IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 2, December 2023

Adagrasib in Non–Small-Cell Lung Cancer

Siddharam Lavate[1], Abhay Gundre[2], Rohit Gaikwad[3], Riushikesh Sarde[4]
B-Pharm Students, Department of Pharmacology[1,2,3]
Assistant Professor, Department of Pharmaceutics[4]
Latur College of Pharmacy, Latur, Maharashtra, India

Abstract: *A terse, transition- essence and protection-free conflation of adagrasib(MRTX849), a new KRASG12C asset medicine lately approved by the FDA, Is reported. Preface of two chiral structure blocks to the tetrahydropyridopyrimidine core was fulfilled via two successional SNArreactions.To estimate the safety and efficacity of the new KRAS- targeting agents, sotorasib and adagrasib, in treating KRAS G12Cmutated non – small cell lung cancer(NSCLC). Adagrasib covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive state, thereby precluding downstream signalling without affecting wild- type KRAS protein. In December 2022, adagrasib entered its first blessing in the USA for the treatment of grown-ups with KRAS G12C- shifted locally advanced or metastatic NSCLC(as determined by an FDA approved test) who have entered ≥ 1 previous systemic remedy Cases with advanced KRASG12C- mutant solid excrescences were treated with adagrasib 150 mg orally formerly daily, 300 mg formerly daily, 600 mg formerly daily, 1,200 mg formerly daily, or 600 mg orally twice a day using an accelerated titration design, which transitioned to a modified toxin probability interval design when a predefined degree of toxin was observed or target adagrasib exposure was achieved. Safety, pharmacokinetics, and clinical exertion were estimated. Adagrasib is an orally bioavailable, largely picky, small- patch, unrecoverable covalent asset of KRAS G12C &. It was approved by the US FDA on December 12, 2022, for cases with excrescences harboring the KRAS G12C & mutation in locally advanced or metastaticnon-small cell lung cancer(NSCLC). Herein, conflation, lozenge and administration, medium of action, pharmacokinetics, pharmacodynamics, and adverse events of adagrasib are described. Adagrasib, vended under the brand name Krazati, is an anticancer drug used to treatnon-small cell lung cancer. Adagrasib is an asset of the RAS GTPasefamily.FDA Approves Adagrasib for Locally Advanced or Metastatic KRAS G12CNSCLC.This review details the preclinical and clinical data for adagrasib in the treatment ofnon-small-cell lung cancer. We also outline practical clinical administration guidelines for this novel remedy, including operation of venom*

Keywords: KRAS; NSCLC; drug resistance; immunotherapy; lung cancer; targeted therapy

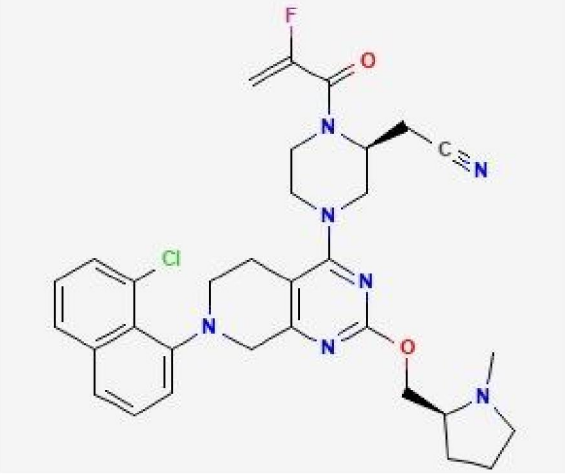
I. INTRODUCTION

What are Adagrasib?

