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Newcastle University

Health Technology Briefing
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Neoadjuvant atezolizumab with chemotherapy followed by adjuvant atezolizumab for treating triple-negative breast cancer

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 20565	NICE ID: 11802	UKPS ID: 665153

Licensing and Market Availability Plans

Currently in phase II/III trials

Summary

Neoadjuvant atezolizumab in combination with chemotherapy followed by adjuvant atezolizumab is currently in clinical development for patients with triple-negative breast cancer (TNBC). TNBC develops in about 1 in 5 women with breast cancer and is one of the most difficult forms of breast cancer to treat due to the lack of receptors that are common targets for treatment in breast cancer. TNBC is often more aggressive compared to other types of breast cancer and there are a lack of safe treatments for this population group.

Atezolizumab is a type of immunotherapy 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. In the phase III trial, atezolizumab is administered via intravenous (IV) infusion. If licenced, neoadjuvant atezolizumab in combination with chemotherapy followed by adjuvant atezolizumab will provide an additional treatment option for patients with TNBC.

Proposed Indication

Neoadjuvant atezolizumab with chemotherapy followed by adjuvant atezolizumab in patients with triple-negative breast cancer (TNBC).[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 in combination with neoadjuvant chemotherapy followed by adjuvant atezolizumab is currently in clinical development for TNBC. In the phase III clinical trial, atezolizumab is administered as intravenous (IV) infusion at 1200mg dose, once every 3 weeks for 4 doses (Cycle 1), once every 3 weeks for 4 doses (Cycle 2) and once every 3 weeks after surgery for 1 year after first dose.[1]

Key Innovation

The main treatment option for patients with TNBC has been chemotherapy, usually with a taxane, however this is associated with side effects including: increased risk of infection; hair loss; sickness; nausea; and fatigue.[3,4] Atezolizumab was the first immunotherapy medicinal product approved that specifically targets the TNBC phenotype.[4] Atezolizumab with nab-paclitaxel is recommended by NICE for the first-line treatment of PD-L1+, advanced TNBC patients and has demonstrated to substantially improve outcomes compared with taxane chemotherapy alone.[5,6] If licenced, neoadjuvant atezolizumab with chemotherapy followed by adjuvant atezolizumab will provide an additional, non-taxane treatment option for patients with TNBC.

Regulatory & Development Status

Atezolizumab has Marketing Authorisation in the EU/UK as a monotherapy 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%
- Adult patients with stage II to IIIA (7th edition of the UICC/AJCC-staging system) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy
- 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
- Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy

Atezolizumab has Marketing Authorisation in the EU/UK as part of a combination therapy for the following indications:[2]

- In combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic, non-squamous non-small cell lung cancer
- 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)
- In combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease

- In combination with bevacizumab for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy

Atezolizumab is currently in phase II/III clinical development for many indications, including:[7]

- Cervical cancer
- NSCLC
- Colorectal Cancer
- Breast cancer
- Head and neck neoplasms
- Bladder cancer
- Melanoma

Patient Group

Disease Area and Clinical Need

TBNC is a less common type of breast cancer. It develops in about 1 in 5 women with breast cancer (15 to 20%).[8] TNBC is one of the most difficult forms of breast cancer to treat due to the lack of oestrogen (ER), progesterone (PR) or human epidermal growth factor 2 (HER-2) receptors that are targets of treatment in other forms of breast cancer.[9] Symptoms of TNBC are similar to other breast cancer types and can include: a new lump or thickening in the breast or armpit; a change in size, shape or feel of the breast; skin changes in the breast such as puckering, dimpling, a rash or redness of the skin; fluid leaking from the nipple in a woman who is not pregnant or breast feeding; changes in the position of nipple.[10] The risk factors for TNBC are not clear. Some breast cancers depend on hormones to grow. These can be linked with risk factors to do with hormones and having children. But TNBC does not seem to share these risk factors. Most women with triple negative breast cancer have no strong history of breast cancer in their family (hereditary breast cancer). But some women with TNBC have an altered BRCA1 gene. This will have been inherited from a parent. An altered BRCA 1 gene can cause breast cancer to run in families. Most breast cancers caused by BRCA1 are triple negative.[8]

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-18).[11] The age standardised incidence rate of breast cancer in England is 169.2 and 1.3 per 100,000 amongst females and males respectively.[12] In England from 2020-21, there were 202,340 finished consultant episodes (FCEs) and 199,226 admissions for malignant neoplasm of breast (ICD-10 code C50), which resulted in 172,062 day cases and 47,613 FCE bed days.[13] Based on statistics that around 15% of breast cancer cases are the TNBC subtype, it can be estimated that there were approximately 30,351 FCEs and 29,884 admissions specifically for TNBC, which results in approximately 25,810 day cases and 7,142 FCE bed days.[11] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for all stages of breast cancer in women were 95.8% and 85% (age-standardised) respectively.[14]

Recommended Treatment Options

For people with triple-negative invasive breast cancer, NICE recommends a neoadjuvant chemotherapy regimen that contains both a platinum and an anthracycline.[15]

Clinical Trial Information

Trial	NCT03281954; EudraCT 2017-002771-25; A Randomized, Double-Blind, Phase III Clinical Trial of Neoadjuvant Chemotherapy With Atezolizumab or Placebo in

	Patients With Triple-Negative Breast Cancer Followed by Adjuvant Continuation of Atezolizumab or Placebo **Phase III –** Active, not recruiting **Location(s):** USA, Canada, Germany and Spain **Primary completion date:** December 2023
Trial Design	Randomised, parallel-assignment, triple-blinded
Population	N=1550 (estimated); adult subjects (18 years and older) who received diagnosis of invasive adenocarcinoma of the breast by core needle biopsy; tumour is ER-negative, PgR-negative and HER2-negative
Intervention(s)	IV atezolizumab at 1200mg dose, once every 3 weeks for 4 doses (Cycle 1), once every 3 weeks for 4 doses (Cycle 2) and once every 3 weeks after surgery for 1 year after first dose Paclitaxel IV, carboplatin IV, doxorubicin IV, cyclophosphamide IV, epirubicin IV
Comparator(s)	Matched placebo + Paclitaxel IV 80mg/m^2, carboplatin IV, doxorubicin IV 60mg/m^2, cyclophosphamide IV 600mg/m^2, epirubicin IV 90mg/m^2
Outcome(s)	**Primary outcome measures:** • Event-free survival (EFS) [Time frame: from randomization until event, through study follow up to the time target number of events is obtained, up to 5 years] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost of atezolizumab 60 mg per 1 ml is £2665.38 for 840mg/14ml concentrate and £3807.69 for 1200mg/20ml concentrate solution for infusion vials.[16]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pembrolizumab for previously treated metastatic triple negative breast cancer (ID1246). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab in combination with chemotherapy for neoadjuvant treatment of triple negative breast cancer (ID1500). Expected November 2022.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). February 2009.
- NICE quality standard. Breast cancer (QS12). September 2011.

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.

Other Guidance

- ESMO Guidelines Committee. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. 2021.[17]
- ESO-ESMO ABC 5 Clinical Practice. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). 2020.[18]
- Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. 2020.[19]

Additional Information

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