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HEALTH TECHNOLOGY BRIEFING
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Mobocertinib for locally advanced or metastatic NSCLC

NIHRIO ID	28551	**NICE ID**	10669
Developer/Company	Takeda UK Ltd	**UKPS ID**	656929

Licensing and market availability plans	Currently in phase I/II clinical trials.

SUMMARY

Mobocertinib (TAK-788) as a monotherapy is in clinical development for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK. In locally advanced or metastatic NSCLC (Stage IIIB or IV), the cancer has spread beyond the lung which was initially affected. Symptoms of lung cancer include a persistent cough, shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable. Advanced NSCLC is not usually curable; there is therefore the need for additional treatment options.

Mobocertinib is an oral drug that targets the proteins EGFR human epidermal growth factor receptor 2 (HER2). It can bind to particular mutant forms of EGFR, including EGFR Exon 20 insertion mutations, to inhibit the growth of tumour cells. If licenced, mobocertinib monotherapy would offer a treatment option for patients with locally advanced or metastatic NSCLC.

PROPOSED INDICATION

Monotherapy in adult patients with locally advanced or metastatic NSCLC.

TECHNOLOGY

DESCRIPTION

Mobocertinib (TAK-788, AP32788) is a novel oral EGFR irreversible TKI.[1,2] It is an inhibitor of specific mutant forms of both human epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2; ERBB2), with potential antineoplastic activity. Upon oral administration, mobocertinib specifically and irreversibly binds to and inhibits certain mutant forms of EGFR and HER2. This prevents EGFR- and HER2-mediated signalling and leads to cell death in EGFR mutant- and HER2 mutant-expressing tumour cells. EGFR and HER2, receptor tyrosine kinases mutated in many tumour cell types, play key roles in tumour cell proliferation and tumour vascularisation.[3] Mobocertinib is specifically designed to potently inhibit oncogenic variants containing activating EGFR exon 20 insertion mutations with selectivity over wild-type EGFR.[1]

In the phase I/II trial, NCT02716116, mobocertinib is administered as oral capsules, at a dose of 160 mg once daily.[2,4]

INNOVATION AND/OR ADVANTAGES

Mobocertinib is a novel medicinal product. The in vitro and in vivo activity of mobocertinib was evaluated in engineered and patient-derived models harbouring diverse EGFR Exon 20 insertion mutations. Mobocertinib inhibited viability of various EGFR Exon 20 insertion-driven cell lines more potently than approved EGFR TKIs and demonstrated in vivo antitumor efficacy in patient-derived xenografts and murine orthotopic models.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Mobocertinib is not licensed for any other indications in the EU/UK.

Mobocertinib was issued an FDA break through designation in April 2020 and an FDA priority review in April 2021.[5,6]

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.[7]

Lung cancer 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.[8] Advanced lung cancer means that the cancer has spread from where it started in the lung. It is also called

metastatic cancer. Advanced cancer cannot usually be cured, but treatment can control it, help symptoms and improve quality of life.[9]

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.[10] However, it should be noted that oncogenic mutationally-driven lung cancer such as EGFR Exon 20, is frequently found in never smokers with lung adenocarcinoma.[11]

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 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.[12]

In 2019/20 there were 111,188 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 132,969 finished consultant episodes (FCEs), resulting in 243,883 FCE bed days.[13] According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,213 diagnosed cases of stage IV lung cancer in 2017, this represents 47% of the overall number of lung cancer cases diagnosed for that year.[14] In the UK it is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 15,481 cases diagnosed with stage IV in 2017 were NSCLC.[15]

In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV was 19.3% at one year and 2.9% at five years.[16] There are around 35,100 lung cancer deaths in the UK every year (based on data from 2016-2018). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer, the presence of oncogenic mutations and the general health of the patient. The main treatment options for advanced NSCLC are surgery, chemotherapy and radiotherapy. At the advanced stages, where patients are not candidates for surgical resection or definitive chemoradiation, treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally includes chemotherapy, targeted drugs, radiotherapy and symptom control treatment.[18]

CURRENT TREATMENT OPTIONS

Platinum-based chemotherapy is the most commonly used first-line chemotherapy in patients with locally advanced or metastatic NSCLC. If disease continues to worsen after chemotherapy, atezolizumab, nintedanib with docetaxel or docetaxel monotherapy are treatment options.[19]

In addition to cytotoxic chemotherapy, immunotherapies targeting PD-(L)1 as monotherapies or in combination with platinum-based chemotherapy may be considered. Pembrolizumab and

nivolumab (nivolumab is only available on the cancer drugs fund) are available for PD-L1 positive tumours.[20]

PLACE OF TECHNOLOGY

Monotherapy in adult patients with locally advanced or metastatic NSCLC.

