NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JUNE 2019

Ramucirumab in addition to erlotinib for EGFR mutation-positive metastatic non-small-cell lung cancer

NIHRIO ID	12126	**NICE ID**	9809
Developer/Company	Eli Lilly and Company Ltd	**UKPS ID**	N/A

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

SUMMARY

Ramucirumab in addition to erlotinib is in clinical development for Epithelial Growth Factor Receptor (EGFR) mutation-positive metastatic 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. Certain genetic mutations to the EGFR are known to play critical role in NSCLC progression and response to treatment due to the fact that overexpression of EGFR is known to accelerate the growth of cancer cells.

Ramucirumab has been designed to attach to a receptor for a protein called Vascular Endothelial Growth Factor (VEGF). The VEGF receptor can be present at high levels in tumours and helps in the development of new blood vessels that supply the tumours. Ramucirumab blocks this action by blocking this receptor, thereby reducing the blood supply to the tumour and slowing the growth of the cancer. Erlotinib is currently a standard of care first-line treatment for locally advanced or metastatic NSCLC with EGFR mutations. It is thought that the addition of ramucirumab to erlotinib might improve its efficacy and provide an additional benefit by delaying/suppressing the EGFR mutation in patients with NSCLC.

PROPOSED INDICATION

First-line treatment in patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations[a]

TECHNOLOGY

DESCRIPTION

Ramucirumab (Cyramza, LY3009806) is a human receptor-targeted antibody that specifically binds VEGF Receptor 2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. Vascular Endothelial Growth Factor (VEGF) Receptor 2 is the key mediator of VEGF induced angiogenesis. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralising ligand-induced proliferation and migration of human endothelial cells.[1]

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor (TKI). Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death. EGFR mutations may lead to constitutive activation of anti-apoptotic and proliferation signaling pathways. The potent effectiveness of erlotinib in blocking EGFR-mediated signalling in these EGFR mutation positive tumours is attributed to the tight binding of erlotinib to the ATP-binding site in the mutated kinase domain of the EGFR. Due to the blocking of downstream-signaling, the proliferation of cells is stopped, and cell death is induced through the intrinsic apoptotic pathway.[2]

Ramucirumab in combination with erlotinib is in clinical development for previously untreated patients with EGFR mutation-positive metastatic non-small cell lung cancer (NSCLC). In the part A and part B of the ongoing phase III clinical trial (NCT02411448; RELAY), participants in the experimental arm are administered 10 milligrams per kilogram (mg/kg) ramucirumab every 2 weeks intravenously (IV) in combination with 150 mg erlotinib daily orally in part A and B. Participants may continue to receive treatment until discontinuation criteria are met.[3]

INNOVATION AND/OR ADVANTAGES

Despite the likelihood of an initial response to EGFR TKIs, EGFR-mutant NSCLC patients develop disease progression. The most frequent mechanism of acquired resistance is the EGFR T790M gatekeeper mutation, present in approximately 50% to 60% of patients at the time of progression. Hence, there continues to be a significant medical need to improve the duration of disease control in the first-line treatment of NSCLC with an EGFR TKI, without adding significant toxicity.

Antiangiogenic agents like ramucirumab, which targets the VEGF pathway has shown clinical activity in NSCLC when used in addition to chemotherapy with improved overall survival in phase III studies. Preclinical studies suggest that antiangiogenic agents in combination with an EGFR TKI (erlotinib) might provide additional benefit in patients with EGFR-mutant NSCLC by delaying and/or suppressing the occurrence of EGFR T790M in NSCLC. The adverse events reported were generally mild and manageable.[4] This combination would also improve the efficacy of erlotinib, which is a standard of care in the first-line treatment of patients with activating EGFR mutations.[5]

[a] Information provided by Eli Lilly and Company Ltd

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ramucirumab is currently licensed in the EU/UK for the following indications:[1]

- As a monotherapy and in combination with paclitaxel for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma
- In combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil) for the treatment of adult patients with metastatic colorectal cancer (mCRC)
- In combination with docetaxel for the treatment of adult patients with locally advanced or metastatic NSCLC

