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HEALTH TECHNOLOGY BRIEFING
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Atezolizumab for stage IV non-squamous or squamous non-small cell lung cancer

NIHRIO ID	11025	**NICE ID**	8396
Developer/Company	Roche Products Ltd	**UKPS ID**	596961

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

SUMMARY

Atezolizumab is in clinical development for stage IV non-squamous or squamous non-small cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK. Stage IV (advanced/metastatic) NSCLC is when the cancer has spread beyond the lung which was initially affected, most often to the liver, the adrenal glands, the bones, and the brain. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable. Currently, chemotherapy remains the main first line option at this stage and often not well tolerated by many patients.

Atezolizumab is a monoclonal antibody against the protein, programed death-ligand 1 (PD-L1), which is highly expressed on certain tumours. This overexpression can lead to reduced activation of immune cells that might otherwise recognise and 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. If licensed, atezolizumab will offer an additional treatment option for patients with untreated stage IV squamous or non-squamous NSCLC.

PROPOSED INDICATION

PD-L1-selected, chemotherapy-naive patients with stage IV non-squamous or squamous Non-Small Cell Lung Cancer (NSCLC).[a]

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) anti-programmed death-ligand 1 (PD-L1) monoclonal antibody. PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the anti-tumour 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. Atezolizumab directly binds to 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.[1]

Atezolizumab is in clinical development for stage IV non-squamous or squamous Non-Small Cell Lung Cancer (NSCLC). In the phase III clinical trial (NCT02409342; IMpower110), atezolizumab 1,200mg is administered as intravenous infusion every 21 days until loss of clinical benefit (as assessed by the investigator), unacceptable toxicity, or death (maximum up to approximately 58 months).[2]

INNOVATION AND/OR ADVANTAGES

About 70% of NSCLC patients are diagnosed with advanced disease at diagnosis. The majority of patients diagnosed with NSCLC are unsuitable for curative treatment. Although immunotherapies targeting PD-L1/PD-1 are currently available for NSCLC, chemotherapy remains the main first line option despite poor survival.[3] 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.[4]

Atezolizumab prevents PD-L1 from interacting with its receptors PD-1 and B7.1, restoring tumour-specific T-cell immunity. Clinical efficacy has been demonstrated with atezolizumab in non-squamous and squamous NSCLC, with phase I and II studies exhibiting durable responses and survival benefit that increases with higher PD-L1 expression on tumour cells and/or tumour-infiltrating immune cells.[3]

Atezolizumab does not have a marketing authorisation as a monotherapy in the UK for untreated metastatic squamous and non-squamous NSCLC. If licensed, atezolizumab will offer an additional treatment option for those with stage IV squamous or non-squamous chemotherapy-naïve NSCLC who currently have few well tolerated and effective therapies available.[3]

[a] Information provided by Roche Products Ltd

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 NSCLC after prior chemotherapy.

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]

Atezolizumab is in phase II and III stages of development for the treatment of various types of cancers such as: urothelial or non-urothelial carcinoma of the urinary tract, advanced renal cell carcinoma, breast cancer and bladder cancer.[5,6]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. NSCLC comprises approximately 87% of lung cancers in the UK. There are three common types of NSCLC; adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways), squamous cell cancer (develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung) and large cell carcinoma (cancer cells which appear large and round under the microscope).[7]

Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of lung cancers. In countries with active tobacco control measures, the incidence of lung cancer has begun to decline in men and is reaching a plateau for women. An increase in the proportion of NSCLC in never-smokers has been observed, especially in Asian countries. These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified.[8]

Several other factors have been described as lung cancer risk factors including; exposure to radiation certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes) and previous lung disease (e.g. tuberculosis and COPD). Other factors include family history of lung cancer and certain genetic mutations and lowered immunity (e.g. due to certain conditions e.g. HIV/AIDS, rheumatoid arthritis and systemic lupus erythematosus, or immunosuppressive medications).[9]

Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[10]

CLINICAL NEED AND BURDEN OF DISEASE

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide.[8] Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2016. There are around 47,200 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2014-2016). 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.[11]

According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,655 diagnosed cases of stage IV lung cancer in 2016, this represents the 48% of the overall number of lung cancer cases diagnosed for that year.[12] In the UK is estimated that up to 87% of lung cancer cases are NSCLC,[13] applying this figure to the number of stage IV lung cancer cases diagnosed in 2016, it can be estimated that approximately 16,230 cases diagnosed with stage IV in 2016 were NSCLC.