Adagrasib is an oral patch that specifically and irreversibly inhibits KRAS G12C, a mutant oncogenic form of the RAS GTPase, KRAS. Adagrasib is a RAS asset that irreversibly and widely binds to KRAS G12C. In the inactive state of mutant KRAS G12C, the mutant cysteine resides coming to a narrow face fund, the P2 fund. Kirsten rat sarcoma viral oncogene homolog(KRAS) is a Membrane- associated guanosine triphosphatase that has the Loftiest mutation rate of all known oncogenes across mortal Cancers.1 KRAS mutations do in roughly 25 ofNon-small cell lung cancer(NSCLC) cases2And the KRASG12CPoint mutation in codon 12 occurs in roughly 14 Of lung adenocarcinomas.3 Historically, KRAS mutations Have been considered to be undruggable; still, this has Changed with recent advances in the capability to target KRASG12C Mutations. Oncogenic mutations in members of the RAS family are common circumstance in mortal cancer, with differences in KRASAccounting for 85 of these mutations. The loftiest rate ofKRAS mutations are in pancreatic(90), colorectal(30 – 40), And lungcancers(2 – 4). In cases with non – small cellLung cancer(NSCLC), the development of brain metastases(BM) isAssociated with increased morbidity and mortality(5 – 7). I KRAS mutations do further generally in Caucasians and African Americans than in Asian patients5 – 7 and are more Common in youngish cases.8, 9 Smoking is associated with both KRAS mutations

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 2, December 2023

and advanced mutational burden Compared to those who have noway smoked.10, 11 Although the prognostic impact remains controversial, a meta- Analysis of 53 studies set up that KRAS mutations relate with poor prognostic(HR1.40; p = 0.01).12 K

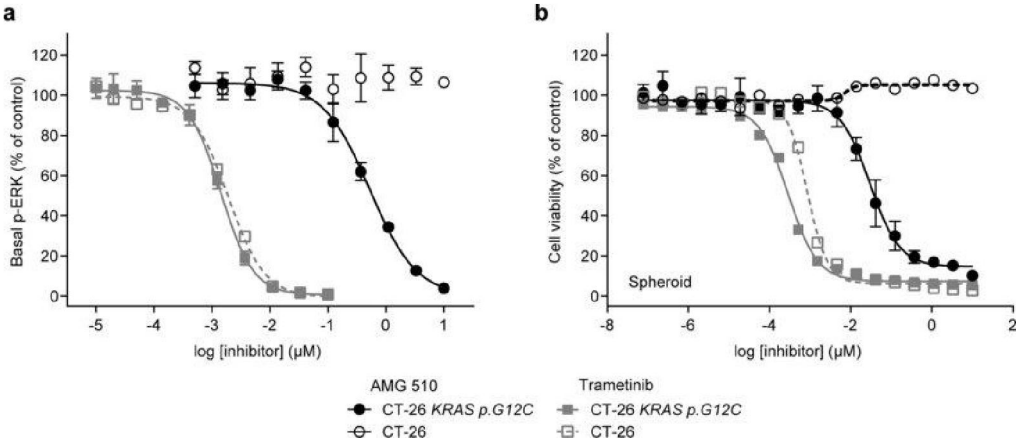


II. MATERIAL AND METHODS

1. Chemical
2. Cell line
3. Drug transporter assay
4. In vitro adagrasib plasma stability assay
5. Animal
6. Oral Drug solutions
7. Bioanalytical analysis

1) Chemicals:-

Adagrasib(MRTX849) was attained from MedKoo Biosciences(Morrisville, NC). Zosuquidar(Zos) was bought from Sequoia Research Products(Pangbourne, United Kingdom) and Ko143 from Tocris Bioscience(Abingdon, United Kingdom).



2) Cell line:-

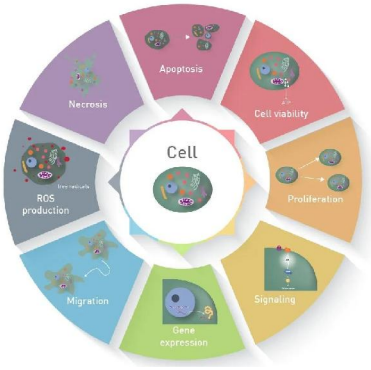
Cell lines MIA PaCa- 2, H1373, H358, H2122, SW1573, H2030, KYSE- 410 cells(G12C); H1299(WT); A549 (G12S), HCT116(G13D) cells attention- Incubation Time 24 h system- All cell lines were maintained at 37 ℃ in a

