NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Atezolizumab for resected non-small cell lung cancer - adjuvant

NIHRIO ID	12762	**NICE ID**	10399
Developer/Company	Roche Products Ltd.	**UKPS ID**	644961

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Atezolizumab is in clinical development as an adjuvant treatment for resectable non-small cell lung cancer (NSCLC). An adjuvant treatment is an additional treatment given after primary treatment that aims to reduce risk of disease recurrence. Lung cancer is one of the most common and serious types of cancer and NSCLC is the most common type of lung cancer. Resectable cancer means that the cancer can be removed by surgery, which means the cancer is normally in earlier stages (I-II). Currently, patients with resectable NSCLC are offered chemotherapy following surgery; there are no immunotherapies (drugs that target the immune system) licensed for this patient group.

Atezolizumab is a type of protein called an antibody, which can bind to a protein called programmed death ligand 1 (PD-L1) to prevent it interacting with its target (PD-1). In doing so, atezolizumab helps immune cells kill cancer cells and is used to treat many different types of cancer that express PD-L1. Atezolizumab is administered intravenously (IV). If licensed, atezolizumab would offer an additional adjunctive treatment option for patients with resectable NSCLC.

PROPOSED INDICATION

As an adjuvant to cisplatin-based chemotherapy in patients with completely resected stage IB-IIIA non-small cell lung cancer.[1]

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is a monoclonal antibody and immune checkpoint inhibitor. Atezolizumab binds to programmed death ligand 1 (PD-L1) to help immune cells kill cancer cells and is used to treat many different types of cancer that express PD-L1.[2]

Programmed death 1 (PD-1) and its ligands PD-L1 and PD-L2 are key co-inhibitory molecules in the modulation of T-cell mediated immune responses. PD-1 is a type I membrane protein that is expressed on the surface of activated T cells in peripheral tissues. PD-L1 and PD-L2 are commonly expressed on dendritic cells and macrophages. Ligation of PD-1 with its two ligands initiates co-inhibitory signalling through the cytoplasmic domain of PD-1, leading to activation of SHP phosphatases that downregulate T-cell receptor signalling by dephosphorylating effector molecules involved in the signalling. As a result, PD-1 signalling prevents excessive or harmful inflammation and maintains immune tolerance to self-antigens under normal conditions.[3]

In the phase III trial, IMpower010 (NCT02486718), participants will receive atezolizumab 1200 mg intravenously (IV) every 3 weeks (Q3W) for sixteen 21-day cycles.[1]

INNOVATION AND/OR ADVANTAGES

If licensed, atezolizumab in combination with platinum-based chemotherapy, would be a novel adjuvant treatment for stage IB-IIIA NSCLC; atezolizumab is currently licensed as a monotherapy for treatment of locally advanced or metastatic NSCLC after prior chemotherapy, or in combination with chemotherapy for the first line treatment of metastatic non-squamous NSCLC.[4,5]

Currently, NIC E recommends surgery in combination with cisplatin based chemotherapy, for patients with resectable, early stage NSCLC. There are no recommendations for an immunotherapy as an adjuvant to chemotherapy following surgical resection of NSCLC, with immunotherapies only offered to non-resectable stage III/IV NSCLC.[5,6]

Immunotherapy offers several advantages to today's standard treatments. The immune system may, when appropriately stimulated, target microscopic disease and disseminated metastases. Further, immunotherapy does not preferentially attack dividing tumour cells, as chemotherapy does. Thus, cancer cells that are slowly dividing or quiescent might be more efficiently targeted by immunotherapy. Depending on the approach, immunotherapy might strike more specifically against the tumour, thus lowering the damage to surrounding healthy tissue and preventing debilitating side effects that are nearly unavoidable with chemotherapy.[7] Immunotherapies, in particular anti-PD-1/PD-L1 therapies have reported grade 3 or 4 toxicities of 10-15%, compared with chemotherapies which are associated with higher toxicities.[8,9]