Survival rates for lung cancer depend on at which stage of disease the cancer is identified.[11] In England between 2012 and 2016, the age-standardised net lung cancer survival for stage IV was 18.7% at one year and 2.6% at five years.[14]

There are around 35,600 lung cancer deaths in the UK every year. Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[11] In England and Wales in 2017 there were 30,131 deaths with malignant neoplasm of trachea, bronchus and lung (ICD-10 codes C33-34) recorded as the underlying cause.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. The main treatment options for stage I, II and III NSCLC are surgery, chemotherapy and radiotherapy.

At stage IV NSCLC treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally include chemotherapy, targeted drugs, radiotherapy and symptom control treatment.[16]

CURRENT TREATMENT OPTIONS

The following are recommended for first-line treatment of patients with advanced non-squamous (stages IIIB and IV) NSCLC, and no specific modifications to the EGFR or ALK genes: [17]

- PD-L1 under 50% (no gene mutation, fusion protein or biomarker):
  - Atezolizumab plus bevacizumab, carboplatin and paclitaxel
  - Pembrolizumab, with pemetrexed and platinum chemotherapy
  - Pemetrexed in combination with cisplatin

- PD-L1 50% or over (no gene mutation, fusion protein or biomarker):
  - Pembrolizumab, with pemetrexed and platinum chemotherapy
  - Pembrolizumab

For treatment of squamous NSCLC, NICE recommends platinum-based chemotherapy (that is, cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel, or vinorelbine) as an option for people with previously untreated stage III or IV NSCLC and good performance status.

Pembrolizumab monotherapy is also recommended as an option for untreated PD-L1-positive metastatic NSCLC if the tumour expresses PD-L1 with at least 50% tumour proportion score and has no EGFR- or ALK-positive mutations.[18,19]

PLACE OF TECHNOLOGY

If licensed, atezolizumab will offer an additional first line treatment option for patients with stage IV non-squamous or squamous NSCLC.

CLINICAL TRIAL INFORMATION

Trial	**IMpower110; NCT02409342; EudraCT-2014-003083-21; atezolizumab vs platinum agent (cisplatin or carboplatin) plus pemetrexed or gemcitabine; phase III**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[2]
Location	9 EU countries (incl. UK), USA and other countries
Design	Randomised/open label/parallel assignment
Participants	N=572;aged 18 years and older; stage IV non-squamous or squamous NSCLC; no prior treatment for stage IV non-squamous or squamous NSCLC; tumour PD-L1 expression; measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST v1.1); adequate haematologic and end-organ function
Schedule	Randomised to: • Active comparator: (Carboplatin/ Cisplatin) + (Pemetrexed/ Gemcitabine) Participants with non-squamous NSCLC will receive chemotherapy with pemetrexed in combination with either cisplatin or carboplatin (per investigator discretion) on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by maintenance therapy with pemetrexed alone as per local standard of care. Participants with squamous NSCLC will receive chemotherapy with gemcitabine on Days 1 and 8 of each 21-day cycle in combination with either cisplatin or carboplatin on Day 1 of each 21-day cycle for 4 or 6 cycles as per local standard of care, followed by best supportive care as per local standard of care until disease progression, unacceptable toxicity, or death (maximum up to approximately 58 months).

