Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
September 2018

Atezolizumab in combination with Nab-paclitaxel for unresectable, locally advanced or metastatic triple-negative breast cancer – first line

NIHRIO ID	11151	**NICE ID**	9497
Developer/Company	Roche Products Ltd	**UKPS ID**	648993

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

SUMMARY

Atezolizumab as an intravenous infusion, which in combination with an intravenous infusion of nab-paclitaxel, is in clinical development for the treatment of unresectable, locally advanced or triple-negative metastatic 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 combined with nab-paclitaxel is the first product to demonstrate positive phase III immunotherapy results in patients with locally advanced or metastatic TNBC who have not received prior systemic therapy. Atezolizumab is a monoclonal antibody that binds to the programmed cell death 1 ligand (PD-L1) and blocks its interaction with the programmed cell death protein 1 (PD-1), thereby enhancing T-cell activity against tumours. Nab-paclitaxel (paclitaxel formulated as albumin bound nanoparticles) is an anti-microtubule agent that inhibits cell growth by preventing mitosis. The combination may offer a first-line treatment option to improve clinical efficacy in the treatment of people with TNBC, an aggressive disease with no approved targeted therapy.

PROPOSED INDICATION

Unresectable, locally advanced or metastatic triple-negative breast cancer – first line[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 – paclitaxel formulated as albumin bound nanoparticles – is designed to overcome the insolubility problems associated with conventional paclitaxel formulations. Nab-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.[2]

Atezolizumab as an intravenous infusion, in combination with an intravenous infusion of nab-paclitaxel, is in clinical development for the treatment of unresectable, locally advanced or metastatic triple-negative breast cancer. In the phase III clinical trial (IMpassion130; NCT02425891) an 840mg fixed dose IV infusion of atezolizumab is administered on Days 1 and 15 of each 28-day cycle along with a 100mg per square meter IV infusion of nab-paclitaxel on Days 1, 8, and 15 of each 28-day cycle. Patients receive both agents until unacceptable toxicity or disease progression.[3]

INNOVATION AND/OR ADVANTAGES

Atezolizumab in combination with nab-paclitaxel is the first product combination to demonstrate positive phase III immunotherapy results in patients with locally advanced or metastatic triple-negative breast cancer who have not received prior systemic therapy for metastatic breast cancer.[4]

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%.
- 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,

[a] Information provided by company

back pain, pyrexia, fatigue, and asthenia.[1]

Nab-paclitaxel is licensed in the EU for the following indications:[5]

- 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 is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.
- in combination with carboplatin is indicated 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.[5]

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

- Non-small cell lung cancer, squamous and non-squamous
- Poorly differentiated thyroid carcinomas
- Pancreatic adenocarcinoma

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is not a single disease but rather a group of several different tumour subtypes.[7] Triple negative breast cancer (TNBC) is an uncommon type of breast cancer whose cells do not have receptors for the hormones oestrogen or progesterone or human epidermal growth factor receptor 2 (HER2) protein.[8] Approximately 10-20% of breast cancers are found to be triple negative. TNBC is most likely to occur before age 40 or 50 years, unlike other breast cancer types which more commonly occur in people aged 60 years and older.[9,10] Most breast cancers caused by faulty BRCA1 are triple negative.[11]

Locally advanced breast cancer has spread into the tissues around the breast while metastatic cancer has spread to another part of the body (most commonly the liver, brain, bones, or lungs).[12, 13]

A number of factors are known to increase the likelihood of breast cancer, including: exposure to radiation, increased alcohol consumption, being overweight or obese, exposure to oestrogen and hormone replacement therapy, greater breast tissue density, and genetic factors.[14] Breast cancer in adults can occur at any age with an increased risk in postmenopausal women. Moreover, a previous benign breast lump or a prior diagnosis of early breast cancer further increases the risk.[15]

Symptoms of TNBC are similar to other breast cancer types and may 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, a blood-stained discharge from the nipple, a rash on a nipple or surrounding area, or a swelling lump in the armpit.[8] Advanced breast cancers that require complete removal of the breast can be very distressing for a woman, affecting sexuality and body image.[16]