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 2, December 2023

humidified incubator at 5 CO2 and were periodically checked for mycoplasma. CellTiter- Glo assay to estimate cell viability performed on seven KRAS G12C- mutant cell lines and threenon-KRAS
G12C- mutant cell lines cells grown in 2D towel culture conditions in a 3- day assay or 3D conditions using 96- well, ULA plates in a 12- day assay

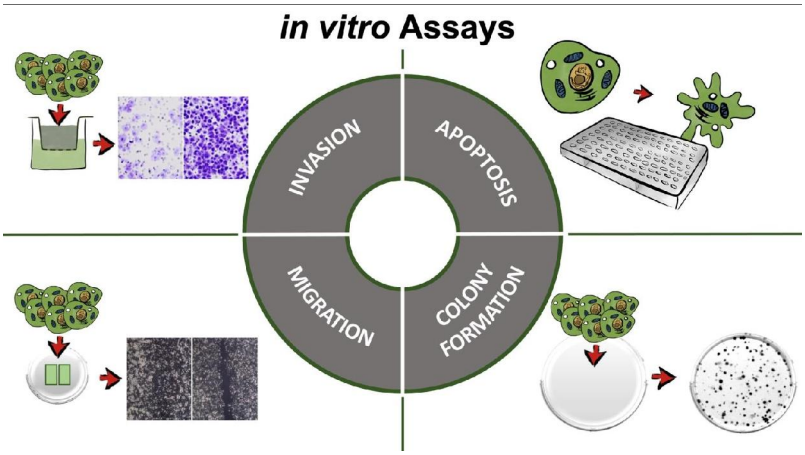
3) Drug transporter assay :-

For the in vitro transepithelial medicine transport assays 12- well plates with microporous polycarbonate membrane sludge inserts(3.0- µm severance size, 12- mm periphery, Transwell 3402, Corning; Amsterdam, The Netherlands) were used. The maternal MDCK- II cells and the transduced subclones were planted at a viscosity of2.5 × 105 cells per well. Prior to the transport assay, the cells were dressed for 3 days to guarantee the conformation of an complete monolayer. The culture medium was replaced one and two days after sowing the cells. Before the launch of the medicine transport assay and latterly, the transepithelial electrical resistance(TEER) situations were measured to confirm the integrity of the monolayer membrane



4) In vitro adagrasib plasma stability :-

Fresh tube was collected from 3 to 6 wild- type and Ces1-/- mice, and independent triplet incubations were set up in the absence or presence of 1 mM BNPP. After 15 min preincubation at 37 °C, adagrasib was spiked at a attention of 2000 ng/ mL and incubation was continued at 37 °C with vigorous shaking. At 0,7.5, 15, 30, 60, 120, and 240 min, samples were taken and pipetted and mixed directly onto a 10 mM BNPP result to a final attention of 1 mM BNPP.



5) Animals :-

Adagrasib was dissolved in DMSO at a attention of 30 mg/ mL, and further10-fold adulterated with polysorbate 80/ ethanol(11, v/ v), and 5(w/ v) glucose in water to yield an adagrasib attention of 3 mg/ mL in the dosing result for

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 2, December 2023

oral administration(127,(v/ v/ v)). Final vehicle attention were 10 v/ v DMSO, 10 v/ v polysorbate 80, 10 v/ v ethanol, and3.5 w/ v glucose. This stock result was further adulterated10-fold with a admixture of polysorbate 80, ethanol and water (201367(v/ v/ v)), to yield an elacridar attention of 5 mg/ mL in the oral dosing result. Final vehicle attention were 10 v/ v DMSO, 18 v/ v polysorbate 80,11.7 v/ v ethanol, and60.3 v/ v water.