	- Cisplatin will be administered as intravenous infusion at a dose of 75 mg per meter squared (mg/m^2) every 21 days for 4 or 6 cycles as per local standard of care. - Gemcitabine will be administered as intravenous infusion at a dose of 1250 mg/m^2 (in combination with cisplatin) or 1000 mg/m^2 (in combination with carboplatin), on Days 1 and 8 of each 21-day cycle for 4 or 6 cycles as per local standard of care. - Carboplatin will be administered as intravenous infusion at a dose of area under the concentration-time curve (AUC) 6 when given in combination with pemetrexed or at a dose of AUC 5 when given in combination with gemcitabine, every 21 days for 4 or 6 cycles as per local standard of care. - Pemetrexed will be administered as intravenous infusion at a dose of 500 mg/m^2 on Day 1 of each 21-day cycle as per local standard of care until disease progression. • Experimental: Atezolizumab Participants with squamous or non-squamous NSCLC will receive atezolizumab 1.200 milligram (mg) as intravenous infusion every 21 days until loss of clinical benefit.
Follow-up	Up to 58 months
Primary Outcomes	Overall Survival (OS) [Time Frame: From randomisation to death from any cause (maximum up to approximately 58 months)]
Secondary Outcomes	• Progression-free survival (PFS) time determined by the investigator using Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) [Time frame: From randomization to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 58 months)] • Percentage of participants with Objective Response (ORR) [Time frame: Every 6 weeks for 48 weeks following day 1, thereafter every 9 weeks after completion of the week 48 tumour assessment, regardless of treatment delays, until radiographic disease progression (maximum up to approximately 58 months)] • Duration of response (DOR) as determined by the investigator using RECIST v1.1 [Time frame: from the first occurrence of a complete response (CR) or partial response (PR), whichever occurs first, until the first date that progressive disease or death is documented, whichever occurs first (up to approximately 58 months)] • Percentage of participants who are alive at 1 and 2 years [Time frame: 1 and 2 years] • Time to deterioration (TTD) in patient-reported lung cancer symptoms score as assessed by the symptoms in lung cancer (SILC) scale symptom score [Time frame: baseline up to approximately 58 months] • Change from baseline in patient-reported lung cancer symptoms score as assessed by the SILC scale symptom score [Time frame: Baseline up to approximately 58 months]

	• TTD as assessed using European organization for the research and treatment of cancer (EORTC) quality of life questionnaire-core (EORTC QLQ-C30) [Time frame: Baseline up to approximately 58 months] • TTD as assessed using EORTC QLQ supplementary lung cancer module (EORTC QLQ-LC13) [time frame: baseline up to approximately 58 months] • OS in participants with pd-l1 expression [Time frame: from randomization to death from any cause (maximum up to approximately 58 months)] • Investigator-assessed PFS in participants with pd-l1 expression according to RECIST v1.1 [Time frame: from randomisation to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 58 months)] • OS in participants with blood tumour mutational burden (BTMB) [Time frame: from randomisation to death from any cause (maximum up to approximately 58 months)] • Investigator-assessed PFS in participants with BTMB according to RECIST v1.1 [time frame: from randomization to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 58 months)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as October 2019

ESTIMATED COST

The NHS indicative price for one vial of atezolizumab 1200mg/20ml (60 mg/1 ml) concentrate for solution for infusion is £3,807.69.[20]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer (ID1277). Expected publication date TBC.
- NICE technology appraisal guidance in development. Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score (ID1247). Expected publication date TBC.
- NICE technology appraisal guidance in development. Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations (ID1143). Expected publication date January 2020.

- NICE technology appraisal guidance in development. Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer (ID1306). Expected publication date July 2019.
- NICE technology appraisal guidance. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557). January 2019.
- NICE technology appraisal guidance. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). June 2019.
- NICE technology appraisal guidance. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE technology appraisal guidance. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal guidance. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- 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.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2019.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.[8]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[21]
- European Society for Medical Oncology. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[22]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[23]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[24]

