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Health Technology Briefing
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Amivantamab with chemotherapy for previously untreated advanced EGFR exon 20 insertion mutations positive non-small cell lung cancer

Company/Developer	Janssen- Cilag Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30786	NICE ID: 10691	UKPS ID: 661729

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Amivantamab in combination with carboplatin-pemetrexed chemotherapy is in development for the treatment of epidermal growth factor receptor (EGFR) exon 20 insertion mutations positive non-small cell lung cancer (NSCLC). NSCLC is one of the most common types of cancer. EGFR is a protein found on certain types of cells that is involved in cell signalling pathways that control cell division and survival. Mutations in this protein can cause increased cell division resulting in tumour growth. Patients with EGFR exon 20 insertion mutations have worse prognosis than those with common EGFR mutations. There are currently no recommended NICE treatment options for this specific indication highlighting the need for a therapy.

Amivantamab, administered intravenously, is a bispecific antibody that binds to the mutated EGFR. When EGFR is mutated on cancer cells, it can lead to faster cell division and therefore, tumour growth. By binding to EGFR, amivantamab blocks binding to the protein required to initiate the cell division ensuring tumour growth is prevented. If licensed, amivantamab in combination with carboplatin-pemetrexed chemotherapy will offer a treatment option for adult patients with advanced EGFR exon 20 insertion mutations positive NSCLC.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. 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. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Treatment of patients with advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) that has documented primary epidermal growth factor receptor (EGFR) Exon 20 insertions (ins) activation mutation.[1]

Technology

Description

Amivantamab (Rybrevant) is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumours with activating and resistance EGFR mutations. Amivantamab binds to the extracellular domains of EGFR. Preclinical studies show amivantamab is active against tumours with primary EGFR activating mutations such as Exon 19 deletions, L858R substitution, and Exon 20 insertion mutations. Amivantamab disrupts EGFR and MET signalling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumour growth and progression. The presence of EGFR and MET on the surface of tumour cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.[2]

In a phase III clinical trial (NCT04538664), 1400 mg (1750 mg if body weight is >=80kg) amivantamab by intravenous infusion (IV) once weekly up to cycle 2 day 1, then 1750 mg (2100 mg if body weight is >=80kg) on day 1 of each 21-day cycle, starting with cycle 3. This will be given with 500 mg/m^2 pemetrexed on day 1 of each 21-day cycle, in combination with carboplatin area under the concentration-time curve 5mg/mL per minute (AUC5) for up to 4 cycles, and then as maintenance monotherapy until disease progression.[1]

Key Innovation

There are currently no available therapies that specifically target EGFR exon 20ins mutations highlighting this technology would be meeting an unmet need.[3] EGFR exon20ins account for approximately up to 10% of all EGFR mutant NSCLCs.[4] Currently approved EGFR tyrosine kinase inhibitors (TKIs) are considered ineffective against exon20ins NSCLC due to resistance against EGFR TKIs, and the standard of care for patients with exon20ins disease remains platinum-based doublet chemotherapy.[5]

If licenced, amivantamab in combination with carboplatin-pemetrexed chemotherapy will offer a treatment option for patients with EGFR exon 20ins mutated NSCLC.

Regulatory & Development Status

Amivantamab has Marketing Authorization in the UK as a monotherapy for treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.[2]

Amivantamab is in phase III/II development, for gastric cancer, esophageal cancer and NSCLC.[6]

Patient Group

Disease Area and Clinical Need

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.[7] Metastatic cancer occurs when the disease has spread, either to both lungs, the chest or beyond.[8] EGFR is a protein found on certain

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types of cells that binds to a substance called epidermal growth factor. The EGFR protein is involved in cell signalling pathways that control cell division and survival. Sometimes, mutations in the EGFR gene, including in exon 20, cause EGFR proteins on tumour cells to be constitutively activated.[9] This causes cancer cells to divide more rapidly.[10] Patients with NSCLC and EGFR exon 20 insertion mutations have a worse prognosis compared to patients with more common EGFR mutations (exon 19 deletions/L858R substitution) due to lack of effective treatment options.[9]

There are around 48,500 new lung cancer cases in the UK annually.[11] The prevalence of EGFR mutations in NSCLC patients is 14.1% in Europe.[12] On top of this, the frequency of EGFR exon 20 insertion mutations has been reported as being between 4 and 14% of all observed EGFR mutations in NSCLC in Europe.[13] In 2020/21 there were 86,043 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days.[14] In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV (metastatic) disease was 19.3% at one year and 2.9% at five years.[15] Specific to this indication, the estimated median overall survival for patients with NSCLC and exon 20 insertion mutations is 16 months or less.[13]

Recommended Treatment Options
There are currently no NICE recommended treatment options for this patient group.[3] The current standard of care for first-line treatment is platinum-based chemotherapy, carboplatin and pemetrexed.[3,5]

Clinical Trial Information

Trial	**PAPILLON; NCT04538664; 2020-000633-40;** A Randomised, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared With Carboplatin-Pemetrexed, in Patients With EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer **Phase III –** recruiting **Location(s):** 8 EU countries, UK, USA, Canada and other countries. **Primary completion date:** January 2022
Trial Design	Randomised; parallel assignment; open label
Population	N=300 (planned); aged 18 years and older; participant must have histologically or cytologically confirmed, locally advanced or metastatic, non-squamous NSCLC with documented primary EGFR Exon 20ins activating mutation
Intervention(s)	Amivantamab 1400mg (1750 mg if body weight is >=80kg) by IV infusion once weekly up to cycle 2 day 1, then 1750mg (2100 mg if body weight is >=80 kg) on day 1 of each 21-day cycle, starting with cycle 3. Pemetrexed 500mg/m^2 IV on day 1 of each 21-day cycle, in combination with carboplatin AUC5 for up to 4 cycles, and then as maintenance monotherapy until disease progression.
Comparator(s)	Pemetrexed 500mg/m^2 IV on day 1 of each 21-day cycle, in combination with carboplatin AUC5 for up to 4 cycles, and then as maintenance monotherapy until disease progression.
Outcome(s)	Primary outcome measure: Progression-Free Survival (PFS) According to RECIST v1.1 as Assessed by Blinded Independent Central Review (BICR) [Time frame: Up to 18 months].

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	See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price for amivantamab is £1079.00 per 350mg vial.[16]

Relevant Guidance

NICE Guidance

- 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). NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2. 2021.[17]
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[18]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[19]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[20]

Additional Information

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