] Bladder cancer can be classified by how far it has spread from the urothelium.[6] Muscle invasive bladder cancer (MIBC) is a cancer that spreads into the thick muscle deep in the bladder wall.[7] MIBC starts in the inner bladder layer and then grows in the deep muscle. While urothelial carcinomas arise along any part of the urinary tract lined with urothelium with majority of cases (90%-95%) in the lower tract (bladder, urethra) and rest (5%-10%) in the upper tract (renal pelvis and ureter).[8] Over time the tumour may grow outside the bladder into tissues close by and then may spread to lymph nodes, the lungs, the liver and other parts of the body.[7,9] It is a more advanced stage and harmful kind of bladder cancer and should be treated with delay.[9] Due to high risk of relapse with surgery alone, pre- and post-surgery (neo/adjuvant chemotherapy) treatments have been used in conjunction with radical cystectomy.[3]

Bladder cancer is caused by changes to the cells of the bladder. It is often linked with exposure to certain chemicals, but the cause is not always known.[10] There are certain factors that can increase the risk of bladder cancer. These include smoking, exposure to chemicals such as arylamines and polycyclic aromatic hydrocarbons, exposure to water disinfection chemicals such as chlorine and trihalomethanes, treatment for some other cancers, other medical conditions such as diabetes and spinal cord injury, bladder infections and chronic bladder irritation, diet and alcohol intake, previous bladder cancer, and family history.[11]

The most common symptom of bladder cancer is blood in the urine that is usually painless. Less common symptoms of bladder cancer include a need to urinate on a more frequent basis, sudden urges to urinate, and a burning sensation when passing urine.[12]

Bladder cancer may have a significant impact on patients' quality of life, especially for those that have undergone a cystectomy for which an alternative way of passing urine out of the body will be created during the operation. Patients with bladder cancer may also experience sexual problems.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Bladder cancer accounted for 3% of all new cancer cases in 2016.[14] In England, in 2017 there were 8,686 registrations of newly diagnosed cases of 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.[15] The European age-standardised incidence rate for bladder cancer is projected to fall by 34% in the UK between 2014 and 2035, from 20.44 cases per 100,000 (10,057 observed cases) to 13.43 cases per 100,000 population by 2035 (10,386 projected cases).[16]

In England, in 2018-19 there were 73,789 finished consultant episodes (FCEs) for malignant neoplasm of the bladder (ICD-10 code C67), and 69,198 admissions resulting in 100,777 bed days and 41,236 day cases. Whilst 1,533 FCEs for malignant neoplasm for renal pelvis (ICD-10 code C65), and 1,386 admissions and resulting 3,219 bed days and 739 day cases and for malignant neoplasm of ureter (ICD-10 code C66) there were 2,445 FCEs, 2157 admissions resulting in 5,579 bed days and 1,032 day cases.[17]

In England in 2017, there were 5,014 deaths with malignant neoplasm of the bladder (ICD-10 code C67) recorded as the underlying cause.[18] The latest published survival statistics for bladder cancer in England (2018, patients diagnosed 2013-2017) report a 1-year survival rate of 74.1% and a 5-year survival rate of 52.6% (age-standardised).[19]

Hospital Episodic Statistics (HES) data for procedures undertaken in English hospitals between 2018 and 2019 reported a total of 494 FCEs and 482 admissions for primary procedure cystectomy, other specified total excision of bladder and unspecified total excision of bladder (OPCS-4 codes M34.3, M34.8 and M34.9). OPCS-4 codes reported as agreed for the Specialised kidney, bladder and prostate cancer services (Adults), NHS England.[17,20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment of MIBC is complex and requires a multidisciplinary collaboration among surgery, radiation and medical oncology.[21] In England, for people diagnosed with MIBC, NICE recommends that a specialist urology multidisciplinary team reviews all cases of MIBC, to offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to patients with MIBC for whom radical therapy is suitable. Ensuring that the choice is based on a full discussion between the patient and an urologist who performs radical cystectomy, a clinical oncologist and a clinical nurse specialist. After radical cystectomy, those patients for whom neoadjuvant chemotherapy was not suitable (because muscle invasion was not shown on biopsies before cystectomy) may be offered cisplatin adjuvant combination chemotherapy.[22]

Due to the low rates of adoption of neoadjuvant chemotherapy, clinicians are often faced with the decision of whether or not to recommend adjuvant chemotherapy for high-risk patients who have not been exposed to neoadjuvant chemotherapy. Thus the role of adjuvant treatment for high-risk remain controversial.[23] Further, there is no widely accepted classification of high-risk in MIBC and therefore treatment options are not recommended according to risk.[24]

CURRENT TREATMENT OPTIONS

According to the current NICE treatment pathway recommends considering adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive urothelial bladder cancer for whom neoadjuvant chemotherapy was not suitable (because muscle invasion was not shown on biopsies before cystectomy). Ensure that the person has an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.[22]

PLACE OF TECHNOLOGY

If licensed, atezolizumab will provide an adjuvant treatment of the patients with muscle-invasive urothelial carcinoma (MIUC) who are at high risk of recurrence following resection.