CLINICAL NEED AND BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, accounting for 15% of all newly diagnosed cancers. However only 1% of breast cancer cases in the UK are in males; 99% of breast cancer cases in the UK are in females.[17] The lifetime risk of developing breast cancer is 1 in 8 women in 2012 in

the UK. Incidence rates for breast cancer are projected to rise by 2% in the UK between 2014 and 2035, to 210 cases per 100,000 females by 2035.[18]

In England in 2016 there were 45,960 registrations of newly diagnosed cancer of the breast (ICD-10 code C50) of which 45,656 occurred among females. The directly age-standardised rate per 100,000 population was 1.3 for males and 167.9 for females. There were 9,626 registrations of death from neoplasm of the breast, and the directly age-standardised rate per 100,000 population was 0.3 for males and 34.3 for females.[19]

In England in 2016/17 there were 207,043 finished consultant episodes (FCEs) and 85,801 FCE bed days with primary diagnosis of ICD-10 code C50 (malignant neoplasm of breast). There were 203,454 hospital admissions, of which 169,800 were day cases.[20]

Approximately 15% of breast cancers are triple negative[8] (around 7,500 women in the UK being diagnosed each year).[21] TNBC tends to be more aggressive than other types of breast cancer and five-year survival rates tend to be lower.[10] TNBC presents with a varied natural history but is collectively associated with poor diagnosis with high risk of relapse and short progression-free survival (PFS) and overall survival (OS). As many of 50% of patients diagnosed with early-stage TNBC (stages I-III) experience disease recurrence, and 37% die in the first 5 years after surgery.[22]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Management of TNBC is challenging because of a lack of targeted therapy, aggressive disease course, and relatively poor prognosis. There are currently no specific treatment guidelines for TNBC and it is usually managed with standard breast cancer treatment.[22,23] TNBC is usually treated through a combination of surgery, radiotherapy, and chemotherapy.[11] Because TNBC is HER2-negative, hormone therapy is unhelpful in treating these cancers.[24]

NICE recommends genetic testing for BRCA1 and BRCA2 mutations to women under 50 years with TNBC, including those with no family history of breast or ovarian cancer. NICE also recommends physicians to consider a neoadjuvant chemotherapy regimen that contains both a platinum-based chemotherapy drug and an anthracycline. Adding a platinum-based chemotherapy drug improves response rates compared with anthracycline-based (with or without taxane) chemotherapy alone and may allow some women who would otherwise need a mastectomy to undergo breast-conserving surgery instead. At the time of this recommendation by NICE (July 2018), however, platinum-based chemotherapies did not have a UK marketing authorisation for this indication.[25]

CURRENT TREATMENT OPTIONS

At present, there is no targeted therapy indicated for the treatment of locally advanced or metastatic triple-negative breast cancer who have not received prior systemic therapy for metastatic breast cancer. General treatment for TNBC include a combination of the following:[8]

- Surgery
    - Wide local excision or lumpectomy
    - Mastectomy
- Radiotherapy
- Chemotherapy: on disease progression, NICE recommends offering systemic sequential therapy to the majority of patients. For patients who are not suitable for anthracyclines, NICE recommends the following sequence of systemic chemotherapy:[26]
    - 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 combination with nab-paclitaxel may offer a first-line treatment option for patients with locally advanced or metastatic triple-negative breast cancer who have not received prior systemic therapy for metastatic breast cancer.