6) Oral Drug Solutions

Beast Studies During the development of a new medicine like Adagrasib, preclinical studies are conducted to assess its safety and efficacity. Beast models, similar as mice or rats, are generally used to estimate the medicine's pharmacokinetics, toxicology, and overall impact on the complainttarget.It's important to note that specific details about the conflation, accoutrements , and beast studies for Adagrasib would be personal and defended by the company developing the medicine. For the rearmost and most accurate information, it's recommended to relate to scientific publications, clinical trial data, or sanctioned statements from Mirati rectifiers or applicable nonsupervisory bodies.

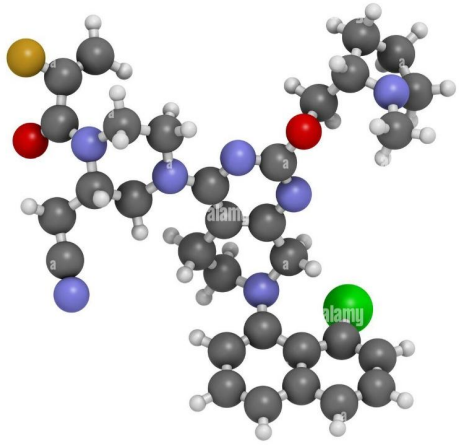
8) Bioanalytical Analysis

A lately developed specific and validated liquid chromatography- tandem mass spectrometry(LCMS/ MS) system was used to measure the attention of adagrasib in DMEM cell culture medium, tube samples

III. HISTORY OF ADAGRASIB MEDICINE

Blessing by the US Food and Drug Administration(FDA) was grounded on KRYSTAL- 1, a multicenter, singlearm, open- marker clinical trial(NCT03785249) which included actors with locally advanced or metastaticnon-small cell lung cancer with KRAS G12C mutations.(2) Adagrasib was granted accelerated blessing in the United States in 2022 for grown-ups with NSCLC with proved KRAS G12C mutations,

Brand Name:-Krazati
Molecular Formula :- C32H35ClFN7O2
Molar mass:- 604.13 g·mol−1 3D model (JSmol):-
3D structure of Adagrasib drug



Mechanism of Action

In normal cells, KRAS is actuated by binding to guanosine triphosphate(GTP), and this promotes the activation of the Chart kinase pathway and intracellular signal transduction. When GTP is hydrolysed to guanosine diphosphate(GDP), KRAS is inactivated. This medium works as an" on"" off" system that regulates cell growth. The negotiation of Gly12 by cysteine in KRAS(KRASG12C) impairs GTP hydrolysis, and maintains KRAS in its active form. Thus, the presence of this mutation leads to unbridled cellular proliferation and growth, as well as nasty metamorphosis.1 Adagrasib is a covalent asset of KRASG12C that irreversibly and widely binds and locks KRASG12C in its inactive,

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 2, December 2023

guanosine diphosphate – set state.2 thus, the use of adagrasib inhibits tumour cell growth and viability in cancers with KRASG12C mutations with minimum off- target exertion.8

Pharmacokinetics:-

Adagrasib(MRTX849) demonstrates directpharmacokinetics.Citation27, Citation28 A single cure of 30 mg/ kg to H358 xenograft- bearing mice redounded in modified bit of KRASG12C 74 at 6 hours and 47 at 72hours.Citation24 This extended effect is harmonious with unrecoverable inhibition of KRASG12C by adagrasib(MRTX849). The half-life is 25 hours after a single cure and 63 hours formerly steady state is Importantly, adagrasib demonstrates CNSpenetration.Citation29, Citation30 Pharmacodynamics- The exposure- response relationship and pharmacodynamic response time course of adagrasib haven't been illustrated. The use of adagrasib can beget QTc interval extension. The increase in QTc is attention-dependent. In cases given 600 mg of adagrasib doubly daily, the mean QTcF change from birth(ΔQTcF) was 18 ms at the mean steady- state outside attention.8 The use of adagrasib can also lead to severe gastrointestinal adverse responses, hepatotoxicity and interstitial lung complaint/ pneumonitis Side goods Along with its demanded goods, a drug may beget some unwanted goods. Although not all of these side goods may do, if they do do they may need medical attention.

