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Crizotinib (Xalcori) for locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC)

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LAY SUMMARY

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about ninety per cent of lung cancers in the UK. A small proportion of NSCLC tumours have a genetic change in a gene called c-METexon14. When NSCLC tumours have advanced or spread to other organs there are very limited treatments available.

Crizotinib is an anticancer drug that can be taken up to twice a day orally as capsules. Crizotinib works by blocking the growth and spread of cancer cells that have c-METexon14 changes to other parts of the body. Crizotinib is already approved for the treatment of a subtype of advanced NSCLC with a different genetic change (ALK mutations) in people that have been previously treated with chemotherapy. If approved for this new indication, crizotinib has the potential to prolong survival for patients with NSCLC and c-MET gene alteration that have advanced or spread to other organs, for which no other treatment is available apart from best supportive care.

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) (metastatic or locally advanced, stage III or IV, c-METexon14 alterations)

TECHNOLOGY

DESCRIPTION

Crizotinib (Xalcori; PF-02341066) is a new class of drug called c-Met/Hepatocyte growth factor receptor (HGFR) tyrosine kinase inhibitors. This compound is also an inhibitor of the anaplastic lymphoma kinase (ALK) tyrosine kinase and ROS receptor tyrosine kinases.[1,2]In MET-dependent cancer cell lines, crizotinib inhibits autophosphorylation of MET, which in turn leads to inhibition of signal transduction and cell proliferation, and induction of apoptosis.[3]

Crizotinib is intended to be used as antineoplastic agent in people with histologically confirmed advanced malignancies that are known to be sensitive to crizotinib inhibition, e.g. ALK, c-MET and ROS. In the currently ongoing dose escalation phase 1 trial (NCT00585195), crizotinib monotherapy is to be taken orally either once or twice a day in doses ranging from 50 mg to 2000 mg/day.[25]

Crizotinib as monotherapy is indicated for:[4]

- The first-line treatment of adults with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC);
- The treatment of adults with previously treated anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC);
- The treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC)

The most common side effects with Crizotinib (seen in more than 1 in 4 patients) are vision problems, nausea (feeling sick), diarrhoea, vomiting, oedema (swelling), increases in liver enzymes in the blood, decreased appetite, constipation, dizziness, neuropathy (pain due to nerve damage) and tiredness. The most serious side effects are liver damage, pneumonitis (lung inflammation), neutropenia (low blood levels of neutrophils, a type of white blood cell) and prolonged QT interval (a problem with the electrical activity of the heart).[4]

Crizotinib is currently at phase III development for the treatment of newly-diagnosed high-risk neuroblastoma or ganglioneuroblastoma.

INNOVATION and/or ADVANTAGES

Crizotinib may work in cancer by blocking the cell growth, migration and invasion of tumour cells for this type of genetic mutation present in advanced NSCLC patients.[4] Therefore, if licensed, crizotinib will offer an additional treatment option for patients with metastatic or locally advanced NSCLC with c-METexon14 alterations.

DEVELOPER

Pfizer Ltd

PATIENT GROUP

BACKGROUND

Lung cancer falls into two histological categories: around 88% are classified as non-small cell lung cancer (NSCLC), with the remaining patients classified as small cell lung cancer. NSCLC may be further grouped by tumour histology into squamous cell carcinoma (SCC), adenocarcinoma and large-cell carcinoma, with the latter two being collectively referred to as 'non-squamous' lung cancer.[5]

Over the past decade, it has become evident that subsets of NSCLC can be further defined at the molecular level by recurrent 'driver' mutations that occur in multiple oncogenes, including AKT1, ALK, BRAF, EGFR, HER2, KRAS, MEK1, MET, NRAS, PIK3CA, RET, and ROS1.[6] 'Driver' mutations lead to constitutive activation of mutant signalling proteins that induce and sustain tumorigenesis. These mutations are rarely found concurrently in the same tumour. Mutations can be found in all NSCLC histologies (including adenocarcinoma, SCC, and large cell carcinoma) and in current, former, and never smokers (defined by individuals who smoked less than 100 cigarettes in a lifetime).[6] MET alterations that result in exon 14 skipping are found in lung cancer in both the presence and absence of MET amplification. Both preclinical and case report evidence suggest that tumours harbouring MET with exon 14 alterations and/or MET amplifications have increased sensitivity to MET inhibitors.[7]

METex14 alterations aberrations tend not to be observed in younger patients with NSCLC and seem to be enriched in pulmonary pleomorphic/sarcomatoid carcinomas. Concurrent MET amplification is observed in approximately 20% of METex14-aberrant NSCLC, and such tumours have also been shown to harbour a significantly total higher mutational burden.[7]

CLINICAL NEED and BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK with an estimated incidence rate of 75.9 per 100,000 persons in 2015.[8] METex14 alterations occur at a prevalence of approximately 3% to 4% in lung adenocarcinoma compared with 2% in squamous cell lung cancer.[9]