The most common side effects with ramucirumab (which may affect more than 1 in 10 people) include fatigue (tiredness) or weakness, leucopenia, neutropenia, diarrhoea, epistaxis and stomatitis. The most serious adverse effects reported (either of ramucirumb alone or in combination with other cancer medicines) included gastrointestinal perforation, severe gastrointestinal haemorrhage and arterial thromboembolic events.[6]

Erlotinib is currently licensed in the EU/UK for the following indications:[2]
Non-Small Lung Cancer:

- As a first-line treatment in locally advanced or metastatic NSCLC with EGFR activating mutations
- As switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy
- For the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In patients with tumours without EGFR activating mutations, Tarceva is indicated when other treatment options are not considered suitable

Pancreatic Cancer:

- As a combination with gemcitabine for treatment of metastatic pancreatic cancer

The most common side effects with erlotinib when used as monotherapy for lung cancer were rash (affecting 75% of patients), diarrhoea (54%), loss of appetite and tiredness (52% each). In the study of erlotinib used in combination with gemcitabine for pancreatic cancer, the most common side effects were tiredness (affecting 73% of patients), rash (69%) and diarrhoea (48%).[7]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or non-small-cell lung cancer (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).[8] The majority of NSCLC presents at the advanced/metastatic stage, and the histological definition is widely based on small biopsy or cytological samples.[9]

Several biomarkers have emerged as predictive and prognostic markers for NSCLC. Predictive biomarkers include the ALK (anaplastic lymphoma kinase) fusion oncogene, ROS1 gene rearrangements, and sensitising EGFR mutations. In patients with NSCLC, the EGFR mutations result in activation of the tyrosine kinase domain with sensitivity to the small molecule tyrosine kinase inhibitors (TKIs). EGFR is a transmembrane receptor tyrosine kinase protein that is expressed in some normal epithelial, mesenchymal, and neurogenic tissue. Overexpression of EGFR has been reported and implicated in the pathogenesis of NSCLC. Some studies have shown that EGFR expression in

NSCLC is associated with reduced survival, frequent lymph node metastasis and poor chemo-sensitivity.[10]

Certain factors can increase the risk of developing lung cancer, including; smoking tobacco, exposure to radiation (by exposure to radon gas and previous radiotherapy treatment), exposure to certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes), previous lung disease (e.g. tuberculosis and COPD), family history of lung cancer, certain genetic mutations and lowered immunity. [11] NSCLC with EGFR activating mutations is considered to be a genetically distinct form of lung cancer which is most common in people with adenocarcinoma, non-smokers, people of Asian origin and females.[12] 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, cough coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[13] Metastatic signs and symptoms may include bone pain, spinal cord impingement, neurologic problems such as headache, weakness or numbness of limbs, dizziness, and seizures.[14]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2015. There are around 46,700 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 years (2013-2015). 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.[15]

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 cases diagnosed for that year.[16] In the UK is estimated that up to 87% of lung cancer cases are NSCLC,[17] 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.[15] 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.[18]

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.[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 1, 2 and 3 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, immunotherapy, radiotherapy and symptom control treatment.[19]

CURRENT TREATMENT OPTIONS

First line treatment options for advanced NSCLC (EGFR-TK mutation) include: afatinib, erlotinib and gefitinib.[20,21]

PLACE OF TECHNOLOGY

If licensed, ramucirumab in addition to erlotinib will offer an additional treatment option to previously untreated patients with EGFR mutation-positive metastatic NSCLC.