Side effects :-

- Cough
- Dark urine dropped
- Quantum of Increased thirst
- Irregular or slow heart rate
- Perversity languor flightiness
- Loss of appetite
- Lower back or side pain Muscle
- Shuddering Nausea Rapid,
- Shallow breathing
- Seizures Sneezing
- Sore throat
- Stomach pain
- Severe torpor lump
- Weakness in the arm or legs on one side of the body, unforeseen and severe

Uses- This drug is used to treat a certain type of lung cancer(non-small cell lung cancer- NSCLC). It workshop by decelerating or stopping the growth of cancer

Clinical Trials: Navigating Adagrasib's Journey from Bench to Bedside

As Adagrasib(MRTX849) transitioned from promising preclinical data, its trip into the clinical arena marked a pivotal juncture in its development. Clinical trials serve as the proving ground, furnishing essential perceptivity into the medicine's safety, efficacity, and connection in different case populations. In this comprehensive disquisition, we navigate through the major clinical trials involving Adagrasib, slipping light on patient populations studied, trial designs, crucial findings, and ongoing objects.

Overview of Major Clinical Trials

Clinical trials involving Adagrasib have been vital in assessing its eventuality as a targeted remedy, particularly for cases harboring KRAS G12C mutations. One of the corner trials, frequently considered the catalyst for posterior examinations, involved cases with advanced solid excrescences harboring KRAS G12C mutations. This phase I trial aimed to establish the safety profile, optimal lozenge, and primary efficacity of Adagrasib in a different cohort of cases, setting the stage for its posterior clinical disquisition. Posterior phase II trials have excavated deeper into

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 2, December 2023

specific cancer types, similar asnon-small cell lung cancer(NSCLC) and colorectal cancer, enriching our understanding of Adagrasib's effectiveness within distinct malice. The nuanced case selection criteria and trial designs have allowed experimenters to knitter the disquisition to the unique characteristics of each cancer type, maximizing the eventuality for meaningful clinical issues.

Case Populations Studied and Trial Design

Clinical trials involving Adagrasib have strategically targeted patient populations with KRAS G12C mutations, feting the significance of this specific inheritable revision in driving oncogenesis. The trial designs encompass both early-phase studies concentrated on safety and cure escalation and latterly- phase trials emphasizing efficacity and long-term issues. The patient populations studied frequently include individualities with heavily pretreated, advanced-stage cancers, reflecting the unmet medical need in this grueling subset of cases. The trial designs generally incorporate scrupulous assessments of Adagrasib's impact on excrescence response, progression-free survival, overall survival, and quality of life. Biomarker analyses are integral factors, abetting in the identification of implicit predictors of response and resistance.

Summary of Key Findings and issues

Primary results from clinical trials involving Adagrasib have been promising, revealing notable responses in cases with KRAS G12C- mutant excrescences. Response rates, duration of responses, and manageable safety biographies have been crucial findings, buttressing the medicine's eventuality as a transformative remedial option. These issues haven't only validated the original preclinical and early- phase clinicaldata but have also deposited Adagrasib as a lamp of stopgap for cases preliminarily facing limited treatment options. The clinical geography has witnessed durable responses in certain cases, motioning a shift in the traditionally grueling narrative of KRAS- mutant cancers. Beforehand- phase trials have laid the root for the posterior expansion of clinical examinations, breeding confidence in Adagrasib's eventuality to address different cancer types with KRAS G12C mutations.

