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HEALTH TECHNOLOGY BRIEFING
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Capmatinib for advanced non-small cell lung cancer

NIHRIO ID	7920	**NICE ID**	8441
Developer/Company	Novartis Pharmaceuticals	**UKPS ID**	638561

Licensing and market availability plans	Currently in phase II clinical trials

SUMMARY

Capmatinib is in clinical development for the treatment of advanced non-small cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK and at the metastatic stage (stage IV), the disease has already spread from the lungs to other sites. 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.

Capmatinib is selective inhibitor of a protein called hepatocyte growth factor receptor known as cMet. By binding to cMet, capmatinib prevents phosphorylation of the protein, inducing cell death in tumour cells. If licensed, capmatinib will offer an additional treatment for patients with advanced NSCLC.

PROPOSED INDICATION

Adult patients with advanced non-small cell lung cancer (NSCLC).[1]

TECHNOLOGY

DESCRIPTION

Capmatinib (INC280, TABRECTA) is an orally bioavailable inhibitor of the proto-oncogene cMet (hepatocyte growth factor receptor [HGFR]) with potential antineoplastic activity. Capmatinib is a small molecule kinase inhibitor targeted against c-Met, a receptor tyrosine kinase that, in healthy humans, activates signalling cascades involved in organ regeneration and tissue repair. Aberrant c-Met activation, via mutations, amplification, and/or overexpression, is known to occur in many types of cancer, and leads to overactivation of multiple downstream signalling pathways.[2] Capmatinib selectively binds to c-Met, thereby inhibiting c-Met phosphorylation and disrupting c-Met signal transduction pathways. This may induce cell death in tumour cells overexpressing c-Met protein or expressing constitutively activated c-Met protein. c-Met, a receptor tyrosine kinase overexpressed or mutated in many tumour cell types, plays key roles in tumour cell proliferation, survival, invasion, metastasis, and tumour angiogenesis.[3]

In a phase II clinical trial (Geometry Mono-1, NCT02414139), capmatinib is administered orally at 400mg twice daily.[1]

INNOVATION AND/OR ADVANTAGES

There is a substantial unmet need among patients with METex14 mutated advanced NSCLC as there are no treatment options approved to specifically target this aggressive form.[4,5]

In a phase II clinical trial, capmatinib led to clinically meaningful antitumor activity in patients with NSCLC with a *MET* exon 14 skipping mutation who had not received treatment previously. Lower efficacy was observed among patients with NSCLC with a *MET* exon 14 skipping mutation who had previously received one or two lines of therapy, however, these values are higher than those reported for current second- or third-line therapies in patients with advanced NSCLC.[6] In a post-hoc analysis of activity in brain metastases, intracranial responses were observed, including some complete responses.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Capmatinib does not currently have Marketing Authorisation in the EU/UK for any indication.

Capmatinib is currently in phase II/III clinical development, as a monotherapy or combination therapy, for hepatocellular carcinoma, renal cell cancer plus other NSCLC indications.[8]

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.[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]

There are three main types of NSCLC:[11]

- Adenocarcinoma – starts in the mucus making gland cells in the lining of airways
- Squamous cell cancer – develops in the flat cells that cover the surface of the airways
- Large cell carcinoma – the cancer appears large and round under the microscope

In addition to being diagnosed by type of lung cancer, patients will also have the cancer graded. 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.[12] 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.[13]

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.[14]

MET exon 14 skipping mutations occur in approximately 3 to 4% of patients NSCLC, typically in the absence of other driver mutations and are associated with poor prognosis.[15-17] MET amplification occurs in 1 to 6% of patients with NSCLC.[18]

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.[19] 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.[20] 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.[11]

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.[21] 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.[22]

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 advanced stage III disease, where patients are not candidates for surgical

resection or definitive chemoradiation and stage IV metastatic disease, 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.[23]

CURRENT TREATMENT OPTIONS

Current treatment options for advanced NSCLC include:.[24]

Current first-line treatment for adults with advanced non-squamous NSCLC with PD-L1 under 50% are:[25]