The findings that treatment with immunotherapy targeting PD-1 and PD-L1 can improve outcomes compared to chemotherapy for select patients in the metastatic setting has led to a number of clinical trials incorporating immunotherapy in earlier stages of the disease. In addition to the improved toxicity profile of immunotherapy compared to cytotoxic

chemotherapy, there is evidence that immune-related changes in the tumour microenvironment may be just as important in early stage NSCLC as in metastatic disease.[10]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab is currently licensed in the EU/UK as a monotherapy for the following indications:[4]

- Adults with locally advanced or metastatic urothelial carcinoma (after prior platinum-containing chemotherapy OR who are considered cisplatin ineligible and whose tumours have PD-L1 expression ≥ 5%)
- Adults with locally advanced or metastatic NSCLC after prior chemotherapy (patients with EGFR mutant or ALK-positive NSCLC should have also received targeted therapies before receiving atezolizumab)

Atezolizumab is currently licensed in the EU/UK as a combination therapy for the following indications:[4]

- In combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic 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
- 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

The most common adverse reactions are: fatigue, decreased appetite, nausea, cough, dyspnoea, pyrexia, diarrhoea, rash, musculoskeletal pain, back pain, vomiting, asthenia, arthralgia, pruritus and urinary tract infection.[4]

The safety of atezolizumab given in combination with other medicinal products, has been evaluated in 3,878 patients across multiple tumour types. The most common adverse reactions were anaemia, neutropenia, nausea, fatigue, alopecia, thrombocytopenia, diarrhoea, rash, constipation, peripheral neuropathy, and decreased appetite.[4]

Atezolizumab is currently in phase III and II development in combination, and as a monotherapy for several lines of treatment and cancers including NSCLC, bladder cancer, melanoma and cervical cancer.[11]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is one of the most common and serious types of cancer. There are usually no signs or symptoms in the early stages of lung cancer, but many people with the condition eventually develop symptoms such as a persistent cough, coughing up blood, persistent breathlessness, unexplained tiredness and weight loss, and/or an ache or pain when breathing or coughing.[12]

Smoking cigarettes is the single biggest risk factor for lung cancer and is responsible for more than 70% of cases. Other risk factors include passive smoking, radon (a radioactive gas), and exposure to chemicals such as arsenic, asbestos, beryllium, cadmium, coal/coke, silica and nickel.[13]

There are three main types of NSCLC: [14]

- Adenocarcinoma – starts in the mucus making gland cells in the lining of airways
- Squamous cell cancer – develops in the flat cells that cover the surface of the airways
- Large cell carcinoma – the cancer appears large and round under the microscope

In addition to being diagnosed by type of lung cancer, patients will also have the cancer graded. Grading is based on how cells look under a microscope, and gives an estimate of how quickly or slowly the cancer is growing, and whether it is likely to spread.[15]

CLINICAL NEED AND BURDEN OF DISEASE

Primary lung cancer remains the most common malignancy after non-melanoma skin cancer, and in 2012, deaths from lung cancer exceeded those from any other malignancy worldwide.[16]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017. There are around 48,000 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2015-2017). Incidence rates for lung cancer are projected to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.[17]

In 2018/19 there were 107,010 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 128,985 finished consultant episodes (FCEs), resulting in 249,196 FCE bed days.[18]

According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,175 diagnosed cases of stage I-III lung cancer in 2017 in England.[19] In the UK, is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage I-III lung cancer cases diagnosed in 2017, it can be estimated that approximately 15,448 cases diagnosed with stage I-III in 2017, were NSCLC.[14]

In England between 2013 and 2017, the age-standardised net lung cancer survival for stage I was 87.7% at one year and 56.6% at five years; for stage II, 73.0% at one year and 34.1% at five years; for stage III, 48.7% at one year and 12.6% at five years.[20] There are around 35,300 lung cancer deaths in the UK every year (based on data from 2015-2017). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[17] In England and Wales in 2018 there were 29,604 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. All patients are advised to stop smoking as soon as diagnosis is suspected; nicotine replacement therapy and other therapies may be offered.[5]

For people who are well enough and for whom curative intent is suitable, surgery (lobectomy, either open or thoracoscopic) may be offered. For people with stage I–IIA NSCLC who decline lobectomy or in whom it is contraindicated, radical radiotherapy with stereotactic ablative radiotherapy (SABR) or sublobar resection is offered. Patients undergoing surgery will also be offered chemotherapy.[5]