Ongoing Trials and Their objects

Adagrasib's trip continues with several ongoing clinical trials, each designed to address specific questions and upgrade our understanding of the medicine's connection. These trials are strategically designed to explore Adagrasib in combination with other agents, probe its efficacity in earlier complaint stages, and assess its eventuality in different case populations. Ongoing trials are examining Adagrasib's part in combination curatives, aiming to maximize its effectiveness by synergizing with other targeted agents or immunotherapies. The objects include not only perfecting response rates but also potentially prostrating resistance mechanisms and expanding the connection of Adagrasib across a broader diapason of cancers. Also, disquisition in earlier complaint stages, similar as adjuvant or neoadjuvant settings, represents a critical avenue for ongoing exploration. Understanding Adagrasib's impact in these surrounds may reshape the geography of treatment strategies, potentially offering restorative options for cases diagnosed at earlier stages. In conclusion, clinical trials involving Adagrasib serve as pivotal chapters in its narrative, furnishing inestimable perceptivity into its safety, efficacity, and implicit clinical impact. The patient populations studied, trial designs, and ongoing objects inclusively contribute to the evolving understanding of Adagrasib's part in perfection cancer remedy. As exploration progresses, the issues of these trials hold the pledge of not only shaping the medicine's unborn nonsupervisory blessings but also transubstantiating the treatment geography for cases with KRAS G12C- mutant cancers.

IV. CONCLUSION

As shown by Janne et al, adagrasib(MRTX849) was shown to have significant clinical exertion in heavily pretreated cases and indeed demonstrated objective responses in cases without response to previous Grounded on these promising results from the phase I II KYRSTAL- 1 trial, expansion cohorts for KRASG12C – shifted NSCLC and CRC are ongoing. While having two new potent medicines of sotorasib and adagrasib in the field of KRAS was a recent major advance, further requirements to be done to overcome the ineluctable resistance of KRAS inhibition and to come up with further efficient and better permitted strategies with focus on personalized genomic approach.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 2, December 2023

REFERENCES

[1]. Christensen JG, Hallin J, Engstrom LD, Hargis L, Calinisan A, Aranda R, Briere DM, Sudhakar N, Bowcut V, Baer BR, Ballard JA, Burkard MR, Fell JB, Fischer JP, Vigers GP, Xue JY, Gatto S, Fernandez-Banet J, Pavlicek A, Velastegui K, Chao RC, Barton J, Pierobon M, Baldelli E, Patricoin EF, Cassidy DP, Marx MA, Rybkin II, Johnson ML, Ou SI, Lito P, Papadopoulos KP, Janne PA, Olson P: The KRASG12C Inhibitor, MRTX849, Provides Insight Toward Therapeutic Susceptibility of KRAS Mutant Cancers in Mouse Models and Patients. Cancer Discov. 2019 Oct 28. Pii: 2159-8290.CD-19-1167. Doi: 10.1158/2159-8290.CD-19-1167. [Article]

[2]. Ou SI, Janne PA, Leal TA, Rybkin II, Sabari JK, Barve MA, Bazhenova L, Johnson ML, Velastegui KL, Cilliers C, Christensen JG, Yan X, Chao RC, Papadopoulos KP: First-in-Human Phase I/IB Dose-Finding Study of Adagrasib (MRTX849) in Patients With Advanced KRAS(G12C) Solid Tumors (KRYSTAL-1). J Clin Oncol. 2022 Aug 10;40(23):2530-2538. Doi: 10.1200/JCO.21.02752. Epub 2022 Feb 15. [Article]

[3]. Janne PA, Riely GJ, Gadgeel SM, Heist RS, Ou SI, Pacheco JM, Johnson ML, Sabari JK, Leventakos K, Yau E, Bazhenova L, Negrao MV, Pennell NA, Zhang J, Anderes K, Der-Torossian H, Kheoh T, Velastegui K, Yan X, Christensen JG, Chao RC, Spira AI: Adagrasib in Non-Small-Cell Lung Cancer Harboring a KRAS(G12C) Mutation. N Engl J Med. 2022 Jul 14;387(2):120-131. Doi: 10.1056/NEJMoa2204619. Epub 2022 Jun 3. [Article]

[4]. Romero D: Two new agents target KRAS G12C. Nat Rev Clin Oncol. 2020 Jan;17(1):6. Doi: 10.1038/s41571-019-0304-3. [Article]