CLINICAL TRIAL INFORMATION

Trial	**RELAY, NCT02411448, EudraCT-2014-004824-22 ; ramucirumab vs placebo, both in combination with erlotinib; phase Ib/III**
Sponsor	Eli Lilly and Company
Status	Ongoing, published
Source of Information	Trial registry[3,22], manufacturer[23], publication[5,24]
Location	7 EU countries, incl UK, USA, Canada and other countries
Design	Randomised; placebo-controlled; double-blind
Participants	N=450 (planned); aged 18 years and older; confirmed diagnosis of stage IV NSCLC; eligible for first line treatment with erlotinib; life expectancy of at least 3 months
Schedule	Part A (phase Ib); • Approximately 12 patients will receive ramucirumab (10 mg/kg) every 2 weeks with erlotinib (150 mg) every day. Dose-limiting toxicity will be assessed during 2 cycles (4 weeks) of treatment. Part B (phase III); • Approximately 450 patients will be randomized in a 1:1 ratio to receive ramucirumab (10 mg/kg) or placebo every 2 weeks with erlotinib (150 mg) daily until disease progression, unacceptable toxicity, or other withdrawal criteria are met.
Follow-up	Participants may continue to receive treatment until discontinuation criteria are met
Primary Outcomes	• Progression Free Survival (PFS) [Time frame: randomisation to measured progressive disease or death from any cause (estimated as 37 months)] • Number of participants with one or more drug related adverse events (AEs) or any serious AEs [Time frame: cycle 1 day 1 through end of study (estimated as 38 months)]
Secondary Outcomes	• Overall Survival (OS) [Time frame: randomisation to date of death from any cause (estimated as 47 months)] • Objective Response Rate (ORR) [Time frame: randomisation to disease progression (estimated as 37 months)] • Disease Control Rate (DCR) [Time frame: randomisation to disease progression (estimated as 37 months)] • Duration of Response (DoR) [Time frame: date of Complete Response (CR) or Partial Response (PR) to date of objective disease progression or death due to any cause (estimated as 37 months)] • Pharmacokinetics (PK): Minimum Concentration (CMIN) of ramucirumab [Time frame: cycle 2 predose through cycle 14 predose (estimated as 28 months)] • Number of participants with anti-ramucirumab antibodies [Time frame: cycle 1 predose through follow-up (estimated as 38 months)] • Change from baseline on the Lung Cancer Symptom Scale (LCSS) [Time frame: baseline, end of study (estimated as 37 months)]

	• Change from baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) [Time frame: baseline, end of study (estimated as 37 months)]
Key Results	Study met its primary endpoint of PFS, demonstrating a statistically significant improvement in the time patients lived without their cancer growing or spreading after starting treatment.
Adverse effects (AEs)	The most common (>5% incidence) Grade ≥3 adverse events occurring at a higher rate (≥5% difference) on the ramicirumab plus erlotinib arm compared to the placebo plus erlotinib arm were hypertension, dermatitis acneiform (an acne-like rash), and diarrhoea.
Expected reporting date	Primary completion date reported as January 2019. Study completion date September 2022.

ESTIMATED COST

Ramucirumab is already marketed in the UK; a 100mg/10ml solution for infusion costs £500 while a 500mg/50ml solution for injection costs £2,500.[25]

Erlotinib is also already marketed in the UK; a pack of 30 x 150mg tablets costs £1,631.53.[26] The dosage used in the clinical trial is 150mg daily.

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. Atezolizumab with carboplatin or cisplatin and pemetrexed for untreated advanced non-squamous non-small-cell lung cancer [ID1495]. Expected publication date August 2020.
- NICE technology appraisal guidance in development. Dacomitinib for untreated EGFR-positive non-small-cell lung cancer (ID1346)). Expected publication date August 2019.
- NICE technology appraisal guidance. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (ID1173). January 2019.
- NICE technology appraisal guidance. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer. October 2016.
- NICE technology appraisal guidance. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal guidance. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (TA310). April 2014
- NICE technology appraisal guidance. 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 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 treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). Updated March 2019.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- 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. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines. 2016.[27]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[28]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[29]

ADDITIONAL INFORMATION

Eli Lilly and Company Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 Electronic Medicines Compendium (emc). *Cyramza 10 mg/ml concentrate for solution for infusion.* Available from: https://www.medicines.org.uk/emc/product/3640/smpc#PHARMACOLOGICAL_PROPS [Accessed 13 May 2019].

2 Electronic Medicines Compendium (emc). *Tarceva 25 mg film-coated tablets.* Available from: https://www.medicines.org.uk/emc/product/8844/smpc#PHARMACODYNAMIC_PROPS [Accessed 13 May 2019].

3 ClinicalTrials.gov. *A Study of Ramucirumab (LY3009806) in Combination With Erlotinib in Participants With EGFR Mutation-Positive Metastatic NSCLC (RELAY). Trial ID: NCT02411448*. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT02411448 [Accessed 13 May 2019].

