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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2019

Atezolizumab in addition to paclitaxel for inoperable, locally advanced or metastatic triple negative breast cancer – first-line

NIHRIO ID	17191	**NICE ID**	10243
Developer/Company	Roche Products Ltd	**UKPS ID**	652801

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

SUMMARY

Atezolizumab as an intravenous infusion in combination with an intravenous infusion of paclitaxel (chemotherapy) is in clinical development for the first-line treatment of locally advanced or metastatic triple-negative breast cancer (TNBC). TNBC is a type of breast cancer in which the cancer cells do not express receptors for oestrogen or progesterone or HER2 protein. Treatment of TNBC is challenging because of a lack of targeted therapy, aggressive disease course, and relatively poor prognosis. Treatment is usually through a combination of surgery, radiotherapy, and chemotherapy.

Atezolizumab is a cancer medicine that enhances T-cell (part of the immune system) activity against tumours. Paclitaxel is a chemotherapy that inhibits cell growth by preventing cell division. The combination may offer an additional first-line treatment option to improve clinical effectiveness in the treatment of people with inoperable, locally advanced or metastatic TNBC, an aggressive disease with no approved targeted therapy.

PROPOSED INDICATION

Treatment naïve patients with inoperable, locally advanced or metastatic triple negative breast cancer (TNBC) – first-line.[1,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.[2]

Atezolizumab in addition to paclitaxel is being developed for the first-line treatment of patients with inoperable locally advanced or metastatic TNBC. In the phase III clinical trial (NCT03125902, IMpassion131), atezolizumab will be administered to patients at a dose of 840 mg via intravenous (IV) infusion on days 1 and 15 (± 3 days) of every 28-day cycle, along with paclitaxel administered at a dose of 90 mg/m^2 via IV infusion on days 1, 8, and 15 of every 28-day cycle until disease progression or unacceptable toxicity.[1]

INNOVATION AND/OR ADVANTAGES

Chemotherapy (including paclitaxel) remains the predominant treatment for metastatic TNBC but clinical outcomes remain poor. TNBC is a rational target for atezolizumab therapy due to high PD-L1 expression on tumour infiltrating immune cells and elevated T-cell tumour infiltration. Furthermore, combining chemotherapy with atezolizumab is hypothesised to enhance antitumour immune response via neoantigen release. Atezolizumab alone and in combination with nab-paclitaxel has demonstrated promising clinical benefit in metastatic TNBC and was well tolerated, with no exacerbation of chemotherapy-associated adverse events.[3,4] Atezolizumab with paclitaxel is a novel combination for metastatic TNBC. The NICE pathway for metastatic TNBC does not currently recommend any PD-L1 inhibitors (either as monotherapy or in combination with chemotherapy).[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab as monotherapy is indicated for:[2]

- 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%.[2]

- the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab

[a] Information provided by Roche Products Ltd

Atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.[2]

Atezolizumab, 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.[2]

Atezolizumab, 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).[2]

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.[2]

Atezolizumab in combination with paclitaxel is also in phase II and/or phase III development for:[6]

- NSCLC
- Breast cancer
- Ovarian, fallopian tube or primary peritoneal cancer
- Metastatic carcinoma of cervix
- Advanced biliary tract and gastroesophageal cancer
- Endometrial cancer

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is the most common cancer in the UK, and mainly affects women, although men can also have the condition. It usually starts in the cells that line the ducts of the breast.[7] Triple-negative breast cancer (TNBC) is defined by the absence of oestrogen receptor (ER), progesterone receptor (PR), and the tyrosine kinase human epidermal growth factor receptor-2 (HER2) overexpression.[8,9]

TNBC is more common in women under 40 and black women.[10] TNBC can also occur in African-American and Hispanic women and in people with BRCA1 mutation.[11] Metastatic breast cancer means that the cancer has spread to other parts of the body, such as liver and bones.[12] Symptoms of TNBC are similar to other breast cancer types and include a lump or thickening in an area of the breast, a change in the size, shape or feel of the breast, dimpling of the skin, a change in the shape of the nipple, particularly if it turns in, sinks into the breast, or has an irregular shape, blood stained discharge from the nipple, rash on a nipple or surrounding area or a swelling or lump in the armpit.[9]

