

**NIHR Innovation Observatory
Evidence Briefing: June 2018**

**Atezolizumab in addition to carboplatin or cisplatin
and pemetrexed for stage IV non-squamous non-
small cell lung cancer (NSCLC)**

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LAY SUMMARY

Lung cancer arises from cells in the lungs that have grown abnormally and multiplied to form a tumour. Non-squamous non-small cell lung cancer (NSCLC) is a type of lung cancer that is differentiated from small-cell lung cancer (SCLC) by the way the tumour cells look under a microscope. Symptoms include a persistent cough, hoarseness, shortness of breath, weight-loss or lack of appetite, feeling weak or tired, coughing up blood and pneumonia/or infections that keep coming back. Stage IV non-squamous NSCLC is the most advanced form of the disease where the cancer has spread beyond the lungs into other areas of the body. The aim of treatment at this stage is to prolong survival, improve quality of life, and control disease-related symptoms.

Atezolizumab is a monoclonal antibody designed to recognise and attach to a protein called 'programmed death-ligand 1' (PD-L1), which is present on the surface of many cancer cells. PD-L1 switches off immune cells that would otherwise attack cancer cells. By attaching to PD-L1 and reducing its effect, atezolizumab increases the ability of the immune system to attack cancer cells and thereby slows the progression of the disease. Atezolizumab is administered by intravenous infusion. If licensed, atezolizumab in addition to the chemotherapy drugs, carboplatin or cisplatin and pemetrexed will offer an additional treatment option for patients with advanced, non-squamous NSCLC.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Non-small cell lung cancer (NSCLC) (non-squamous, stage IV) – chemotherapy-naïve, add on therapy; atezolizumab in combination with carboplatin or cisplatin and pemetrexed

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 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. PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. 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

Carboplatin or cisplatin and pemetrexed are standard chemotherapies used to treat a wide range of cancers including non-small cell lung cancer (NSCLC). They exert their antineoplastic effects via different mechanisms to inhibit and destroy the growth of rapidly dividing cells.²

In the phase III trial (IMpower 132, NCT02657434) participants will receive intravenous (IV) infusion of 1200 milligrams (mg) of atezolizumab on Day 1 every 3 weeks (q3w), IV infusion of 500 milligrams per meter square (mg/m²) pemetrexed on Day 1 q3w, and as per investigator's choice either IV infusion of carboplatin on Day 1 q3w with a dose calculated using 'Calvert formula' to obtain area under concentration versus time (AUC) = 6 milligrams per millilitre per minute (mg/mL/min) or IV infusion of 75 mg/m² cisplatin q3w on Day 1 q3w, during induction dosing period of 4 or 6 cycles (cycle length=21 days). Participants who experience clinical benefit during the induction phase will begin maintenance therapy. Participants will receive IV infusion of 1200 mg of atezolizumab and 500 mg/m² of pemetrexed on Day 1 q3w until disease progression in the maintenance period.³

Atezolizumab is licensed in the UK for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible. Atezolizumab is also licensed as monotherapy indicated for the treatment of 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 ($\geq 1/10$) adverse effects of atezolizumab include fatigue, decreased appetite, nausea, dyspnoea, diarrhoea, rash, pyrexia, vomiting, arthralgia, asthenia and pruritus.¹

Atezolizumab is also in phase II and phase III clinical development, as a monotherapy or in combination with other therapies, for the treatment of a range of cancers including bladder, pancreatic, gastric, breast, and solid tumours.⁴

INNOVATION and/or ADVANTAGES

Non-squamous NSCLC is often diagnosed late in life and causes debilitating and distressing symptoms. There are few treatment options for non-squamous NSCLC, many of which are associated with high toxicity. Chemotherapy is often not well tolerated, and any improvement in quality of life and extension to life would be a significant benefit to patients and their families.⁵ If licensed, atezolizumab in addition to carboplatin or cisplatin and pemetrexed will offer an additional treatment option for those with stage IV non-squamous chemotherapy-naïve NSCLC who currently have few well tolerated and effective therapies available.