CLINICAL TRIAL INFORMATION

Trial	NCT02716116, 2016-001271-68; A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer **Phase I/II** – Fully recruited and ongoing **Location(s):** 3 EU countries, UK, United states and other countries **Primary completion date:** March 2022
Trial design	Non-randomised, sequential assignment, open label
Population	N = 395 (estimated), confirmed locally advanced (and not a candidate for definitive therapy) or metastatic NSCLC disease (Stage IIIB or IV) or other solid tumors, aged 18 years and older.
Intervention(s)	- Mobocertinib treatment - Mobocertinib treatment in combination with pemetrexed/carboplatin - Mobocertinib monotherapy with primary antidiarrhea prophylaxis - Mobocertinib in combination with pemetrexed/carboplatin treatment with primary antidiarrhea prophylaxis
Comparator(s)	No comparator
Outcome(s)	Primary Outcome Measures: - Part 1, Dose Escalation Component: RP2D of Orally Administered mobocertinib [Time Frame: Cycle 1 (Cycle length is equal to [=] 28 days)] - Part 1A, Dose Escalation Combination Component: RP2D/MTD of Orally Administered mobocertinib in Combination With Pemetrexed/ Carboplatin [Time Frame: Up to Cycle 2 (Cycle length=21 days)] - Part 1A, Dose Escalation Combination Component: Identify DLTs of Orally Administered mobocertinib in Combination With Pemetrexed/ Carboplatin [Time Frame: Up to Cycle 2 (Cycle length=21 days)] - Part 2, Expansion Cohorts 1, 2, 4, 5 and 7: Confirmed Objective Response Rate (ORR) Assessed by the Investigator [Time Frame: Up to 36 months after first dose] - Part 2, Expansion Cohort 3: Intracranial ORR (iORR) Assessed by Independent Review Committee (IRC) [Time Frame: Up to 36 months after first dose] - Part 2, Expansion Cohort 6: Confirmed ORR Assessed by IRC [Time Frame: Up to 36 months after first dose]

	- Part 3, Extension Cohort: Confirmed ORR Assessed by IRC [Time Frame: Up to 36 months after first dose] - Part 1B: Number of Participants With Treatment Emergent Adverse Events (TEAEs) of >= Grade 3 Diarrhea Occurring During the First 4 Cycles of TAK-788 Dosing [Time Frame: Up to 4 Cycles (each cycle length is 28 days)] See trial record for full list of other outcomes.
Results (efficacy)	Among 28 EGFR Exon20 insertion patients treated at 160 mg daily, the investigator-assessed confirmed response rate was 43% (12/28; 95% confidence interval (CI): 24-63%) with median duration of response of 14 months (5.0-not reached), and median progression-free survival of 7.3 months (4.4-15.6).[4] In a 3-part, open-label, multicentre dose-escalation/expansion study (NCT02716116) among platinum-pretreated patients (n=114), the confirmed ORR per IRC was 28% (35% per investigator), including 1 complete response. The disease control rate was 78% [95% CI: 69–85] and median duration of response (DOR) was 17.5 months.[21]
Results (safety)	Among 136 patients treated with 160 mg daily, the most common any grade treatment-related adverse events (TRAEs; >25%) were diarrhea (83%), nausea (43%), rash (33%), and vomiting (26%), with diarrhea (21%) the only grade 3 TRAE >5%.[4] Additional safety data for 114 platinum-pretreated patients (PPP): Treatment-related adverse events (TRAEs; >20%) in PPP were diarrhea (91%), rash (45%), paronychia (38%), decreased appetite (35%), nausea (34%), dry skin (31%), vomiting (30%), increased blood creatinine (25%), stomatitis (24%), and pruritus (21%); the only grade ≥3 TRAE in ≥5% was diarrhea (22%). AEs leading to discontinuation in >2% were diarrhea (4%) and nausea (4%).[21]

ESTIMATED COST

The cost of mobocertinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). June 2019.
- NICE technology appraisal guidance. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2012. Last updated December 2019.

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

OTHER GUIDANCE

- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018 updated 2020.[22]
- British Medical Journal (BMJ). Lung cancer: diagnosis and management: summary of updated NICE guidance. 2019.[23]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[24]

ADDITIONAL INFORMATION

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