Breast cancer patients experience physical symptoms and psychosocial distress that adversely affect their quality of life (QOL). Treatment, including chemotherapy, can cause physical and psychological problems that adversely affect patient QOL, and cancer can have other effects including anger, grief, suffering and pain.[13]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017 there were 46,109 registrations of newly-diagnosed breast cancer (ICD-10 code: C50).[14] Statistics from Cancer Research UK report that in UK in 2014 there were

54,833 observed cases of breast cancer in females, an age standardised rate of 204.93 per 100,000, and predict that this will increase to 71,022 cases in 2035, with an age-standardised rate of 209.51 per 100,000.[15] In 2016, there were 2,309 cases diagnosed with stage 4 breast cancer.[16] It is estimated that approximately 15% of breast cancers are triple negative.[9] Based on the newly diagnosed cases of breast cancer in 2017, 6,916 would be TNBC.

In England in 2017/2018 there were 212,840 finished consultant episodes, and 209,061 hospital admissions with a primary diagnosis of malignant neoplasm of breast (ICD-10 code C50), resulting in 80,769 bed days and 177,174 day cases.[17]

In England and Wales in 2017, there were 10,219 deaths with malignant neoplasm of breast (ICD-10 code C50) recorded as the underlying cause.[18] The latest published survival statistics for breast cancer for women in England (patients diagnosed between 2013-2017) report 1-year survival rate of 95.8% and 5-year survival rate of 85.0% (age-standardised) for all stages. For stage 4 breast cancer, 1-year survival rate of 66% and 5-year survival rate of 26.2% was reported. [19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main treatments for TNBC are surgery and chemotherapy, depending on where the cancer is, the stage and grade of the cancer confirmed by pathology, and the patient's general health. Chemotherapy may be given before surgery, and is also usually given following surgery.[9]

CURRENT TREATMENT OPTIONS

NICE recommends considering gemcitabine in combination with paclitaxel, within its licensed indication, as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate treatment.[20]

For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:[20]

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine
- third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment)

PLACE OF TECHNOLOGY

If licensed, atezolizumab in addition to paclitaxel may offer an additional first-line treatment option for patients with inoperable, locally advanced or metastatic TNBC.

CLINICAL TRIAL INFORMATION

Trial	**IMpassion131, NCT03125902, EudraCT 2016-004024-29, MO39196; atezolizumab vs placebo both in combination with paclitaxel; phase III**
Sponsor	Hoffmann-La Roche
Status	Ongoing

Source of Information	Trial registry[1,21]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled, parallel assignment
Participants	n=600 (planned); aged 18 yrs and older; males and females; TNBC; locally advanced or metastatic; no prior chemotherapy or targeted systemic therapy
Schedule	Patients will be randomised to: • Atezolizumab administered at a dose of 840 mg via IV infusion on days 1 and 15 (± 3 days) of every 28-day cycle, along with paclitaxel administered at a dose of 90 mg/m^2 via IV infusion on days 1, 8, and 15 of every 28- day cycle until disease progression or unacceptable toxicity. or • Placebo matching to atezolizumab will be administered via IV infusion on days 1 and 15 (± 3 days) of every 28-day cycle, along with paclitaxel administered at a dose of 90 mg/m2 via IV infusion on days 1, 8, and 15 of every 28- day cycle until disease progression or unacceptable toxicity.
Follow-up	Active treatment period: until disease progression or unacceptable toxicity or end of study, whichever occurs first (maximum up to approximately 40 months
Primary Outcomes	Time frame: From day 1 to disease progression (PD) or death from any cause, assessed up to end of study (up to approximately 40 months • Progression-Free Survival (PFS) assessed using Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) in the subpopulation with Programmed Death-Ligand 1 (PD-L1)-positive tumour status • PFS assessed using RECIST v1.1 in the Intent-to-Treat (ITT) population
Secondary Outcomes	• Overall Survival (OS) in the PD-L1-positive subpopulation [Time frame: from day 1 to death from any cause, assessed up to end of study (up to approximately 40 mths)] • OS in the ITT Population [Time frame: From Day 1 to death from any cause, assessed up to end of study (up to approximately 40 months)] • Percentage of participants who are alive at 12 and 18 mths [Time frame: from day 1 to death from any cause, assessed up to 12 and 18 mths] • Time to deterioration (TTD) in Global Health Status/ Health Related Quality of Life (HRQoL) [Time frame: from day 1 to deterioration, assessed up to end of study (up to approximately 40 mths)] • Percentage of participants who are alive without progression event at mth 12 assessed Using RECIST v1.1 [Time frame: from day 1 to PD or death from any cause, assessed up to 12 mths] • Percentage of participants with objective response assessed using RECIST v1.1 in the PD-L1-positive subpopulation [Time frame: from day 1 to PD, assessed up to end of study (up to approximately 40 mths)] • Percentage of participants with objective response assessed using RECIST v1.1 in the ITT population [Time frame: from day 1 to PD, assessed up to end of study (up to approximately 40 mths)]