DEVELOPER

Roche Products Ltd

REGULATORY INFORMATION/ MARKETING PLANS

Atezolizumab was designated Breakthrough Therapy for NSCLC by FDA in February 2015.⁶

PATIENT GROUP

BACKGROUND

Cancer that starts in the lung is called primary lung cancer. There are different types of primary lung cancer, divided into two main groups of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Approximately 87% of lung cancers in the UK are NSCLC. The three main types of NSCLC are squamous cell carcinoma, adenocarcinoma and large cell (undifferentiated carcinoma) of the lung. The latter two lung adenocarcinomas comprise non-squamous histology which account for approximately 50-55% of NSCLC diagnoses in the EU.⁷

Lung cancer may be suspected if a person has symptoms such as persistent cough or chest infection, breathlessness, hoarseness, chest pain or coughing up blood. Other symptoms may be fever, appetite loss, unexplained weight loss and fatigue.⁸ Smoking cigarettes is the main cause of lung cancer. However, people who don't smoke can still develop lung cancer. If someone stops smoking, their risk of developing lung cancer falls quickly and within 15 years will be similar to that of non-smokers. Other risk factors may include second hand smoke inhalation, old age, influence of familial heredity, previous radiotherapy of the chest, and environmental factors such as exposure to high concentrations of radon gas or asbestos.⁹

Stage IV non-squamous NSCLC is the most advanced form of the disease where the cancer has spread beyond the lungs into other areas of the body. The aim of treatment at this stage is to prolong survival, improve quality of life (QoL), and control disease-related symptoms.¹⁰ Progress of the disease, severity of its symptoms, and treatment side effects decrease significantly the QoL in lung cancer patients. The QoL in lung cancer patients is lower than in healthy population and patients suffering from other malignancies. Fatigue and respiratory problems reduce psychological dimensions of QoL, while sleep problems reduce cognitive functioning. Physical dimensions (related to growing disability) decrease in most patients, and many are unable to engage in their family and social roles. The disease is a frequent reason of irritation, distress, and depression.¹¹

CLINICAL NEED and BURDEN OF DISEASE

As of 2016, lung cancer was the third most common cancer in the UK accounting for 12.7% of cancer registrations in England. It was the second most common malignant cancer for both males and females in 2016, with 38,381 (20,560 males and 17,821 females) cases of lung cancer registered in England. The age-standardized rate for lung cancer has decreased in males from 101.5 per 100,000 males in 2006 to 89.8 cases per 100,000 in 2016; whilst lung cancer in females has increased in this same period, from 57.9 cases per 100,000 females in 2006 to 65.5 per 100,000 in 2016. This change in incidence could be explained by the changes in smoking habits over the last decade or so, as smoking has been identified as the most common cause of lung cancer.¹²

NSCLC is the more common type of lung cancer, found in approximately 85% to 90% of patients.¹³ Adults diagnosed with late cancer (stage IV) in 2015, which had already spread to other parts of the body, have lower 1-year survival compared with those diagnosed in the earliest stage (stage I), with the lowest survival in lung cancer in men (17.1%) and women (21.6%). Age-standardized 5-year net survival for men and women (aged 15 to 99 years) diagnosed with lung cancer between 2011 and 2015, and followed up to 2016, was 13.1% for men and 17.1% for women. In 2015, almost half of lung cancer were diagnosed at stage IV.¹⁴

Lung cancer is the most common cause of cancer death in the UK, account for 21% of all cancer deaths. In 2016, there were 35,620 deaths in the UK attributed to lung cancer.¹⁵ In England in 2016-17, there were 112,905 finished consultant episodes for malignant neoplasm of bronchus and lung (ICD-10: C34), resulting in 91,902 hospital admissions and 267,931 FCE bed days.¹⁶

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Atezolizumab for untreated non-squamous non-small-cell lung cancer (ID1210). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer [ID1306]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer (ID1277). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Lung cancer (non-small-cell, advanced or metastatic second line) - erlotinib (in combination with bevacizumab) (ID43). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Lung cancer (non-small-cell, advanced or metastatic maintenance treatment) - erlotinib (in combination with bevacizumab) (ID44). Expected date of issue to be confirmed.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520).
- NICE technology appraisal. Nivolumab for previously treated squamous non-small-cell lung cancer (TA483). November 2017.
- NICE technology appraisal. Nivolumab for previously treated non-squamous non-small-cell lung cancer (TA484). November 2017.

- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA447). June 2017.
- NICE technology appraisal. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (TA416). October 2016.
- NICE technology appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). September 2016.
- NICE technology appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). August 2016.
- NICE technology appraisal. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (TA403). August 2016.
- NICE technology appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
- NICE technology appraisal. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (TA374). December 2015.
- NICE technology appraisal. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (TA258). June 2012.
- NICE technology appraisal. Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer (TA227). June 2011.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (TA190). June 2010.
- NICE technology appraisal. Topotecan for the treatment of relapsed small-cell lung cancer (TA184). November 2009.
- NICE technology appraisal. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009.
- NICE technology appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.
- NICE interventional procedure guidance. Microwave ablation for treating primary lung cancer and metastases in the lung (IPG469). November 2013.
- NICE interventional procedure guidance. Irreversible electroporation for treating primary lung cancer and metastases in the lung (IPG441). February 2013.
- NICE diagnostics guidance. EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer (DG9). August 2013.