CLINICAL TRIAL INFORMATION	
Trial	IMpassion130, NCT02425891, WO29522, 2014-005490-37; atezolizumab vs placebo, both in combination with nab-paclitaxel; phase III
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[3]; Press release[4]
Location	EU (including UK), USA, Canada, and other countries
Design	Randomised, placebo-controlled
Participants	N = 900 (planned); aged 18 years and older; males and females; metastatic or locally advanced triple-negative breast cancer; no prior chemotherapy or targeted systemic therapy
Schedule	Participants were randomised to receive one of two treatment arms: • **Experimental Arm:** 840mg, fixed dose, IV infusion of atezolizumab on Days 1 and 15 of each 28-day cycle and 100mg per square meter, IV infusion of nab-paclitaxel on Days 1, 8, and 15 of each 28-day cycle. Patients received both agents until unacceptable toxicity or disease progression. • **Placebo Arm**: 100mg per square meter, IV infusion of nab-paclitaxel on Days 1, 8, and 15 of each 28-day cycle and IV infusion of placebo on Days 1 and 15 of each 28-day cycle. Participants received both agents until unacceptable toxicity or disease progression.
Follow-up	Up to 53 months
Primary Outcomes	• Progression free survival (PFS) • Overall survival (OS)
Secondary Outcomes	• Objective response of Complete Response (CR) or Partial Response (PR) • Duration of Response (DOR) • Time to Deterioration (TTD) in Global Health Status/Health-Related QoL • Adverse Events (AEs) or Serious AEs (SAEs) • Anti-Therapeutic Antibodies (ATAs) against atezolizumab • Cmax and Cmin for atezolizumab • Plasma concentrations of total paclitaxel
Key Results	*Interim efficacy data* Combination of atezolizumab plus nab-paclitaxel as first-line treatment significantly reduced the risk of disease worsening or death (PFS) in the intention-to treat and PD-L1 positive population with metastatic or unresectable locally advanced TNBC. OS was encouraging in the PD-L1 positive population at interim analysis.
Adverse effects (AEs)	*Interim safety data* Safety in atezolizumab plus nab-paclitaxel arm appeared consistent with known

	safety profiles of individual medicines; no new safety signals were identified.
Expected reporting date	Estimated study completion date reported as April 2020

ESTIMATED COST

The NHS indicative price for atezolizumab 1200mg/20ml concentrate for solution for infusion vials is £3807.69.[27] The NHS indicative price for nab-paclitaxel (Abraxane) 100mg powder for suspension for infusion vials is £246.00.[28] Both products are subject to separate, confidential patient access schemes.[29]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Early and locally advanced breast cancer: diagnosis management (NG101). July 2018.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). Published February 2009, updated 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). Published June 2013, updated 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). Published September 2011, updated June 2016.
- NICE cancer service guideline. Improving outcomes in breast cancer (CSG1). August 2002.

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. Manual for prescribed specialised services 2017/18: 105 – Specialist cancer services (adults).

OTHER GUIDANCE

- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer (2017).

- Primary breast cancer: ESMO clinical Practice Guidelines for diagnosis, treatment and follow-up (2015).

REFERENCES

[1] Electronic Medicines Compendium (eMC). *Tecentriq 1,200 mg concentrate for solution for infusio*n. Available from: https://www.medicines.org.uk/emc/product/8442/smpc#PHARMACOLOGICAL_PROPS [Accessed 6th September 2018]

[2] Electronic Medicines Compendium (eMC). *Summary of Product Characteristics (SPC): Abraxane 5 mg/ml powder for suspension for infusion*. 2016; Available from: https://www.medicines.org.uk/emc/medicine/21384 [Accessed 6th September 2018]

[3] ClinicalTrials.gov. *A Study of Atezolizumab in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Participants With Previously Untreated Metastatic Triple-Negative Breast Cancer (IMpassion130)*. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02425891 [Accessed 6th September 2018]

[4] F. Hoffman-La Roche Ltd. *Phase III IMpassion130 study showed Roche's Tecentriq plus Abraxane significantly reduced the risk of disease worsening or death in people with metastatic triple negative breast cancer* (Media Release). Available from: https://www.roche.com/media/releases/med-cor-2018-07-02.htm [Accessed 6th September 2018]

[5] European Medicines Agency. *Abraxane: Summary of Product Characteristics*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000778/WC500020435.pdf [Accessed 6th September 2018]

[6] ClinicalTrials.gov. *Search results: Atezolizumab AND nab-paclitaxel | Phase 2,3*. Available from: https://clinicaltrials.gov/ct2/results?term=atezolizumab+AND+nab-paclitaxel&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 6th September 2018]

