Health Technology Briefing
September 2024

Atezolizumab for adjuvant treatment of muscle-invasive bladder cancer

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31110	NICE ID: Not available	UKPS ID: 671585

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Atezolizumab is currently in clinical development for the adjuvant treatment of circulating tumour DNA test (ctDNA) positive muscle-invasive bladder cancer (MIBC) following cystectomy. Bladder cancer is a disease in which certain cells in the bladder become abnormal and multiply uncontrollably to form a tumour. MIBC is when the cancer has spread beyond the lining of the bladder and into the muscle layer. ctDNA is DNA found in the bloodstream that has come from cancerous cells. The most well-known risk factor for MIBC is smoking, and the most common symptom is blood in the urine. A common treatment option for patients with MIBC treated with curative intent is a radical cystectomy, a surgery where parts or all the bladder is removed. The relapse rate is high in patients with high risk MIBC if they only receive standard treatment.

Atezolizumab is a monoclonal antibody, a type of protein designed to attach to a protein called PD-L1, which is present on many cancer cells. PD-L1 acts to switch off immune cells that would otherwise attack cancer cells. By attaching to PD-L1 and reducing its effects, atezolizumab increases the immune system's ability to attack cancer cells and thereby slow down progression of the disease. If licenced for the treatment of MIBC, atezolizumab would provide an additional treatment option to address an unmet need in patients with ctDNA positive MIBC following cystectomy.

Proposed Indication

Adjuvant treatment for adult patients with high-risk muscle-invasive bladder cancer (MIBC) who are circulating tumour DNA (ctDNA) positive following cystectomy.[1]

Technology

Description

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to 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 antitumour 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.[2]

Atezolizumab is in clinical development for adjuvant treatment in adult patients with MIBC after cystectomy who are ctDNA positive. In the phase III clinical trial (IMvigor011, NCT04660344), participants will receive 1680 mg atezolizumab intravenously every 4 weeks for 12 cycles or up to 1 year.[1]

Key Innovation

Despite standard curative-intent treatment with neoadjuvant cisplatin-based chemotherapy, followed by radical surgery in eligible patients, relapse rates post-surgery remain high, with approximately 50% of patients developing local or distant recurrence within 2 years of surgery and a 5-year survival of only 50-60%. Monitoring patients for ctDNA is a minimally invasive approach that appears attractive for selecting patients potentially suitable for adjuvant treatment with checkpoint inhibitors.[3,4] Adjuvant atezolizumab may be associated with improved outcomes in patients who are positive for ctDNA and who are at a high risk of relapse.[5] If licensed, atezolizumab as an adjuvant therapy could offer a new treatment option for adult patients with MIBC.

Regulatory & Development Status

Atezolizumab monotherapy currently has Marketing Authorisation in the EU/UK for the following indications:[2]

- 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 ≥ 5%
- As adjuvant treatment following complete resection for adult patients with Stage II to IIIA non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 50% of tumour cells and whose disease has not progressed following platinum-based adjuvant chemotherapy
- For the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC
- For the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy

Atezolizumab is also in phase II/III clinical development for many indications, some of which include:[6]

- Malignant neoplasm
- NSCLC
- Recurrent small cell lung cancer
- Urinary tract cancer
- Colorectal cancer
- Breast cancer

Atezolizumab has been awarded a Breakthrough Therapy designation by the US FDA for bladder cancer in May 2016.[7]

Patient Group

Disease Area and Clinical Need

Bladder cancer is when a growth of abnormal tissue, known as a tumour, develops in the bladder lining. When the cancerous cells spread beyond the lining into the surrounding bladder muscle, it is known as MIBC. MIBC 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.[8] ctDNA is a promising minimally invasive blood-based biomarker for early detection of metastatic relapse and monitoring of treatment response in bladder cancer. Several factors, including tumour stage and tumour size impact ctDNA detection.[9] There are certain factors that can increase the risk for 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, infection and chronic irritation of the bladder, diet and alcohol intake, previous bladder cancer and family history.[10] The most common symptom of bladder cancer is blood in the urine that is usually painless. Less common symptoms include a need to urinate on a more frequent basis, sudden urges to urinate and a burning sensation when passing urine. Other symptoms include pelvic pain, bone pain, unintentional weight loss, and swelling of the legs.[11]