[5]. Brazel D, Arter Z, Nagasaka M: A Long Overdue Targeted Treatment for KRAS Mutations in NSCLC: Spotlight on Adagrasib. Lung Cancer (Auckl). 2022 Nov 10;13:75-80. Doi: 10.2147/LCTT.S383662. eCollection 2022. [Article]

[6]. Tian H, Yang Z, He J: Adagrasib: A landmark in the KRAS(G12C)-mutated NSCLC. MedComm (2020). 2022 Nov 25;3(4):e190. Doi: 10.1002/mco2.190. eCollection 2022 Dec.

[7]. Cancer Network: New Drug Application for Adagrasib Accepted by FDA for KRAS G12C+ NSCLC [Link]

[8]. FDA Approved Drug Products: KRAZATI (adagrasib) tablets for oral use [Link]

[9]. PR NewsWire: Mirati Therapeutics Announces U.S. FDA Accelerated Approval of KRAZATI (adagrasib) as a Targeted Treatment Option for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) with a KRASG12C Mutation [Link]

[10]. Liu P, Wang Y, Li X. Targeting the untargetable KRAS in cancer therapy. Acta Pharm Sin B 2019;9:871-879

[11]. Pakkala S, Ramalingam SS. Personalized therapy for lung cancer: striking a moving target. JCI Insight 2018;3(15):e120858-e120858.

[12]. Nassar AH, Adib E, Kwiatkowski DJ. Distribution of KRAS (G12C) somatic mutations across race, sex, and cancer type. N Engl J Med 2021;384:185-187.

[13]. Salem M, El-Refai S, Sha W, et al. Characterization of KRAS mutation variants and prevalence of KRAS-G12C in gastrointestinal malignancies. In: Proceedings and Abstracts of the 2021 Annual Meeting of the European Society for Medical Oncology, September 16–21, 2021. Lugano, Switzerland: European Society for Medical Oncology, 2021.

[14]. SI, Jänne PA, Leal TA, et al. First-in-human phase I/IB dose-finding study of adagrasib (MRTX849) in patients with advanced KRASG12C solid tumors (KRYSTAL-1). J Clin Oncol 2022 February 15 (Epub ahead of print).

[15]. Spira AI, Tu H, Aggarwal S, et al. A retrospective observational study of the natural history of advanced non-small-cell lung cancer in patients with KRAS p.G12C mutated or wild-type disease. Lung Cancer 2021;159:1-9.

[16]. Hallin J, Engstrom LD, Hargis L, et al. The KRASG12C inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. Cancer Discov 2020;10:54-71.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 2, December 2023

[17]. Lito P, Solomon M, Li LS, Hansen R, Rosen N. Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism. Science 2016;351:604-608.Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a KRAS(G12C) mutation. N Engl J Med. 2022; 387(2): 120-131.

[18]. Hallin J, Engstrom LD, Hargis L, et al. The KRAS(G12C) inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. Cancer Discov. 2020; 10(1): 54-71.

[19]. Adagrasib in non–small-cell lung cancer. N Engl J Med. 2022;387(13):1238-1239.

[20]. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature. 2019; 575(7781): 217-223.

[21]. Briere DM, Li S, Calinisan A, et al. The KRAS(G12C) inhibitor MRTX849 reconditions the tumor immune microenvironment and sensitizes tumors to checkpoint inhibitor therapy. Mol Cancer Ther. 2021; 20(6): 975-985. [PMC free article]

[22]. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.

[23]. World Cancer Research Fund International. Lung cancer statistics. Accessed August 9, 2023. https://www.wcrf.org/cancer-trends/lung-cancer-statistics/

[24]. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res. 2016;5(3):288-300

[25]. American Cancer Society. Cancer facts and figures 2023. Published 2023. Accessed August 9, 2023. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf

[26]. Yanagawa J, Riely GJ. Management of patients with resectable and metastatic non–small cell lung cancer. J Natl Compr Canc Netw. 2022;20(5.5):1-5.