	• Duration of Objective Response (DOR) assessed using RECIST v1.1 [Time frame: from objective response to PD, assessed up to end of study (up to approximately 40 mths)] • Percentage of participants with clinical benefit assessed using RECIST v1.1 [Time frame: from day 1 to PD, assessed up to end of study (up to approximately 40 mths)] • Minimum Observed Serum Concentration (Cmin) of atezolizumab [Time frame: Pre-dose (0 hours) on day 1 of cycles 1-4 and at treatment discontinuation (TD), (approximately 9 mths)] • Maximum Observed Serum Concentration (Cmax) of atezolizumab [Time frame: Pre-dose (0 hours) on day 1 of cycles 1-4 and at treatment discontinuation (TD) (approximately 9 mths)] • Minimum Observed Plasma Concentration (Cmin) of paclitaxel [Time frame: Pre-dose (0 hours) on day 1 of cycles 1 and 3 (1 cycle = 28 days)] • Maximum Observed Plasma Concentration (Cmax) of paclitaxel [Time frame: Pre-dose (0 hours), 5-10 min before and after paclitaxel infusion, 60 min after paclitaxel infusion on day 1 of cycles 1 and 3 (paclitaxel infusion duration= 60 min) (1 cycle = 28 days)] • Percentage of participants with Adverse Events (AEs) and Serious AEs (SAEs) [Time frame: from day 1 to 90 days after last dose of study drug, assessed up to end of study (up to approximately 40 mths)] • Percentage of participants with Drug Antibodies (ADAs) [Time frame: Pre-dose (0 hours) on day 1 of cycles 1, 2, 3, 4, 8, 12, 16, and at every 8 cycles thereafter until TD, at TD, and at 90-150 days after TD (maximum up to 45 mths) (1 cycle = 28 days)] • Change from baseline in PD-L1 expression by immunohistochemistry at approximately 45 mths [Time frame: from day 1 up to end of study (up to approximately 40 mths)] • Confirmed Objective Response Rate (C-ORR) [Time frame: from day 1 to PD, assessed up to end of study (up to approximately 40 mths)] • Duration of Confirmed Response (C-DoR) [Time frame: from objective response to PD, assessed up to end of study (up to approximately 40 mths)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Jan 2020.

ESTIMATED COST

The NHS indicative price for one vial of atezolizumab 1200mg/20ml (60 mg/1 ml) concentrate for solution for infusion is £3807.69.[22] The NHS indicative price for one vial of paclitaxel 100mg/16.7ml (6 mg/1 ml) concentrate for infusion is £200.35.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab in combination with chemotherapy for neoadjuvant treatment of triple negative breast cancer (GID-TA10399). Expected publication date: TBC.
- NICE technology appraisal in development. Pembrolizumab in combination for untreated, locally advanced or metastatic, triple negative breast cancer (GID-TA10417). Expected publication date: TBC.
- NICE technology appraisal in development. Atezolizumab for untreated, locally advanced or metastatic, triple negative, PD-L1 positive breast cancer (GID-TA10433). November 2019.
- NICE technology appraisal. Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (TA263). August 2012.
- NICE technology appraisal. Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (TA214). February 2011.
- NICE quality standard. Breast cancer (QS12). September 2011. Updated June 2016.
- NICE clinical guidelines. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018.

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

- European Society for Medical Oncology. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). 2018.[24]

ADDITIONAL INFORMATION

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