In England in 2017, there were 8,686 newly diagnoses cases and 4,736 deaths registrations for malignant neoplasm of bladder (ICD-10 code C67).[12] The age-standardised 1-year and 5–year survival for patients diagnosed with bladder cancer in England in 2017 was 74.1% and 52.6% respectively.[13] In England in 2022-2023, a total of 66,634 finished consultant episodes (FCE) were reported for malignant neoplasm of bladder, resulting in 62,831 hospital admissions, 87,622 FCE bed days and 41,531 day cases.[14]

Recommended Treatment Options

Treatment for MIBC can include cystectomy, radiotherapy, chemotherapy and immunotherapy.[8] The treatment options recommended by the National Institute for Health and Care Excellence (NICE) for MIBC patients include:[15]

- Neoadjuvant chemotherapy
- Radical cystectomy
- Radical radiotherapy
- Adjuvant chemotherapy after radical cystectomy
- Nivolumab for adjuvant treatment of muscle-invasive urothelial cancer/MIBC that is at high risk of recurrence after radical resection in adults whose tumours express PD-L1 at a level of 1% or more. Only if adjuvant treatment with platinum-based chemotherapy is unsuitable and the company provides it according to the commercial arrangement[16]

NICE does not have any specific recommendations for ctDNA positive MIBC following cystectomy.

Clinical Trial Information

Trial	**IMvigor011**; NCT04660344, 2020-004418-36 ; A Phase III, Double-Blind, Multicenter, Randomized Study of Atezolizumab (Anti-PDL1 Antibody) Versus Placebo as Adjuvant Therapy in Patients With High-Risk Muscle-Invasive Bladder Cancer Who Are ctDNA Positive Following Cystectomy **Phase III**: recruiting **Location(s):** Nine European countries, UK, US, and other countries **Primary completion date:** March 2025
Trial Design	Randomised, parallel assignment, double blinded
Population	N=800 (estimated) adults patients aged 18 years and over with high risk muscle-invasive bladder cancer who are ctDNA positive following cystectomy
Intervention(s)	Atezolizumab 1,680 mg intravenously every 4 weeks on day 1 of each 28-day cycle
Comparator(s)	Placebo

Outcome(s)	Primary outcome measures:
	• Investigator-assessed disease-free survival (DFS) in participants who are ctDNA positive within 24 weeks of cystectomy [Time frame: randomization up to first occurrence of DFS event (up to approximately 46 months)]
	• Investigator assessed DFS in participants who are ctDNA positive within 24 weeks of cystectomy (primary analysis population), defined as the time from randomization to the first occurrence of a DFS event, defined as any of the following:
	  • Local (pelvic) recurrence of urothelial carcinoma (UC) (including soft tissue and regional lymph nodes)
	  • Urinary tract recurrence of uc (including all pathological stages and grades)
	  • Distant metastasis of UC
	  • Death from any cause

Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price of 1 vial of atezolizumab is:[17]

- for 1200mg/20ml concentrate for solution for infusion vials £3,807.69
- for 840mg/14ml concentrate for solution for infusion vials £2,665.38.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Durvalumab for neoadjuvant and adjuvant treatment of muscle-invasive bladder cancer (GID-TA11115). Expected publication date to be confirmed.

- NICE technology appraisal in development. Nivolumab with BMS-986205 and chemotherapy for neoadjuvant treatment of muscle-invasive bladder cancer (GID-TA11336). Expected publication date to be confirmed.
- NICE technology appraisal in development. Enfortumab vedotin with pembrolizumab for neoadjuvant and adjuvant treatment of cisplatin-eligible muscle-invasive bladder cancer (GID-TA11338). Expected publication date to be confirmed.
- NICE technology appraisal in development. Durvalumab with enfortumab vedotin for neoadjuvant and adjuvant treatment of muscle-invasive bladder cancer when cisplatin is unsuitable (GID-TA11517). Expected publication date to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of cisplatin-eligible muscle-invasive bladder cancer (GID-TA11137) Expected publication date to be confirmed.
- NICE technology appraisal guidance. Nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence (TA817). August 2022.
- 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). 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.
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Other Guidance

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Additional Information

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