NHS ENGLAND and POLICY 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. 2016 Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. 16024/P.
- NHS England. 2013 Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small Cell Lung Cancer (Adult). B01/P/a.

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2016¹⁷
- Scottish Intercollegiate Guidelines Network. Management of lung cancer. 2014¹⁸
- National Comprehensive Cancer Network. The NCCN clinical practice guidelines in oncology – non-small cell lung cancer. 2013¹⁹

CURRENT TREATMENT OPTIONS

Treatment of non-squamous NSCLC varies by location within the lung and/or body, how far the cancer has spread (the stage), abnormality of cells (the grade), and the general health and level of fitness of the patient. Treatment options may include surgery, chemotherapy and/or radiotherapy, and a variety of symptom control management treatments. NSCLC is referred to as metastatic or stage IV disease when it has spread beyond the lung which was initially affected. It is rarely possible to remove metastatic NSCLC with surgery or to treat it radically with chemotherapy.⁸

Intravenous chemotherapy with a two-drug combination (with or without the addition of the targeted therapy called bevacizumab) is the main treatment option for patients with metastatic or stage IV NSCLC. New options using first-line immunotherapy are under evaluation and pembrolizumab has recently been approved in the EU for use in this setting. Immunotherapy is likely to replace or complement first-line chemotherapy in selected patients in the next few years.⁸

In the clinical management of treatment-naïve non-squamous NSCLC, platinum therapy may be given as an initial treatment in people whose disease is not epidermal growth factor receptor mutation (EGFR) or anaplastic lymphoma kinase (ALK) positive.²⁰ In patients whose tumours express high amounts of PD-L1, pembrolizumab may be given.²¹ For those with EGFR-positive disease, treatment may start with a targeted tyrosine kinase inhibitor (TKI) such as erlotinib, followed by a platinum therapy option after the disease stops responding to TKI therapy.²⁰ For people with ALK-positive NSCLC, an ALK-inhibitor such as alectinib, ceritinib or crizotinib are typically the standard treatment of choice.^{5,20,22}

Updates to NICE clinical guideline (CG121) for the diagnosis and management of lung cancer are expected in March of 2019.²³ NICE technology appraisal guidance for the use of atezolizumab for untreated non-squamous non-small-cell lung cancer (ID1210) is also in development, with expected publication date to be confirmed.²⁴

EFFICACY and SAFETY

Trial	IMpower 132, NCT02657434; stage IV non-squamous non-small cell lung cancer (NSCLC); atezolizumab in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed; phase III
Sponsor	Hoffman-La Roche
Status	Ongoing
Source of Information	Trial registry ³
Location	15 EU countries (incl UK), USA, and other countries
Design	Randomised, active-controlled, parallel assignment, open label

Participants	n=568 (planned); aged ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; histologically or cytologically confirmed, Stage IV non-squamous NSCLC; no prior treatment for Stage IV non-squamous NSCLC; participants who have received prior neo-adjuvant, radiotherapy, adjuvant chemotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomisation since the last dose of chemotherapy and/or radiotherapy; measurable disease, as defined by RECIST v1.1; adequate hematologic and end organ function
Schedule	<p>Experimental: Arm A (Atezolizumab + carboplatin or cisplatin + pemetrexed) Participants will receive IV infusion of 1200 mg of atezolizumab on Day 1 q3w, IV infusion of 500 milligrams per meter square (mg/m²) pemetrexed on Day 1 q3w, and as per investigator's choice either IV infusion of carboplatin on Day 1 q3w with a dose calculated using 'Calvert formula' to obtain area under concentration versus time (AUC) = 6 mg/mL/min or IV infusion of 75 mg/m² cisplatin q3w on Day 1 q3w, during induction dosing period of 4 or 6 cycles (Cycle length=21 days). Participants who experience clinical benefit during the induction phase will begin maintenance therapy. Participants will receive IV infusion of 1200 mg of atezolizumab and 500 mg/m² of pemetrexed on Day 1 q3w until disease progression in the maintenance period.</p> <p>Active Comparator: Arm B (Carboplatin or Cisplatin + Pemetrexed) Participants will receive IV infusion of 500 mg/m² pemetrexed on Day 1 q3w, and as per investigator's choice of either IV infusion of carboplatin on Day 1 q3w with a dose calculated using 'Calvert formula' to obtain AUC =6 mg/mL/min or IV infusion of 75 mg/m² cisplatin q3w on Day 1 q3w, during induction dosing period for 4 or 6 cycles (Cycle length=21 days). Participants who do not experience disease progression during the induction phase will begin maintenance therapy. Participants will receive IV infusion of 500 mg/m² of pemetrexed on Day 1 q3w until disease progression in the maintenance period.</p>
Follow-up	Not reported
Primary Outcomes	<ul style="list-style-type: none"> • Progression Free Survival as assessed by the investigator using Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) [Time frame: Baseline then every 6 weeks for 12 months after Cycle (Cy length=21 days) 1 Day (D) 1;every 9 weeks until radiographic disease progression, consent withdrawal, death, or study termination by Sponsor, whichever occurs first (up to approximately 44 months)] • Overall Survival [Time frame: Baseline then every 6 weeks for 12 weeks following Cy1D1 (Cy length=21 days) & then every 9 weeks until death (up to approximately [app] 44 months)]
Secondary Outcomes	<ul style="list-style-type: none"> • Percentage of participants who survived at Year 1 [Time frame: Year 1] • Percentage of participants who survived at Year 2 [Time frame: Year 2] • Percentage of participants with an Objective Response (Complete Response or Partial Response) assessed by the investigator using RECIST V1.1 [Time frame: Baseline then every 6 weeks for 12 months following Cy1D1 (Cy length=21 days) thereafter every 9 weeks until radiographic disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first (up to app 44 months)] • Duration of response as determined by the investigator using RECIST v1.1 [Time frame: Baseline then every 6 weeks for 12 months following Cy1D1