In England in 2016 there were a total of 38,363 newly diagnosed cases of cancer of the bronchus and lung (ICD-10 code C34).[10] According to Cancer Research UK, about 87 out of 100 lung cancers in the UK (87%) are NSCLC,[11] this percentage applied to the 2016 newly diagnosed cases gives a total of 33,375.81 newly diagnosed cases of NSCLC in England in 2016. For all lung cancers, across the UK, the incidence rate is expected to decrease from 94.41 per 100,000 European age-standardised rate (EASR) (46,400 observed cases) in 2014 to 87.99 per 100,000 EASR (62,832.19 cases) in 2035.[12]

In England and Wales in 2016 there were a total of 30,570 deaths registered were malignant neoplasm of trachea, bronchus and lung was recorded as the underlying cause (ICD-10 codes C33-C34).[13] For all lung cancers (ICD-10 codes C33-C34), latest published survival statistics (2016, patients diagnosed in 2011-2015) report 1-year survival rate of 38.5% and 5-year of 15.2% (age-standardised).[14]

The latest Hospital Episodes Statistics (HES) data for 2016-17 recorded 91,902 admissions due to malignant neoplasm of bronchus and lung (ICD-10 code C34) of which 64,257 were day cases.[15] While it is generally established that MET amplification is a poor prognostic factor in NSCLC, the prognostic significance of METex14 alterations in NSCLC is unknown.[3]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Ceritinib for untreated ALK-positive non-small-cell lung cancer (TA500) January 2018
- NICE technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). August 2016.
- NICE technology appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). September 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 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. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

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. 2013/14 NHS Standard Contract for Positron Emission Tomography – Computed Tomography (PET-CT) scanning (all Ages)

OTHER GUIDANCE

- Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017[16]
- Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016[17]
- Eberhardt WEE, De Ruysscher D, Weder W, Le Péchoux C, De Leyn P, Hoffmann H, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. 2015[18]

CURRENT TREATMENT OPTIONS

There are several distinct subtypes of lung cancer, which can be distinguished by their features as seen under a microscope, and sometimes by their appearance and behaviour on CT scans. Determining the exact cancer subtype for individual patients is important, as the specific treatment varies for each.[19]

For locally advanced or metastatic NSCLC, the aim of treatment is to prolong survival, improve quality of life, and control disease-related symptoms.[20] Treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient's age, performance status, comorbidities, and preferences. Patients who smoke should be encouraged to cease, as cessation improves treatment outcomes.[21] Current NICE Pathways reflect these recommendations.[22] Patients with stage IIIB and IV NSCLC are usually offered chemotherapy with the option of surgery. Radiation is an option for treatment in patients who are not candidates for surgery.[23]

For people with locally advanced or metastatic NSCLC whose disease has progressed after non-targeted chemotherapy, NICE recommends chemotherapy combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. [21,22]

Treatment choices may be influenced by the presence of genetic markers (such as mutations in EGFR-TK), histology (squamous or non-squamous) and previous treatment experience. Supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated.[24]

EFFICACY and SAFETY

Trial	PROFILE 1001, NCT00585195; crizotinib in combination with rifampin and itraconazole; phase I
Sponsor	Pfizer
Status	Ongoing
Source of Information	Trial registry[25]
Location	Australia, Japan, Republic of Korea and United States
Design	Open label, single arm trial
Participants	n=600 (planned); aged 18 years and older; Histologically confirmed advanced malignancies that are known to be sensitive to PF-02341066 inhibition, e.g. ALK, c-MET and ROS
Schedule	• Drug: Crizotinib (PF-02341066) Escalating doses of crizotinib will be administered orally on a continuous dosing schedule. Doses to be evaluated will range from 50 mg to 2000 mg/day administered either once or twice a day. A treatment cycle is considered to be 28 days (or 21 days depending on the cohort). • Drug: Rifampin 600 mg once a day administered from Cycle 1, Day 16 to Cycle 2, Day 1 (14 days of dosing) in combination with crizotinib. • Drug: Itraconazole Multiple Dose Design: 200 mg once a day administered from Cycle 1, Day 1 to Cycle 1, Day 16 (16 days) in combination with crizotinib.

Follow-up	Active treatment period not reported, follow-up for 2.5 years
Primary Outcomes	• Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time Frame: 2.5 years]; • Area under the Concentration-Time Curve (AUC) [Time Frame: 2.0 years]; • Maximum tolerated dose (MTD) [Time Frame: 2.5 years]
Secondary Outcomes	• Percentage of Participants With Objective Response [Time Frame: 4.0 years]; • Area under the Concentration-Time Curve (AUC) for crizotinib when co-administered with rifampin [Time Frame: 2.0 years]; • Area under the Concentration-Time Curve (AUC) for crizotinib when co-administered with itraconazole [Time Frame: 3.0 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study and primary completion date reported as July 2023

ESTIMATED COST and IMPACT

COST

Crizotinib is marketed in the UK for the treatment of previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer and first-line treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer; packets of 60 200 mg or 250 mg capsules both cost £4,689.00.[26]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ 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

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☒ Clinical uncertainty or other research question identified: *trial not yet finished and results not available*

☐ None identified

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