- Atezolizumab combination
- Pembrolizumab with pemetrexed and platinum chemotherapy
- Pemetrexed with cisplatin

Current first-line treatment for adults with advanced non-squamous NSCLC with PD-L1 over 50% are:[26]

- Pembrolizumab
- Pembrolizumab with pemetrexed and platinum chemotherapy

Current first-line treatment for adults with advanced squamous NSCLC with PD-L1 under 50% are:[27]

- Pembrolizumab with carboplatin and paclitaxel

Current first-line treatment for adults with advanced squamous NSCLC with PD-L1 over 50% are:[28]

- Pembrolizumab
- Pembrolizumab with carboplatin and paclitaxel

Current second line or further treatments for non-squamous NSCLC are:[29]

- Platinum doublet chemotherapy
- Pemetrexed with carboplatin
- Pemetrexed maintenance
- Docetaxel +/- Nintedanib
- Atezolizumab
- Nivolumab
- Pembrolizumab

Current second line or further treatment for squamous NSCLC are:[30]

- Atezolizumab
- Nivolumab
- Pembrolizumab
- Gemcitabine + Carboplatin or Cisplatin
- Vinorelbine + Carboplatin or Cisplatin
- Docetaxel

PLACE OF TECHNOLOGY

If licensed, capmatinib will offer an additional treatment for adult patients with advanced non-small cell lung cancer.

CLINICAL TRIAL INFORMATION

Trial	**Geometry Mono-1**; NCT02414139; 2014-003850-15; A Phase II, Multicenter Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type (wt), Advanced Non-small Cell Lung Cancer (NSCLC)

	Phase II - Active, not recruiting **Location(s):** US, Canada, EU (incl UK) plus other countries **Primary completion date:** January 2023
Trial design	Non-randomised, parallel assignment, open label
Population	N=368; 18 years and older; Stage IIIB or IV NSCLC
Intervention(s)	400mg capmatinib – twice daily – orally
Comparator(s)	No comparator
Outcome(s)	Overall Response Rate (ORR) [time frame: at least 18 weeks] See trial record for full list of other outcomes

Results (efficacy)	• Overall response was observed in 41% (95% confidence interval [CI], 29 to 53) of 69 patients who had received one or two lines of therapy previously and in 68% (95% CI, 48 to 84) of 28 patients who had not received treatment previously;
	• The median duration of response was 9.7 months (95% CI, 5.6 to 13.0) and 12.6 months (95% CI, 5.6 could not be estimated), respectively.
	• Limited efficacy was observed in previously treated patients with *MET* amplification who had a gene copy number of less than 10 (overall response in 7 to 12% of patients).
	• Among patients with *MET* amplification and a gene copy number of 10 or higher, overall response was observed in 29% (95% CI, 19 to 41) of previously treated patients and in 40% (95% CI, 16 to 68) of those who had not received treatment previously.[6]
	• 13 patients with NSCLC MET exon 14 skipping mutation had evaluable baseline brain metastases at baseline [3.3 brain lesions/pt (range 1–8)][7]
	  ○ 7 of the 13 patients (54%) had intracranial response of which 4 patients had complete resolution of all brain lesions.
	  ○ The other 3 responders had (i) complete resolution in 3 lesions, −50% reduction in 1 lesion, stabilisation in remaining 4 lesions (total 7 lesions), (ii) complete resolution in 2 lesions, stabilisation in 1 remaining lesion (total 3 lesions), and (iii) complete resolution in 1 lesion, stabilisation in 3 remaining lesions (total 4 lesions).
	  ○ Intracranial disease control was achieved in 12/13 patients.

Results (safety)	• The most frequently reported adverse events were peripheral oedema (in 51%) and nausea (in 45%); these events were mostly of grade 1 or 2.[6]

ESTIMATED COST

The cost of capmatinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

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- NICE technology appraisal. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer. [TA600]. September 2019
- NICE technology appraisal. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. [TA584]. June 2019.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. [TA520]. May 2018.
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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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