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EVIDENCE BRIEFING
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Atezolizumab in combination with nab-paclitaxel as neoadjuvant treatment for early stage triple-negative breast cancer

NIHRIO ID	16129	**NICE ID**	9710
Developer/Company	Roche Products Ltd	**UKPS ID**	645030

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

SUMMARY

Atezolizumab as an intravenous infusion in combination with an intravenous infusion of nab-paclitaxel (chemotherapy) is in clinical development for the neoadjuvant treatment of early stage triple-negative breast cancer (TNBC). TNBC is an uncommon 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. Nab-paclitaxel is a chemotherapy that combines the chemotherapy drug paclitaxel with a protein called albumin. It inhibits cell growth by preventing cell division. The combination may offer an additional neoadjuvant treatment option to improve clinical efficacy in the treatment of people with early stage TNBC, an aggressive disease with no approved targeted therapy.

PROPOSED INDICATION

Early stage triple-negative breast cancer (TNBC) - neoadjuvant[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]

Nab-paclitaxel (Abraxane; paclitaxel formulated as albumin bound nanoparticles) is designed to overcome the insolubility problems associated with conventional paclitaxel formulations.[2] Paclitaxel is an anti-microtubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.[3]

Atezolizumab as an intravenous (IV) infusion, in combination with an IV infusion of nab-paclitaxel is in clinical development for the treatment of early stage TNBC. In the phase III clinical trial (Impassion031; NCT03197935), an 840mg IV infusion dose of atezolizumab is administered every 2 weeks in combination with an 125mg/m^2 IV infusion of nab-paclitaxel every week for 12 weeks, followed by atezolizumab (840 mg) every 2 weeks in combination with doxorubicin (60mg/m^2) and cyclophosphamide (600mg/m^2) every 2 weeks via IV infusions with filgrastim or pegfilgrastim support for 4 doses. Participants will continue to receive unblinded atezolizumab post-surgery at a fixed dose of 1200mg by IV infusion every 3 weeks for 11 doses, for a total of approximately 12 months of atezolizumab therapy.[4]

INNOVATION AND/OR ADVANTAGES

The company indicate that atezolizumab as a monotherapy and in combination with nab-paclitaxel is well tolerated, showing promise in metastatic TNBC, which supports its investigation in early stage disease.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab is licensed in the EU as a monotherapy for the following indications:[1]

- adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5%.

[a] Company information from UK PharmaScan

- adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving atezolizumab.

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

Nab-paclitaxel is licensed in the EU for the following indications:[6]

- Monotherapy treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.
- In combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.
- In combination with carboplatin for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

The most common clinically significant adverse reactions associated with the use of nab-paclitaxel have been neutropenia, peripheral neuropathy, arthralgia/myalgia, and gastrointestinal disorders.[6]

Atezolizumab in combination with nab-paclitaxel is also in phase II and/or phase III development for:[7]

- Non-small-cell lung cancer, squamous and non-squamous
- Poorly differentiated thyroid carcinomas
- Pancreatic adenocarcinoma
- Locally advanced or metastatic TNBC

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.[8] TNBC is an uncommon type of breast cancer where the cells do not have receptors for the hormones oestrogen and progesterone or HER2 protein. Early-stage TNBC has been previously defined as patients who have cancer between stage I and stage III.[9, 10]

Patients with TNBC do not respond to hormone treatment therapies targeted at HER2 receptors. Some women with TNBC also have a BRCA1 gene fault, which can increase the risk of breast cancer within families.[11] TNBC is more common in women under 40 years of age and black women.[12]

Patients with TNBC have worse clinical outcomes and a unique pattern of recurrence compared with the other major subtypes of breast cancer (HR+ and HER2+). Patients with TNBC have been shown to have the highest rate of recurrence within the first 5 years after diagnosis, with a significant decrease and plateauing of the recurrence rate afterwards. Post-recurrence survival is also decreased compared to patients with HR+ tumours.[13]

Symptoms of TNBC are similar to other breast cancer types, and can include a lump or thickening in an area of the breast, changes in the size, shape or feel of the breast or nipple, or a swelling in the armpit.[11]

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.[14]

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that approximately 15% of breast cancers are triple negative.[11]

In England in 2016 there were 45,960 registrations of newly-diagnosed breast cancer (ICD-10 C50).[15] Using the above estimate, this would equate to 6,894 cases of TNBC. 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.[16] Approximately 20–40% of patients with early-stage TNBC develop metastatic disease.[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 (2016, patients diagnosed in 2011-2015) report 1-year survival rate of 95.6% and 5-year survival rate of 86.0% (age-standardised).[19]

In England in 2016/2017 there were 203,454 hospital admissions with a primary diagnosis of malignant neoplasm of breast (ICD-10 code C50), resulting in 85,801 bed days and 169,800 day cases.[20]

PATIENT TREATMENT PATHWAY

PATIENT 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. Surgery may be a lumpectomy (usually followed by radiotherapy to the rest of the breast tissue) or a mastectomy. Chemotherapy may be given before surgery, and is also usually given following surgery.[11]

CURRENT TREATMENT OPTIONS

NICE recommends considering the following treatment options for TNBC:[21]

- Neoadjuvant chemotherapy for invasive TNBC that contains both a platinum and an anthracycline. Although this use is common in UK clinical practice, at the time of publication of the relevant NICE guideline (July 2018), platinums did not have UK marketing authorisations for this indication.