	<p>(Cy length=21 days) thereafter every 9 weeks until radiographic disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first (up to app 44 months)]</p> <ul style="list-style-type: none"> • Time to deterioration in patient-reported lung cancer symptoms as assessed by European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 (QLQ-C30) Symptom Score [Time frame: Baseline up to 3 and 6 months after disease progression or loss of clinical benefit (up to app 44 months)] • Time to deterioration in patient-reported lung cancer symptoms as assessed by EORTC Quality-of-Life Lung Cancer Module (QLQ-LC13) Symptom Score [Time frame: Baseline up to 3 and 6 months after disease progression or loss of clinical benefit (up to approximately 44 months)] • Change from baseline in patient-reported lung cancer symptoms as reported using the Symptoms in Lung Cancer (SILC) Scale Score [Time frame: Baseline up to 3 and 6 months after disease progression or loss of clinical benefit (up to app 44 months)] • Minimum observed serum atezolizumab concentration prior to infusion [Time frame: Predose (Prd; 0 hour [h]) on D1 of Cy1,2,3,4,8,16 (Cy length=21 days) and thereafter on D1 of every 8th cycle (up to app 44 months)] • Maximum observed serum atezolizumab concentration prior to infusion [Time frame: Prd (0h) on D1 of Cy1,2,3,4,8,16 (Cy length=21 days) & thereafter on D1 of every 8th cy; 0.5h post infusion (infusion duration=1h) on Cy1D1; at treatment discontinuation & then every 30 days (up to 120 days) after atezolizumab last dose (up to app 44 months)] • Plasma concentrations for carboplatin in Arm A (atezolizumab + carboplatin or cisplatin + pemetrexed) [Time frame: Prd (0 h), 5-10 minutes (mins) before end of carboplatin infusion (infusion duration=1-2 h), 1 h post-infusion on D1 of Cy1,3 (Cy length=21 days)] • Plasma concentrations for cisplatin in Arm A (atezolizumab + carboplatin or cisplatin + pemetrexed) [Time frame: Prd (0 h), 5-10 mins before end of cisplatin infusion (infusion duration=30-60 mins), 1 h post-infusion on D1 of Cy1,3 (Cy length=21 days)] • Plasma concentrations for pemetrexed in Arm A (atezolizumab + carboplatin or cisplatin + pemetrexed) [Time frame: Prd (0 h), 5-10 mins before end of pemetrexed infusion (infusion duration=10 mins), 1 h post-infusion on D1 of Cy1,3 (Cy length=21 days)] • Percentage of participants with anti-therapeutic antibodies of atezolizumab [Time frame: Prd (0 h) on D1 of Cy1,2,3,4,8,16 (Cy length=21 days) and thereafter on D1 of every 8th cycle, at treatment discontinuation & then every 30 days (up to 120 days) after last dose of atezolizumab (up to app 44 months)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date November 2019.

ESTIMATED COST and IMPACT

COST

Atezolizumab is already reimbursed and marketed in the UK for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible. Atezolizumab is also reimbursed and marketed as a monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy.¹

The cost of atezolizumab 20 mL /1,200 mg concentrate for solution for infusion vials is £3807.69.²⁵

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- None identified

IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs
- Reduced drug treatment costs
- None identified

OTHER ISSUES

- None identified

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