CURRENT TREATMENT OPTIONS

Patients with NSCLC are offered the following chemotherapy drugs, in combination with cisplatin or carboplatin:[22]

- Vinorelbine
- Gemcitabine
- Paclitaxel (Taxol)
- Docetaxel (Taxotere)
- Etoposide
- Pemetrexed

PLACE OF TECHNOLOGY

If licensed, adjuvant atezolizumab would offer new immunotherapy option to adjuvant cisplatin-based chemotherapy in patients with completely resected stage IB-IIIA NSCLC.[1]

CLINICAL TRIAL INFORMATION

Trial	**IMpower010 (**NCT02486718**),** A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients With Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer **Phase III** – active, not recruiting **Location(s):** Europe (including the UK), US and other countries **Primary completion date:** November 2020
Trial design	Randomized, parallel assignment, open-label
Population	- N = 1280 - Completely resectable stage IB-IIIA NSCLC - Adults aged 18 years and older
Intervention(s)	- Enrolment Phase: Participants will receive four 21-day cycles of cisplatin-based chemotherapy (cisplatin plus either vinorelbine or docetaxel or gemcitabine or pemetrexed [non-squamous cell NSCLC only]). - Randomization Phase: Participants will receive atezolizumab 1200 milligrams (mg) intravenously (IV) every 3 weeks (Q3W) for sixteen 21-day cycles
Comparator(s)	- Enrolment Phase: Participants will receive four 21-day cycles of cisplatin-based chemotherapy (cisplatin plus either vinorelbine or docetaxel or gemcitabine or pemetrexed [non-squamous cell NSCLC only]) - Randomization Phase: After enrolment phase participants will receive only the best supportive care
Outcome(s)	Disease-Free Survival (DFS), Assessed Using Computed Tomography (CT)/Magnetic Resonance Imaging (MRI)/X-Ray [Time Frame: From randomization to the date of first recurrence of NSCLC, occurrence of new primary NSCLC, or death from any cause, whichever occurs first (up to approximately 131 months)]

	See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Atezolizumab 1200mg/20mL concentrate for solution for infusion vials costs £3807.69 per vial; 840mg/14mL concentrate for solution for infusion vials costs £2665.38 per vial.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE quality standard. Lung cancer in adults (QS17). March 2019.
- NICE technology appraisal guidance. Pemetrexed for the first-line treatment of non-small cell lung cancer (TA181). September 2009.
- NICE technology appraisal guidance. Pemetrexed for the treatment of non-small cell lung cancer (TA124). August 2007.

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 lung resection for primary lung cancer. 16024/P.2016

OTHER GUIDANCE

- European Society of Medical Oncology (ESMO). ESMO Guideline. Early and locally advanced non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow up. 2020.[24]
- European Society of Medical Oncology (ESMO). ESMO Guideline. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow up. 2017.[25]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[26]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[27]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. *Study to Assess Safety and Efficacy of Atezolizumab (MPDL3280A) Compared to Best Supportive Care Following Chemotherapy in Patients With Lung Cancer [IMpower010].* Available from: https://clinicaltrials.gov/ct2/show/NCT02486718 [Accessed 22 Jul 2020].