PLACE OF TECHNOLOGY

If licensed, atezolizumab in combination with nab-paclitaxel may offer an additional neoadjuvant treatment option for patients with early stage TNBC.

CLINICAL TRIAL INFORMATION	
Trial	IMpassion031, NCT03197935, EudraCT 2016-004734-22; atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel; both in addition to chemotherapy; phase III
Sponsor	Roche Products Ltd
Status	Ongoing
Source of Information	Trial registry[4]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled study
Participants	n=204 (planned); ≥ 18 years old; triple-negative breast cancer (negative HER2, ER and PgR status), stage at presentation: cT2-cT4, cN0-cN3, cM0.
Schedule	Participants were randomised to receive either: • 840mg IV infusion dose of atezolizumab every 2 wks in combination with an 125mg/m^2 IV infusion of nab-paclitaxel every wk for 12 wks, followed by atezolizumab (840mg) every 2 wks in combination with doxorubicin (60mg/m^2) and cyclophosphamide (600mg/m^2) every 2 wks via IV infusions with filgrastim or pegfilgrastim support for 4 doses. Participants will continue to receive unblinded atezolizumab post-surgery at a fixed dose of 1200mg by IV infusion every 3 wks for 11 doses, for a total of approximately 12 mths of atezolizumab therapy • Placebo matched to atezolizumab via IV infusion every 2 wks in combination with nab-paclitaxel (125mg/m^2) via IV infusion every wk for 12 weeks, followed by placebo matched to atezolizumab every 2 wks in combination with doxorubicin (60mg/m^2) and cyclophosphamide (600mg/m^2) every 2 wks via IV infusions with filgrastim or pegfilgrastim support for 4 doses. Participants will be unblinded post-surgery and will continue to be followed.
Follow-up	Active treatment for 12 wks.
Primary Outcomes	Percentage of participants with Pathologic Complete Response (pCR) using American Joint Committee on Cancer (AJCC) Staging System [time frame: wk 21]
Secondary Outcomes	• Percentage of participants with pCR in subpopulation with PD-L1-selected tumour status (tumour-infiltrating immune cell [IC] 1/2/3) using AJCC Staging System [time frame: wk 21] • Event-Free Survival (EFS) using AJCC Staging System [time frame: from randomisation until documented disease recurrence, progression, or death from any cause (up to approx 51 mths)] • Overall survival (OS) [time frame: from randomisation to the date of death from any cause (up to approx 51 mths)] • Changes from baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Score [time frame: baseline (cycle 1 day 1), and on day 1 of every cycle thereafter (cycle length = 28 days from cycles 1 to 5, and 21 days from cycles 6 to 16) (up to approximately 15 mths)] • Percentage of participants with adverse events (AEs) [time frame: baseline up to approximately 51 mths] • Serum concentration of atezolizumab [time frame: pre-infusion (0 hour), 30 mins post-infusion on wk 1 day 1; pre-infusion on day 1 of wks 5, 9, 13, 21, 27, 39, 51; at treatment discontinuation (last dose = up to 15 mths), 120 days after last dose (infusion length = 60 mins)]

	• Percentage of participants with anti-drug antibodies (ADAs) to atezolizumab [time frame: pre-infusion (0 hour) on day 1 of wks 1, 5, 9, 13, 21, 27, 39, 51; at treatment discontinuation (last dose = up to 15 mths), 120 days after last dose (infusion length = 60 mins)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as Mar 2019

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 nab-paclitaxel (Abraxane) 100mg powder for suspension for infusion is £246.00.[23] Both products are subject to separate, confidential patient access schemes.[24]

ADDITIONAL INFORMATION

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 to be confirmed.
- NICE guideline. Early and locally advanced breast cancer: diagnosis management (NG101). July 2018.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 2017.
- NICE clinical guideline. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). March 2017.
- NICE diagnostics guidance in development. Tumour profiling tests to guide adjuvant chemotherapy decisions in people with breast cancer (update of DG10) (GID-DG10015). Expected publication date October 2018.
- NICE quality standard. Breast cancer (QS12). June 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

OTHER GUIDANCE

- European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). 2018.[25]

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