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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

AMG 510 for KRAS G12c mutated metastatic non-small cell lung cancer - after prior standard therapy

NIHRIO ID	27433	**NICE ID**	10283
Developer/Company	Amgen Ltd	**UKPS ID**	653443

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

SUMMARY

AMG 510 is in clinical development for the treatment of adults with $KRAS^{G12C}$ mutated, metastatic non-small cell lung cancer (NSCLC). NSCLC is the most common form of lung cancer and a small proportion of patients with NSCLC have tumours which carry the genetic mutation $KRAS^{G12C}$. Metastatic NSCLC describes tumours that have spread from the lungs to other parts of the body. Current NSCLC treatment depends largely on the stage of the cancer and any genetic mutations identified in the tumours and can include surgery, chemotherapy, radiotherapy, targeted cancer drugs and immunotherapy. Despite a wide range of treatments being available for lung cancers, there are currently no approved treatments for $KRAS^{G12C}$ mutated, metastatic NSCLC.

AMG 510 is a small molecule which binds to a site on the protein KRAS and locks it in an inactive state. This blocks signals between tumour cells and stops further growth. AMG 510 is the first molecule which has been able to target the protein KRAS effectively. It is given as an oral tablet and is intended to be used following prior standard therapy for NSCLC. If licensed AMG 510, has the potential to be the first available treatment targeted for patients with $KRAS^{G12C}$ mutated NSCLC.

PROPOSED INDICATION

Adult patients with KRAS^{G12C} mutated, metastatic NSCLC after prior standard therapy.[a]

TECHNOLOGY

DESCRIPTION

AMG 510 is a small molecule that specifically and irreversibly inhibits KRAS^{G12C} by locking it in an inactive GDP-bound state.[1] The KRAS oncoprotein is a GTPase and a vital mediator of intracellular signalling pathways which may drive the growth and survival of tumour cells. Mutations in KRAS are a hallmark of cancer and prevent the association of GTPase-activating proteins to KRAS, which allows for enhanced KRAS signalling. AMG 510 binds to KRAS^{G12C}, a mutated cysteine residue on KRAS, and has been shown to inhibit cell signalling and growth. AMG 510 was the first KRAS^{G12C} inhibitor in clinical development.[2]

AMG 510 is currently in clinical development for the treatment of adult patients with KRAS^{G12C} positive, metastatic NSCLC who have already received standard therapy.[a] In the phase I/II clinical trial (NCT03600883), participants received AMG 510 180 mg via oral tablet to begin. This dose was then subject to dose escalation if dose-limiting toxicity did not occur.[3]

INNOVATION AND/OR ADVANTAGES

AMG 510 was the first investigational KRAS^{G12C} inhibitor to advance to a clinical setting and has a novel mechanism of action.[4] There have been few clinical molecules under investigation to date that are selective for KRAS mutated tumours and prior to AMG 510, the KRAS oncoprotein was considered impossible to target with drugs.[2] If approved, AMG 510 would represent the first targeted therapy for patients with KRAS^{G12C} mutations who have already received standard therapy to treat NSCLC.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

AMG 510 does not currently have Marketing Authorisation in the EU/UK for any indication.

AMG 510 has the following regulatory designations/awards:

- Orphan drug designation in the USA in May 2019 for treatment of KRAS^{G12C} positive NSCLC.[5]
- Fast track designation in the USA in September 2019 for treatment of KRAS^{G12C} positive NSCLC.[6]

PATIENT GROUP

DISEASE BACKGROUND

[a] Information provided by Amgen on UK PharmaScan

NSCLC is the most common form of lung cancer in the UK with subtypes that can be defined as adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[7] A $KRAS^{G12C}$ mutation is a mutation of a glycine residue at codon 12 of the KRAS gene. This mutation causes activation of RAS signalling, which can lead to spontaneous tumour development and the creation of a tumour microenvironment allowing for proliferation and maintenance of the tumour.[8]

