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

NIHRIO ID	29640	**NICE ID**	10440
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	656865

Licensing and market availability plans	Currently in phase I clinical development.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Amivantamab is in clinical development in the treatment of patients with advanced non-small-cell lung cancer (NSCLC) who have previously been treated with platnum-based chemotherapy. NSCLC makes up the majority of lung cancers in the UK. Metastatic NSCLC is when the cancer has spread beyond the lung that was initially affected, most often to the liver, the adrenal glands, the bones, and the brain. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable.

Amivantamab is an intravenously administered drug that can bind to both EGFR and another receptor that helps tumours grow, hepatocyte growth factor receptor (cMet). Binding to these receptors slows tumour growth by stopping them receiving signals and making them a target to be brokendown and destroyed by for immune cells. If licenced amivantamab will provide a treatment for patients with advanced NSCLC who have previously been treated with platnum-based chemotherapy, who have limited therapies available.

PROPOSED INDICATION

Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of platinum-based chemotherapy.[1]

TECHNOLOGY

DESCRIPTION

Amivantamab (JNJ-61186372) is a human bispecific antibody that targets both EGFR and hepatocyte growth factor receptor (HGFR or cMet). Upon administration, it targets and binds to wild-type or certain mutant forms of both EGFR and cMet that are expressed on cancer cells, preventing receptor phosphorylation. This prevents activation of both EGFR and cMet-mediated signalling pathways. Additionally, this binding results in degradation of receptors, further inhibiting these signalling pathways. Amivantamab may also cause antibody dependent cellular cytotoxicity. All of these mechanisms result in the inhibition of tumour cell proliferation.[2] As amivantamab binds to the extracellular portion of the receptor, it has activity against all known EGFR- tyrosine kinase mutant receptor forms. This is particularly important for tumours bearing exon 20 insertions as they are not typically bound by the EGFR tyrosine kinase inhibitors (TKIs) used to treat the more common EGFR-TK mutations.[3,4]

In the phase I clinical trial (NCT02609776), amivantamab 140mg was administered to patients via IV infusion once weekly during cycle 1 and once every 2 weeks during subsequent cycles. Treatment cycles were 28 days long.[1] The dosing schedule is 1050 mg, with an adjustment to 1400 mg for subjects >80 kg body weight.[1]

INNOVATION AND/OR ADVANTAGES

Amivantamab, as a bispecific antibody, targets both EGFR and cMet and therefore inhibits resistance pathways, allowing for improved treatment outcomes.[3] This is an advantage as bispecific antibodies show greater antitumor efficacy compared to a combination of monospecific monoclonal antibodies via potential synergistic effects, and they increase selectivity by simultaneous targeting of both receptors, favouring overexpressing cells as a consequence of avidity effects.[5] Furthermore as an antibody amivantamab binds the the extracellular receptor domain and thus has activity against EGFR-TK mutations that are resistant to EGFR TKI therapy.[3] This is particularly important for tumours bearing exon 20 insertions as they are not typically bound by the EGFR TKIs used to treat the more common EGFR-TK mutations.[6] In a phase I trial amivantamab demonstrated robust and durable antitumor activity in patients with Exon 20 insertion disease, with a manageable safety profile.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

This product is not licensed for any other cancer indications in the EU/UK.

In March 2020 amivantamab was granted U.S. Food and Drug Administration (FDA) Breakthrough Therapy Designation for the treatment of NSCLC.[8]

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 80 to 85% 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).[9] Metastatic cancer has spread, either to both lungs, the chest or beyond.[10]

Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of lung cancers. In countries with active tobacco control measures, the incidence of lung cancer has begun to decline in men and is reaching a plateau for women. An increase in the proportion of NSCLC in never-smokers has been observed, especially in Asian countries. These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified.[11]

Several other factors have been described as lung cancer risk factors including; exposure to radiation certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes) and previous lung disease (e.g. tuberculosis and COPD). Other factors include family history of lung cancer and certain genetic mutations.[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, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[13,14]

CLINICAL NEED AND BURDEN OF DISEASE

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide.[11] 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.[15]

