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HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Tepotinib for advanced non-small cell lung cancer harbouring MET exon14- skipping mutations

NIHRIO ID	21642	**NICE ID**	10123
Developer/Company	Merck Serono Ltd	**UKPS ID**	651169

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

SUMMARY

Tepotinib is in clinical development for patients with advanced non-small cell lung cancer (NSCLC) whose tumours have alterations in the MET gene. Advanced/metastatic (stage IV) NSCLC is when the cancer has spread to other organs most often to the liver, the adrenal glands, the bones and the brain. NSCLC is called locally advanced when it has spread into tissues around the lungs. Symptoms of NSCLC include fatigue, cough, shortness of breath, loss of appetite, coughing up phlegm, mucus or blood and chest pain. Most patients with metastatic NSCLC are diagnosed at the late stage where curative treatment with surgery is unsuitable. Currently, chemotherapy remains the main first line treatment option at this stage and is often not well tolerated by many patients.

Tepotinib is given as film coated tablets and it is a highly selective blocker of the protein c-MET which plays a key role in cell survival, growth and invasion. Tepotinib may help to induce death in tumour cells which overexpress c-MET. If licensed, tepotinib will offer an additional treatment option for patients with untreated stage IIIB/IV squamous or non-squamous NSCLC.

PROPOSED INDICATION

Treatment of patients with advanced (stage IIIB/IV) NSCLC whose tumours harbour MET exon 14 (METex14) skipping mutation for all treatment lines.[a]

TECHNOLOGY

DESCRIPTION

Tepotinib is a small molecule, type II inhibitor of the protein c-MET.[1,2] Tepotinib inhibits both hepatocyte growth factor (HGF) dependent and independent c-MET activation in low nanomolar concentrations.[2] c-MET is a tyrosine kinase receptor and is the product of the proto-oncogene MET which is overexpressed in many tumour cell types. This protein plays a key role in tumour cell proliferation, survival, invasion, metastasis and tumour angiogenesis. Tepotinib selectively binds to MET tyrosine kinase and disrupts MET signal transduction pathways. Since MET signal transduction is responsible for cell proliferation then tepotinib may induce apoptosis in tumour cells which are overexpressing this kinase.[3]

Tepotinib is currently in clinical development for the treatment of stage IIIB/IV metastatic NSCLC harbouring METex14 skipping-mutations. In the phase II clinical trial VISION (NCT02864992) patients receive 500 mg of tepotinib once daily, through oral administration, until death, disease progression or toxicity.[4]

INNOVATION AND/OR ADVANTAGES

One of the key challenges with molecularly targeted agents is addressing the inevitable development of drug resistance. Any mutations that directly or indirectly weaken the interactions between type I inhibitors and the MET activation loop may potentially lead to drug resistance. Switching from type I to type a type II MET inhibitor, such as tepotinib, may overcome such type I acquired mutations.[1]

Currently NICE guidelines for NSCLC do not include recommendations specifically for METex14-skipping mutations.[5] In a phase II study, preliminary data demonstrated that tepotinib had a favourable safety profile and showed encouraging efficacy (in evaluable patients, objective response rate was 45-55%) in advanced NSCLC harbouring METex14 skipping mutations.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Tepotinib was granted a breakthrough therapy designation by the US FDA for patients with metastatic NSCLC with METex14 skipping alterations who progressed following platinum-based cancer therapy in September 2019.[7]

Tepotinib is currently in phase II/III development for hepatocellular carcinoma and other forms of NSCLC.[8]

[a] Information provided by Merck Serono Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

There are two major types of lung cancer, NSCLC and small cell lung cancer. NSCLC is the most common type of lung cancer accounting for 87% of lung cancers. NSCLC can be further classified into three types: squamous-cell carcinoma, adenocarcinoma and large-cell carcinoma.[9,10] Metastatic cancer is a cancer that has spread from the part of the body where it started to other parts of the body, lung cancer tends to spread to the liver, bones, adrenal glands or brain.[11] The cancer is named and treated based on the part of the body where the cancer started.[12]

Cancers occur when genetic mutations build up in critical genes, specifically those that control cell growth and division (proliferation) or the repair of damaged DNA. These changes allow cells to grow and divide uncontrollably to form a tumour. In nearly all cases of lung cancer, these genetic changes are acquired during a person's lifetime and are present only in certain cells in the lung. These changes, which are called somatic mutations, are not inherited. Somatic mutations in many different genes have been found in lung cancer cells.[13]

The MET gene is a proto-oncogene that codes for c-MET tyrosine kinase. This cell surface receptor is expressed in the epithelial cells of many organs. c-MET binds hepatocyte growth factor (HGF) promoting cell proliferation, survival, motility, scattering, differentiation and morphogenesis.[14] Exon 14 on the MET gene (METex14) encodes a juxtamembrane domain containing the Y1003 residue which is a ubiquitin ligase CBL binding site necessary for c-MET degradation. Mutations that disrupt splice sites represent an important mechanism of oncogenesis. Base substitutions or indels that disrupt the branch point of intron 13, the 3' splice site of intron 13, or the 5' splice site of intron 14 can effectively result in METex14 skipping so there is less degradation and increased stability of c-MET.[15]

A person's risk of developing lung cancer depends on many factors including age, genetics and exposure to risk factors. The greatest risk factor is long-term tobacco smoking, which increases a person's risk of developing lung cancer 25-fold. Other risk factors include exposure to air pollution, radon, asbestos, certain metals and chemicals, or second-hand smoke; long-term use of hormone replacement therapy for menopause; and a history of lung disease such as tuberculosis, emphysema, or chronic bronchitis. A history of lung cancer in closely related family members is also an important risk factor; however, because relatives with lung cancer are frequently smokers, it is unclear whether the increased risk is the result of genetic factors or exposure to second hand smoke.[16] Key symptoms of lung cancer include a cough, breathlessness, coughing up blood, chest pain, weight loss and loss of appetite, fatigue and chest infections.[17]

