NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
May 2023

Adagrasib for previously treated KRAS G12C mutated advanced non-small-cell lung cancer

Company/Developer	Mirati Therapeutics Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID:27474	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II clinical trials.

Summary

Adagrasib is currently in clinical development for the treatment of KRAS G12C mutated advanced non-small-cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. Only a small subset of NSCLC patients carry the KRAS G12C mutation. When NSCLC spreads to other parts of the body, it is called advanced NSCLC. Treatment options vary depending on the cancer stage and mutations identified within the tumours. These options may include surgery, chemotherapy, radiotherapy, targeted drugs, and immunotherapy. However, patients with KRAS G12C mutated advanced NSCLC have limited treatments available, which highlights the need for further effective therapies for this subtype of advanced NSCLC.

Adagrasib is a small molecule that selectively inhibits the activity of the KRAS protein. It is developed to target the KRAS G12C genetic mutation. Adagrasib continuously inhibits KRAS protein. This is particularly significant because KRAS protein typically regenerates every 24 hours. Adagrasib is orally administered. If licensed, adagrasib will offer an additional treatment option for patients with previously treated KRAS G12C mutated advanced NSCLC.

Proposed Indication

Treatment of adult patients with previously treated KRAS G12C mutated advanced non-small-cell lung cancer (NSCLC).[1,2]

Technology

Description

Adagrasib (MRTX849) is an orally-available small molecule inhibitor of KRAS G12C.[1] Adagrasib is a potent, selective, and covalent KRAS G12C inhibitor that exhibits favourable drug-like properties, selectively modifies mutant cysteine 12 in GDP-bound KRAS G12C, and inhibits KRAS-dependent signalling.[3] Preclinical models have demonstrated that the inhibition of KRAS G12C by adagrasib results in tumour regression.[4]

Adagrasib is currently in development for treatment of patients with advanced NSCLC that have KRAS G12C mutations. In the phase I/II clinical trial (NCT03785249) adagrasib was administered as 150mg orally once daily, 300mg once daily, 600mg once daily, 1,200mg once daily or 600mg orally twice a day using an accelerated titration design, which transitioned to a modified toxicity probability interval design when a predefined degree of toxicity was observed or target adagrasib exposure was achieved. The recommended phase II dose of adagrasib is 600mg orally twice daily.[5]

Key Innovation

KRAS mutations have been recognised as undruggable for many years.[6] KRAS is one of the most frequently mutated oncogenes in cancer.[3] In normal cells, KRAS proteins cycle between guanosine triphosphate (GTP)-bound active and guanosine diphosphate (GDP)-bound inactive states. KRAS has a protein resynthesis half-life of approximately 24 hours. Substitution of Gly12 by cysteine prevents GTP hydrolysis, thereby maintaining KRAS in a constitutively active GTP-bound state; this results in uncontrolled cellular proliferation and growth, as well as malignant transformation.[5,7] Efforts to directly target KRAS have been largely unsuccessful due to its high affinity for GTP/GDP and the lack of a clear binding pocket.[3]

Adagrasib specifically targets the KRAS G12C mutation. In a phase II cohort study , adagrasib led to durable clinical benefit in patients with previously treated, advanced KRAS G12C-mutated NSCLC.[2] If licensed, adagrasib would provide an additional treatment option for patients with advanced NSCLC harbouring a KRAS G12C mutation.

Regulatory & Development Status

Adagrasib does not currently have marketing authorisation in the EU/UK for any indication.

Adagrasib has been granted accelerated approval in the USA by the FDA in December 2022 for treatment of KRAS G12C mutated NSCLC.[8]

Adagrasib is in phase III and II clinical development for advanced colorectal cancer with KRAS G12C mutation, malignant neoplastic disease and solid tumours.[9]