[7] Berman AT, Thukral AD, Hwang W-T, Solin LJ, Vapiwala N. *Incidence and Patterns of Distant Metastases for Patients With Early-Stage Breast Cancer After Breast Conservation Treatment*. Clinical Breast Cancer. 2013;13(2):88-94. Available from: https://10.1016/j.clbc.2012.11.001

[8] Cancer Research UK. *Triple negative breast cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/types/triple-negative-breast-cancer [Accessed 6th September 2018]

[9] Breastcancer.org. *Triple-negative breast cancer*. Available from: https://www.breastcancer.org/symptoms/diagnosis/trip_neg [Accessed 6th September 2018]

[10] Breastcancer.org. *What is triple-negative breast cancer?* Available from: https://www.breastcancer.org/symptoms/diagnosis/trip_neg/behaviour [Accessed 6th September 2018]

[11] MacMillan Cancer Support. *Triple negative breast cancer*. Available from: https://www.macmillan.org.uk/information-and-support/breast-cancer/understanding-cancer/types-of-breast-cancer/triple-negative-breast-cancer.html [Accessed 6th September 2018]

[12] Cancer Research UK. *About advanced cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/advanced/about [Accessed 6th September 2018]

[13] BreastCancer.org. *Metastatic Breast Cancer*. Available from: https://www.breastcancer.org/symptoms/types/recur_metast [Accessed 6th September 2018]

[14] NHS Choices. *Breast cancer (female) – Causes*. Available from: https://www.nhs.uk/conditions/breast-cancer/causes/ [Accessed 6th September 2018]

[15] Kataja V, Castiglione M. *Primary breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up*. Annals of Oncology. 2009;20(suppl_4):iv10-iv4. Available from: https://doi.org/10.1093/annonc/mdv298

[16] Kocan S, Gursoy A. *Body Image of Women with Breast Cancer After Mastectomy: A Qualitative Research.* J. Breast Health. 2016 Oct; 12(4):145-150. Available from: https://doi.org/10.5152/tjbh.2016.2913

[17] Cancer Research UK. *Breast cancer incidence (invasive) statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero [Accessed 6th September 2018]

[18] Cancer Research UK. *Breast Cancer Statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer [Accessed 6th September 2018]

[19] Office for National Statistics. *Cancer Registration Statistics, England, 2016*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 6th September 2018]

[20] NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17*. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 6th September 2018]

[21] The Institute of Cancer Research. *Promising drug target for aggressive 'triple negative' breast cancers identified*. Available from: https://www.icr.ac.uk/news-archive/promising-drug-target-for-aggressive-triple-negative-breast-cancers-identified [Accessed 6th September 2018]

[22] Costa R, Gradishar W. *Triple-negative breast cancer: current practice and future directions.* Available from: http://ascopubs.org/doi/full/10.1200/JOP.2017.023333

[23] Yadav BS, Sharma SC, Chanana P, Jhamb S. *Systemic treatment strategies for triple –negative breast cancer*. World J Clin Oncol (2014) 5:2, 125-133. Available from: http://dx.doi.org/10.5306/wjco.v5.i2.125

[24] American Cancer Society. *Breast Cancer Hormone Receptor Status*. Available from: https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html [Accessed 6th September 2018]

[25] National Institute for Health and Care Excellence. *Early and locally advanced breast cancer: diagnosis and management (NG101)*. Available from: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532914901 [Accessed 6th September 2018]

[26] National Institute for Health and Care Excellence. *Managing advanced breast cancer*. Available from: http://pathways.nice.org.uk/pathways/advanced-breast-cancer [Accessed 6th September 2018]

[27] British National Formulary. *Atezolizumab*. Available from: https://bnf.nice.org.uk/medicinal-forms/atezolizumab.html [Accessed 6th September 2018]

[28] British National Formulary. *Paclitaxel*. Available from: https://bnf.nice.org.uk/medicinal-forms/paclitaxel.html [Accessed 6th September 2018]

[29] National Institute for Health and Care Excellence. *List of recommended technologies that include a commercial arrangement*. Available from: https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit/list-of-technologies-with-approved-patient-access-schemes [Accessed 6th September 2018]

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.