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 and an incidence rate of 72.2 per 100,000 in 2016.[18] 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.[19] METex14 mutations are found in approximately 3-4% of all patients with NSCLC.[20]

In 2017, there were 18,655 diagnosed cases of stage IV lung cancer in England. Based on the estimate that 87% of these would be NSCLC and a further 4% would harbour METex14 skipping mutations this would equate to approximately 650 cases.[20,21]

In England, 2013-2017 followed up to 2018, the 1 year survival rate for people with stage 4 lung cancer was 19.3% and the 5 year survival rate was 2.9%.[22] In 2017 there were 30,131 registrations of death from cancer in England for malignant neoplasms of trachea, bronchus and lung in England (ICD-10 code C33-34).[23] In 2018/19 there were 128,985 finished consultant episodes (FCE) for malignant neoplasm of bronchus and lung resulting in 249,196 FCE day cases.[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of cancer and the general health of the patient.[25] The main treatment option for the locally advanced or metastatic disease includes surgery, systemic anti-cancer therapy (SACT) and radiotherapy.[26]

At stage IV, NSCLC 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 to help patients breathe more easily.[27]

CURRENT TREATMENT OPTIONS

There are currently no treatments approved by NICE to specifically target METex14 skipping mutation or c-MET gene amplification.[5]

The following treatments are recommended for first-line treatment of patients with advanced (stages IIIB and IV) NSCLC, and no specific modifications to the EGFR or ALK genes:[28]

- PD-L1 expression under 50%
    - Atezolizumab plus bevacizumab, carboplatin and paclitaxel (non-squamous)
    - Pembrolizumab with pemetrexed and platinum chemotherapy (non-squamous)
    - Pemetrexed in combination with cisplatin (non-squamous)
    - Pembrolizumab with carboplatin and paclitaxel (squamous)

- PD-L1 expression 50% or over
    - Pembrolizumab, with pemetrexed and platinum chemotherapy (non-squamous)
    - Pembrolizumab (squamous and non-squamous)
    - Pembrolizumab with carboplatin and paclitaxel (squamous)

PLACE OF TECHNOLOGY

If licensed, tepotinib will offer a new treatment option for patients with advanced NSCLC whose tumours harbour METex14 skipping mutation.

CLINICAL TRIAL INFORMATION

Trial	**VISION,** NCT02864992**,** MS200095-0022, 2015-005696-24; adults aged 18 years and older; tepotinib; phase II
Sponsor	EMD Serono Research and Development Institute, Inc.
Status	Ongoing
Source of Information	Trial registry;[4,29] Abstract[6]
Location	6 EU countries (not including UK), USA and Japan
Design	Single-arm study
Participants	n=280 (planned); adults aged 18 years and older; measurable disease in accordance with RECIST version 1.1; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1; female subjects must not be pregnant or breastfeeding; female subjects must agree to use highly effective contraception if they are of child-bearing age; males must agree to use and to have their female partners of childbearing potential to use highly effective contraception; histologically or cytologically confirmed advanced (stage IIIB/IV) NSCLC (all types including squamous and sarcomatoid); treatment naive patients in first-line or pre-treated patients with no more than 2 lines of prior therapy; subjects with MET alterations
Schedule	Subjects will receive 500 mg of tepotinib through oral administration once daily in cycles of 21-day duration until disease progression, death, adverse event or withdrawal of consent.
Follow-up	Baseline up to 20 months.
Primary Outcomes	• Objective response as assessed by independent review committee [Time Frame: Baseline up to 20 months]
Secondary Outcomes	[Time Frame: Baseline up to 20 months] • objective response assessed as per investigator • duration of response as assessed by independent review committee • duration of response as assessed by investigator • objective disease control as assessed by independent review committee • objective disease control as assessed by investigator • progression free survival as assessed by independent review committee • progression free survival as assessed by investigator • overall survival • occurrence of treatment emergent adverse event and deaths • percentage of subjects with markedly abnormal clinical laboratory tests, vital signs, electrocardiogram and Eastern Cooperative Oncology Group Performance Status • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 • EuroQol Five Dimension Five Level Scale • Number of subjects with markedly abnormal clinical laboratory tests [Time Frame: pre-dose, at 1.5 hours post-dose and at 4 hours post-dose on cycle 1, day 1, and on cycle 2, day 1]

	• Maximum plasma concentration of drug Trough plasma concentration of drug
Key Results	In evaluable patients, objective response rate was 45-55%. Duration of response was >1 year in all groups and >50% of patients were event free at 12 months (55-70%). mPFS was 9.5 – 12.2 months.
Adverse effects (AEs)	Any/grade 3 treatment-related adverse events (TRAEs) reported >15% of 87 treated patients were peripheral oedema (48.3/8.0%), nausea (23.0/0%), diarrhoea (20.7/1.1%). No TRAEs were grade 4/5.
Expected reporting date	Estimated primary completion date reported as December 2021.

ESTIMATED COST

The cost of tepotinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Nivolumab for previously treated squamous non-small-cell lung cancer (TA483). November 2017.
- NICE technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). August 2016
- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019
- NICE interventional procedures guidance. Microwave ablation for treating primary lung cancer and metastases in the lung (IPG469). November 2013.

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. 2019.[30]
- British Medical Journal (BMJ). Lung cancer: diagnosis and management: summary of updated NICE guidance. 2019.[31]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[32]

ADDITIONAL INFORMATION

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