Patient Group

Disease Area and Clinical Need

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.[10] Metastatic NSCLC (stage 4) is when the cancer spreads to other parts of the body such as the bones, lungs, brain, liver or adrenal glands.[11] Locally advanced NSCLC (Stage 3A) is cancer that has spread into tissues around the lungs.[12] The KRAS G12C mutation is the most common and occurs in 12% of non-small-cell lung cancer (NSCLC) tumours in the UK.[13] 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.[14] The most common symptoms of lung cancer include cough, breathlessness, coughing up phlegm with blood, pain in the chest or shoulder, recurrent chest infections, loss of appetite, weight loss and fatigue.[15] Some studies have shown an association of smoking status with different KRAS mutations and codon variants. Patients with the KRAS G12C mutation from surgically resected lung adenocarcinomas had significantly worse 2-year overall survival compared with patients with non–KRAS G12C mutations or wild-type KRAS.[16]

Lung cancer is the 3rd most common cancer in the UK, accounting for 13% of all new cancer cases (2016-18).[17] In England (2021-22), there were 119,396 finished consultant episodes (FCEs) and 99,551 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34), which resulted in 75,969 day cases and 206,640 FCE bed days.[18] There were 38,888 patients diagnosed with malignant neoplasm of bronchus and lung , 28,170 deaths registered with malignant neoplasm of bronchus and lung being the underlying cause in England (2017).[19] In 2013-2017 in England, the 1 year survival rate for all stages of lung cancer was 40.6% , with 19.3% being specifically for stage IV lung cancer. The 5 year survival rate for all stages of lung cancer was 16.2%, with 2.9% also for stage IV in particular.[20]

Recommended Treatment Options
National Institute for Health and Care Excellence (NICE) recommends sotorasib for use within the cancer drug funds as an option for treating KRAS G12C mutation-positive locally advanced or metastatic NSCLC in adults whose disease has progressed on, or who cannot tolerate, platinum-based chemotherapy or anti-PD-1/PD-L1 immunotherapy.[13]

Clinical Trial Information

Trial	**KRYSTAL-1;** NCT03785249; A Phase 1/2 Multiple Expansion Cohort Trial of MRTX849 in Patients with Advanced Solid Tumours with KRAS G12C Mutation. **Phase 1/2:** Recruiting **Location(s):** USA and Puerto Rico **Primary completion date:** December 2023
Trial Design	Non-Randomised, Sequential Assignment
Population	N=822; patients with advanced solid tumours with KRAS G12C mutation. N=116; adult patients with locally advanced or metastatic KRAS G12C mutated NSCLC.[2]
Intervention(s)	Adagrasib 600mg administered orally twice daily[2]
Comparator(s)	No comparator
Outcome(s)	Primary outcome:

	• Characterise the safety of adagrasib in patients having advanced solid tumour malignancies with KRAS G12C mutation [Time frame: 20 months] • Evaluate the pharmacokinetics of adagrasib [Time frame: 20 months] • Evaluate clinical activity/efficacy of adagrasib [Time frame: 20 months] See trial record for full list of other outcomes
Results (efficacy)	A total of 116 patients with KRAS G12C-mutated NSCLC had been treated (median follow-up, 12.9 months); 98.3% had previously received both chemotherapy and immunotherapy. Of 112 patients with measurable disease at baseline, 48 (42.9%) had a confirmed objective response. The median duration of response was 8.5 months (95% confidence interval [CI], 6.2 to 13.8), and the median progression-free survival was 6.5 months (95% CI, 4.7 to 8.4). As of January 15, 2022 (median follow-up, 15.6 months), the median overall survival was 12.6 months (95% CI, 9.2 to 19.2). Among 33 patients with previously treated, stable central nervous system metastases, the intracranial confirmed objective response rate was 33.3% (95% CI, 18.0 to 51.8)..[2]
Results (safety)	Treatment-related adverse events occurred in 97.4% of the patients - grade 1 or 2 in 52.6% and grade 3 or higher in 44.8% (including two grade 5 events) - and resulted in drug discontinuation in 6.9% of patients.[2]

Estimated Cost

The cost of adagrasib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (TA781). March 2022.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2023

NHS England (Policy/Commissioning) Guidance

Other Guidance

- National Comprehensive Cancer Network (NCCN) Guidelines Insights: Non–Small Cell Lung Cancer, Version 2. 2021.[21]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up 2019.[22]

Additional Information

Mirati Therapeutics Inc. did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources.

UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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