CLINICAL TRIAL INFORMATION

Trial	**IMvigor010, NCT02450331, WO29636 EUDRACT- 2014-005603-25; adults ≥ 18 years; atezolizumab *vs.* observation; phase III**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[2,25]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, parallel assignment, open-label
Participants	n=809; aged ≥ 18 years; males or females; muscle-invasive UC of the bladder or upper urinary tract; patients who have received prior neoadjuvant chemotherapy are eligible, but must have tumour staging of ypT2-4a or ypN+ (ypT2-4 or ypN+ for patients with UTUC) and M0 at pathological examination of the surgical resection specimen; patients who have not received prior neoadjuvant chemotherapy must be ineligible for or declined treatment with cisplatin-based adjuvant chemotherapy and have tumour staging of pT3-4a or pN+ (pT3-4 or pN+ for patients with muscle-invasive UTUC) and M0
Schedule	Patients randomised to • Atezolizumab administered at a dose of 1200 mg via IV intravenous on day 1 of each 21-day cycle for 16 cycles (up to 1 year) Or • Participants will undergo observation starting on day 1 for 16 cycles (up to 1 year)
Follow-up	Up to 6 years
Primary Outcomes	• Disease-Free Survival (DFS) [Time frame: randomisation up to first occurrence of DFS event (assessed at screening/randomisation, every 12 weeks after randomisation in first 3 years, every 24 weeks for years 4 and 5, and at year 6)
Secondary Outcomes	• Overall Survival (OS) [Time frame: randomisation until death due to any cause (up to approximately 8 years)] • Disease-Specific Survival (DSS) [Time frame: randomisation until death due to UC (up to approximately 8 years)] • Distant Metastasis-Free Survival (DMFS) [Time frame: randomisation up to diagnosis of distant metastases or death from any cause (assessed

	at screening/randomisation, every 12 weeks after randomisation in first 3 years, every 24 weeks for years 4 and 5, and at year 6)] • Non-urinary tract recurrence-free survival (NURFS) [Time frame: randomisation up to time of first occurrence of a NURFS event (assessed at screening/randomisation, every 12 weeks after randomisation in first 3 years, every 24 weeks for years 4 and 5, and at year 6)] • Percentage of participants with adverse events (AEs) [Time frame: screening up to approximately 1 year] • Percentage of participants with Anti-Therapeutic Antibodies (ATAs) to atezolizumab [Time frame: pre-dose (hour 0) on day 1 of cycles 1, 2, 3, 4, and every 8 cycles from cycle 8; at treatment discontinuation (up to 1 year); 120 days after last dose (last dose = up to 1 year) (cycle length = 21 days)] • European Quality of Life (EuroQoL) group 5-dimension 5-level (EQ-5D-5L) self-report questionnaire health utility score [Time frame: Day 1 of cycle 1 up to 6 years (detailed time frame is provided in outcome description section)] • Minimum observed serum atezolizumab concentration (Cmin) [Time frame: Pre-dose (hour 0) on day 1 of cycles 1, 2, 3, 4, every 8 cycles from cycle 8, at treatment discontinuation (up to 1 year), 120 days after treatment discontinuation (up to 1 year 4 months)] • Maximum observed serum atezolizumab concentration (Cmax) [Time frame: Pre-dose (hour 0) and 0.5 hours after end of infusion on day 1 of cycle 1 (infusion duration = 60 minutes, cycle length = 21 days)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date as January 2020. Estimated study completion date reported as May 2022.

ESTIMATED COST

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

- Tecentriq 1200mg/20 ml concentrate for solution for infusion (1 vial) costs £3807.69
- Tecentriq 840mg/14ml concentrate for solution for infusion (1 vial) cost £2665.38

RELEVANT GUIDANCE

NICE GUIDANCE

- 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. 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.

- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. July 2016. 16033/P

OTHER GUIDANCE

- NHS England. Guidelines for the Management of Bladder Cancer. 2016.
- European Society for Medical Oncology (ESMO). Bladder cancer. ESMO practice Guidelines for diagnosis, treatment and follow-up. 2014.[27]

ADDITIONAL INFORMATION

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