In 2018/19 there were 107,010 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 128,985 finished consultant episodes (FCEs), resulting in 249,196 FCE bed days.[16]

Survival rates for lung cancer depend on at which stage of disease the cancer is identified.[15] In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV (metastatic) was 19.3% at one year and 2.9% at five years.[17] In England and Wales in 2018 there were 29,604 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[18]

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 stage IV NSCLC, 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.[19]

CURRENT TREATMENT OPTIONS

NICE has recommended the following treatment for NSCLC after progression on chemotherapy:[20]

- Atezolizumab
- Nivolumab
- Pembrolizumab
- Nintedanib with docetaxel
- Docetaxel monotherapy

PLACE OF TECHNOLOGY

If licenced amivantamab will provide a treatment for patients with advanced NSCLC who have progressed on chemotherapy and have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**CHRYSALIS, NCT02609776;** A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer **Phase I** - Recruiting **Location(s):** 3 EU countries, UK, United States, Canada and other countries. **Primary completion date**: March 30, 2021
Trial design	Non-randomised, open label, parallel assignment.
Population	N=460, aged 18 years and older, histologically or cytologically confirmed non-small cell lung cancer (NSCLC) that is metastatic or unresectable, EGFR mutated disease, either progressed after or be ineligible for prior standard of care therapy.
Intervention(s)	Part 1: Amivantamab monotherapy + combination dose escalations Part 2: Amivantamab monotherapy + combination dose expansion
Comparator(s)	None
Outcome(s)	Primary Outcome Measure(s) : • Part 1: Number of Participants With Dose Limiting Toxicity (DLT) [Time Frame: Up to Day 28] • Part 2: Number of Participants With Adverse Events (AEs) and Serious AEs [Time Frame: Screening up to follow-up (30 [+7] days after the last dose)] • Part 2: Overall Response Rate (ORR) [Time Frame: Up to End of Treatment Follow (EOT) Up Period (30 [+7] days after the last dose)] • Part 2: Duration of Response (DOR) [Time Frame: Up to EOT Follow Up Period (30 [+7] days after the last dose)] • Part 2: Percentage of Participants With Clinical Benefit [Time Frame: Up to EOT Follow Up Period (30 [+7] days after the last dose)] • Trough Serum Concentration (Ctrough) of JNJ-61186372 [Time Frame: Up to EOT (30 days after last dose)]

	• Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of JNJ-61186372 [Time Frame: Up to EOT (30 days after last dose)] See trial for full list.
Results (efficacy)	• Among the 39 response-evaluable patients, with a median follow-up of 4 months (1–26), the overall response rate (≥partial response [PR]) was 36% (95% CI, 21–53), and 41% (95% CI, 24–61) for the 29 patients who had prior platinum based chemotherapy (PBCT). • The clinical benefit rate (≥PR or stable disease ≥11 weeks) was 67% for response-evaluable patients and 72% for patients who had prior PBCT. • Among all 14 responders, median duration of response was 10 months (1–16), with ongoing responses in 9 patients at data cutoff. • Median progression-free survival was 8.3 months (95% CI, 3.0–14.8) for response-evaluable pts and 8.6 months (95% CI, 3.7–14.8) for patients who had prior PBCT.[7]
Results (safety)	• In the 50 patients harbouring exon20ins mutations treated at the RP2D, the most common adverse events (AEs) reported were rash (72%), infusion related reaction (60%), and paronychia (34%). Additional EGFR-related AEs included stomatitis (16%), pruritus (14%), and diarrhoea (6%).[7]

ESTIMATED COST

The cost of amivantamab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Cimavax for treating wild-type EGFR-positive non-small-cell lung cancer (GID-TA10225). Expected publication to be confirmed.
- NICE technology appraisal guidance. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
- NICE technology appraisal guidance. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). Updated March 2019.
- NICE Diagnostics guidance. EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer (DG8). August 2013.

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 for diagnosis, treatment and follow-up. 2016.[22]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[23]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[24]

ADDITIONAL INFORMATION

This medicinal product could be considered a Tumour Agnostic Therapy (TAT) since EGFR and cMet, both upregulated or mutated in a variety of tumour cell types, play key roles in tumour cell proliferation.[1]

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