4 Reck M, Garon EB, Paz-Ares L, Ponce S, Jaime JC, Juan O, et al. Randomized, Double-Blind Phase Ib/III Study of Erlotinib With Ramucirumab or Placebo in Previously Untreated EGFR-Mutant Metastatic Non–Small-Cell Lung Cancer (RELAY): Phase Ib Results. *Clinical Lung Cancer*. 2018 2018/05/01/;19(3):213-20.e4. Available from: https://doi.org/10.1016/j.cllc.2017.11.003.

5 Garon EB, Reck M, Paz-Ares L, Ponce S, Jaime JC, Juan O, et al. Treatment Rationale and Study Design for the RELAY Study: A Multicenter, Randomized, Double-Blind Study of Erlotinib With Ramucirumab or Placebo in Patients With Epidermal Growth Factor Receptor Mutation-Positive Metastatic Non–Small-Cell Lung Cancer. *Clinical Lung Cancer*. 2017 2017/01/01/;18(1):96-9. Available from: https://doi.org/10.1016/j.cllc.2016.05.023.

6 European Medicines Agency. *Cyramza; ramucirumab.* Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/cyramza [Accessed 14 May 2019].

7 European Medicines Agency. *Tarceva; erlotinib.* Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tarceva [Accessed 14 May 2019].
8 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].
9 Righi L, Vavalà T, Rapa I, Vatrano S, Giorcelli J, Rossi G, et al. Impact of Non–Small-Cell Lung Cancer-Not Otherwise Specified Immunophenotyping on Treatment Outcome. *Journal of Thoracic Oncology*. 2014 2014/10/01/;9(10):1540-6. Available from: https://doi.org/10.1097/JTO.0000000000000271.
10 Bethune G, Bethune D, Ridgway N, Xu Z. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. *Journal of thoracic disease*. 2010;2(1):48-51. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256436/.
11 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].
12 National Institute for Health and Care Excellence. *Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer; Final scope.* Available from: https://www.nice.org.uk/guidance/ta310/documents/lung-cancer-non-small-cell-egfr-mutation-positive-afatinib-final-scope2 [Accessed 30 May 2019].
13 National Health Service. *Symptoms of lung cancer.* Available from: https://www.nhs.uk/conditions/lung-cancer/symptoms/ [Accessed 15 May 2019].
14 Medscape oncology. *Non-Small Cell Lung Cancer (NSCLC).* Available from: https://emedicine.medscape.com/article/279960-overview [Accessed 30 May 2019].
15 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].
16 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].
17 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].
18 Office for National Statistics and Public Health England. *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/bulletins/cancersurvivalinengland/nationalestimatesforpatientsfollowedupto2017 [Accessed 30 May 2019].
19 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].
20 National Institute for Health and Care Excellence. *Advanced non-squamous (stages IIIB and IV) non-small-cell lung cancer: systemic anti-cancer therapy.* Available from: https://pathways.nice.org.uk/pathways/lung-cancer/advanced-non-squamous-stages-iiib-and-iv-non-small-cell-lung-cancer-systemic-anti-cancer-therapy.pdf [Accessed 21 May 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 EU Clinical Trials Register. *A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination with Ramucirumab or Placebo in Previously Untreated Patients with EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer*. *Trial ID: 2014-004824-22*. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-004824-22/GR [Accessed 20 May 2019].
23 Eli Lilly and Company. *Lilly's CYRAMZA® (ramucirumab) Phase 3 RELAY trial met primary endpoint, significantly improving progression-free survival in first-line treatment of patients*

with metastatic EGFR-mutated non-small cell lung cancer. Available from: https://investor.lilly.com/node/40981/pdf [Accessed 21 May 2019].

24 Nakagawa K, Garon EB, Seto T, Nishio M, Ponce Aix S, Chiu C-H, et al. RELAY: A multinational, double-blind, randomized Phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with epidermal growth factor receptor mutation-positive (EGFRm) metastatic non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology*. 2019;37(15_suppl):9000-. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.9000.

25 British National Formulary (BNF). *RAMUCIRUMAB.* Available from: https://bnf.nice.org.uk/medicinal-forms/ramucirumab.html [Accessed 21 May 2019].

26 British National Formulary (BNF). *ERLOTINIB.* Available from: https://bnf.nice.org.uk/medicinal-forms/erlotinib.html [Accessed 21 May 2019].

27 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.

28 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.

29 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].

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.