Metastatic NSCLC is a stage of NSCLC where the cancer has spread from the primary site (in the lung) to a secondary site in other parts of the body.[9] NSCLC would usually be considered metastatic at stage IV.[10]

The most common symptoms of lung cancer include a cough, breathlessness, coughing up phlegm with blood in, pain in the chest or shoulder, recurrent chest infections, loss of appetite, weight loss and fatigue.[11]

The most common risk factors associated with the development of lung cancer include smoking, passive smoking, old age, radon gas, asbestos, immunosuppression and genetic factors.

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK and accounted for 13% of all new cancer cases on average across 2014-2016.[12] Of these cases, 87% are diagnosed as NSCLC.[7] 38,381 new cases of lung cancer were diagnosed in England in 2016[12], meaning that there was approximately 33,391 cases of NSCLC diagnosed in England in the same period. Mutations of the oncoprotein KRAS occur in 20-40% of all lung adenocarcinomas[13] and $KRAS^{G12C}$ mutations occur in approximately 13% of lung adenocarcinomas.[2]

In 2018-19, there were 107,010 admissions and 128,985 finished consultant episodes (FCE) with main diagnoses of malignant neoplasm of bronchus and lung (ICD code C34) in hospitals in England.[14]

In 2017 in England and Wales there were 30,131 deaths from malignant neoplasm of trachea, bronchus and lung (ICD code C33-C34).[15] Lung cancer is the most common cause of cancer death in the UK and accounted for 21% of all cancer-related deaths in 2017.[16] In 2013-2017 in England, the 1 year survival rate for all stages of lung cancer was 40.6%, which fell to 19.3% for stage IV lung cancer. The 5 year survival rate for all stages of lung cancer was 16.2%, dropping to 2.9% for stage IV.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Current treatment for NSCLC varies largely based on the stage of disease and the presence of a number of genetic mutations. In general, treatment options include surgery, chemotherapy, radiotherapy, targeted cancer and drugs and immunotherapy. All patients with a suspected diagnosis of lung cancer will be referred to a multidisciplinary team for treatment. In metastatic NSCLC, treatment mostly aims to delay disease progression and relieve symptoms.[10]

CURRENT TREATMENT OPTIONS

There are currently no recommended treatment options for treating $KRAS^{G12C}$ mutated, metastatic NSCLC.

The current treatment options for second line or greater treatment of metastatic NSCLC are often stratified by genetic mutation and can include:[18,19]

- Docetaxel
- Pemetrexed
- Brigatinib

PLACE OF TECHNOLOGY

If licensed, AMG 510 will offer a treatment option for adult patients with $KRAS^{G12C}$mutated, metastatic NSCLC who have received prior standard therapy, who currently have no effective therapies available.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**CodeBreak 100; NCT03600883, EudraCT 2018-001400-11; A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumours With KRAS p.G12C Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With KRAS p.G12C Mutation (CodeBreak 100)** **Phase I/II - ongoing** **Locations: US, Europe (not including the UK), other countries**
Trial design	Non-randomised, sequential assignment, open label
Population	N=350 (planned); aged 18 to 100 years, pathologically documented, locally-advanced or metastatic malignancy with, KRAS p.G12C mutation identified through DNA sequencing
Intervention(s)	AMG 510 oral tablet
Comparator(s)	No comparator
Outcome(s)	Primary outcomes: • Number of Participants With Abnormal Laboratory Values [Time Frame: 24 months] • Number of subjects with clinically significant changes in vital signs [Time Frame: 24 months] • Number of subjects with changes on ECG [Time Frame: 24 Months] • Objective response rate (ORR) assessed by RECIST 1.1 criteria of AMG 510 as monotherapy in subjects with KRAS p.G12C mutated advanced tumours [Time Frame: 24 Months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of AMG 510 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

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.[20]

ADDITIONAL INFORMATION

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