2 National Cancer Institute. *Atezolizumab*. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/atezolizumab [Accessed 22 Jul 2020].
3 Lee, H., Lee J., Lim H., Lee S., Moon Y., Pyo H., et al. *Molecular mechanism of PD-1/PD-L1 blockade via anti-PD-L1 antibodies atezolizumab and durvalumab*. Scientific reports. 2017;7:5532. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5514103/
4 Electonic Medicines Consortium. *Tecentriq 1,200 mg concentrate for solution for infusion*. Available from: https://www.medicines.org.uk/emc/product/8442/smpc#UNDESIRABLE_EFFECTS [Accessed 22 Jul 2020].
5 National Institute for Health Care Excellence. *Lung cancer: diagnosis and management*. Available from: https://www.nice.org.uk/guidance/ng122/chapter/Recommendations#treatment [Accessed 23 Jul 2020].
6 Cancer Research UK. *Treatment for non small cell lung cancer (NSCLC)*. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/non-small-cell-lung-cancer [Accessed 23 Jul 2020].
7 Dimberu, P. M., Leonhardt R. M. *Cancer immunotherapy takes a multi-faceted approach to kick the immune system into gear*. The Yale journal of biology and medicine. 2011;84(4):371-80. Available from: https://pubmed.ncbi.nlm.nih.gov/22180675
8 Ventola, C. *Cancer Immunotherapy, Part 2: Efficacy, Safety, and Other Clinical Considerations*. Pharmacy and Therapeutics. 2017;42(7):452-63. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481296/
9 Cancerworld. *Management of toxicities related to immunotherapies*. Available from: https://cancerworld.net/e-grandround/management-of-toxicities-related-to-immunotherapies/ [Accessed 21 Jul 2020].
10 Owen, D., Chaft J. *Immunotherapy in surgically resectable non-small cell lung cancer*. Journal of Thoracic Disease. 2018;10:404-11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5861266/
11 Clinicaltrials.gov. *Search result: Atezolizumab, phase 2, 3* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Atezolizumab+&type=&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 30 Jul 2020].
12 National Health Service. *Overview - Lung cancer*. Available from: https://www.nhs.uk/conditions/lung-cancer/ [Accessed 23 Jul 2020].
13 National Health Service. *Causes - Lung cancer*. Available from: https://www.nhs.uk/conditions/lung-cancer/causes/ [Accessed 23 Jul 2020].
14 Cancer Research UK. *Types of lung cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 23 Jul 2020].
15 Cancer Research UK. *Stages and grades of lung cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stages-grades [Accessed 23 Jul 2020].
16 Planchard, D., Popat S., Kerr K., Novello S., Smit E., Faivre-Finn C., et al. *Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up*. Annals of Oncology. 2018;1(29):192-237. Available from: https://pubmed.ncbi.nlm.nih.gov/30285222/
17 Cancer Research UK. *Lung cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 23 Jul 2020].
18 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care Statistics*. 2018-19. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 23 Jul 2020].
19 National Cancer Registration and Analysis Service (NCRAS). *Survival by stage*. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 23 Jul 2020].
20 Office for National Statistics. *Cancer survival in England - adults diagnosed*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 23 Jul 2020].
21 Office for National Statistics. *Deaths registered in England and Wales - 21st century mortality*. 2018. Available from:

https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Accessed 23 Jul 2020].
22 Cancer Research UK. *Chemotherapy treatment for lung cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/chemotherapy/chemotherapy-treatment [Accessed 23 Jul 2020].
23 British National Formulary (BNF). *Atezolizumab*. Available from: https://bnf.nice.org.uk/medicinal-forms/atezolizumab.html [Accessed 22 Jul 2020].
24 Postmus, P., Kerr K., Oudkerk M., Senan S., Wallller J., Vansteenkiste J., et al. *28*. 4. 2017. Available from: https://www.esmo.org/guidelines/lung-and-chest-tumours/early-stage-and-locally-advanced-non-metastatic-non-small-cell-lung-cancer/eupdate-early-and-locally-advanced-non-small-cell-lung-cancer-nsclc-treatment-recommendations
25 Postmus, P., Kerr K., Oudkerk M., Senan S., Waller D., Vansteenkiste J., et al. *Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Annals of Oncology. 2017;28(4):1-21. Available from: https://www.rug.nl/research/portal/publications/early-and-locally-advanced-nonsmallcell-lung-cancer-nsclc(3f345470-1014-44b2-97b4-c9a976c2ce59)/export.html
26 Ettinger, D., Wood D., Aisner D., Akerley W., Bauman J., Chirieac L., et al. *Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology*. Journal of the National Comprehensive Cancer Network. 2017;15(4):504-35. Available from: https://jnccn.org/view/journals/jnccn/15/4/article-p504.xml
27 Scottish Intercollegiate Guidelines Network (SIGN). *Management of lung cancer (SIGN 137)*. Available from: http://www.stnba.org.ar/images/biblioteca/guias_consensos/guia_6317.pdf [Accessed 23 Jul 2020].

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.