ADDITIONAL INFORMATION

REFERENCES

1 Electronic Medicines Compendium (emc). *Tecentriq 1,200 mg concentrate for solution for infusion.* Available from:

https://www.medicines.org.uk/emc/product/8442#PHARMACOLOGICAL_PROPS [Accessed 03 June 2019].
2 ClinicalTrials.gov. *A Study of Atezolizumab (MPDL3280A) Compared With a Platinum Agent (Cisplatin or Carboplatin) + (Pemetrexed or Gemcitabine) in Participants With Stage IV Non-Squamous or Squamous Non-Small Cell Lung Cancer (NSCLC) [IMpower110]. Trial ID: NCT02409342*. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT02409342 [Accessed 04 June 2019].
3 Herbst RS, Marinis FD, Jassem J, Lam S, Mocci S, Sandler A, et al. *Mpower110: Phase III Trial Comparing 1L Atezolizumab with Chemotherapy in PD-L1eSelected ChemotherapyNaive NSCLC Patient*. Available from: https://www.jto.org/article/S1556-0864(16)31040-1/pdf [Accessed 19 June 2019].
4 National Institute for Health and Care Excellence. *Nivolumab for previously treated nonsquamous non-small-cell lung cancer*. 2017. Available from: https://www.nice.org.uk/guidance/ta484/resources/nivolumab-for-previously-treated-nonsquamous-nonsmallcell-lung-cancer-pdf-82605026489029 [Accessed 19 June 2019].
5 ClinicalTrials.gov. *35 Studies found for: Atezolizumab | roche [Lead] | Phase 3*. Available from: https://clinicaltrials.gov/ct2/results?intr=Atezolizumab&lead=roche&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 18 June 2019].
6 ClinicalTrials.gov. *28 Studies found for: Atezolizumab | roche [Lead] | Phase 2*. Available from: https://clinicaltrials.gov/ct2/results?intr=Atezolizumab&lead=roche&age_v=&gndr=&type=&rslt=&phase=1&Search=Apply [Accessed 18 June 2019].
7 Cancer Research UK. *Types of Lung cancer*. 2017. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 15 May 2019].
8 Planchard D, Popat S, Kerr K, Novello S, Smit EF, 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;29(Supplement_4):iv192-iv237. Available from: https://doi.org/10.1093/annonc/mdy275.
9 Cancer Research UK. *Lung cancer; Risks and causes*. 2017. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes [Accessed 15 May 2019].
10 Cancer Research UK. *Symptoms of lung camcer*. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/symptoms [Accessed 18 June 2019].
11 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 15 May 2019].
12 National Cancer Registration and Analysis Service (NCRAS). *Stage breakdown by CCG 2016*. Available from: http://www.ncin.org.uk/view?rid=3604 [Accessed 21 September 2018].
13 Cancer Research UK. *Lung cancer; Stages, types and grades*. 2017. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 21 May 2019].
14 Office for National Statistics (ONS). *Cancer Survival in England: adults diagnosed between 2012 and 2016 and followed up to 2017*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed
15 Office for National Statistics (ONS). *Death Registrations Summary Statistics, England and Wales, 2017*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Downloaded August 2018].
16 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 15 May 2019].
17 National Institute for Health and Care Excellence. *Advanced non-squamous (stages IIIB and IV) non-small-cell lung cancer: PD-L1 under 50% (no gene mutation, fusion protein or biomarker)*. Available from: https://pathways.nice.org.uk/pathways/lung-cancer/advanced-non-squamous-stages-iiib-and-iv-non-small-cell-lung-cancer-pd-l1-under-50-no-gene-mutation-fusion-protein-or-biomarker.pdf [Accessed 19 June 2019].

18 National Institute for Health and Care Excellence. *Systemic anti-cancer therapy: management options for people with squamous non-small-cell carcinoma.* Available from: https://www.nice.org.uk/guidance/ng122/resources/algorithm-for-systemic-treatment-options-for-advanced-squamous-nsclc-pdf-6722110910 [Accessed 08 July 2019].

19 National Institute for Health and Care Excellence. *Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]: Final scope.* Available from: https://www.nice.org.uk/guidance/gid-ta10245/documents/final-scope [Accessed 08 July 2019].

20 British National Formulary (BNF). *ATEZOLIZUMAB.* Available from: https://bnf.nice.org.uk/medicinal-forms/atezolizumab.html [Accessed 04 June 2019].

21 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017 Apr;15(4):504-35. Available from: https://jnccn.org/view/journals/jnccn/15/4/article-p504.xml.

22 Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2018;29(Supplement_4):iv238-iv55. Available from: https://doi.org/10.1093/annonc/mdy308.

23 Besse B, Members P, Adjei A, Members P, Baas P, Members P, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Annals of Oncology*. 2014;25(8):1475-84. Available from: https://doi.org/10.1093/annonc/mdu123.

24 Scottish Intercollegiate Guidelines Network. *Management of lung cancer (SIGN 137).* Last Update Date: Available from: https://www.sign.ac.uk/assets/sign137.pdf [Accessed 21 May 2019].

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