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Treatment Strategy Among KRAS mutant NSCLC: A Scoping Review

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ADMINISTRATIVE INFORMATION

Support - MSD China.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - Lu Zheng and Suijun Xiao are employees of MSD China. The remaining authors declare no other competing interests.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 May 2026 and was last updated on 29 May 2026.

INTRODUCTION

Review question / Objective To summarize the current treatment patterns of KRAS mutant non-small cell lung cancer (NSCLC). To extract mechanisms of action (MOA) of novel drugs and corresponding translational explorations.
To overview the current KRAS testing patterns including region disparity analysis and patient characteristics.

Background KRAS is the most frequently mutated oncogene in human solid tumors, accounting for approximately 17% of all solid malignancies, with high prevalence in pancreatic (90%), colorectal (50%) and lung cancers (25%). Most KRAS mutations are missense mutations at codons 12, 13, or 61, with G12C, G12V, and G12D being the most common subtypes. KRAS mutations represent a common key driver mutation in non-small cell lung cancer (NSCLC), and they are particularly prevalent in lung adenocarcinoma, with significant differences in allele frequency/amplification and regional distribution1. For decades, all attempts to target KRAS mutations in patients, either directly or indirectly through upstream regulators or downstream effectors, have proven ineffective or excessively toxic, leading to the widespread notion that KRAS mutations were undruggable. Traditional chemotherapy exhibits limited efficacy, and the efficacy of immunotherapy (IO) varies significantly due to co-mutations and other confounding factors.
KRAS G12C accounts for approximately 40% of cases and is the most common variant in lung adenocarcinoma. Consequently, early clinical development efforts for mutant-selective KRAS G12C inhibitors have primarily focused on this variant type. Since 2021, FDA has accelerated approved sotorasib and adagrasib, which are mutant-selective covalent KRAS G12C off-state inhibitors, for the treatment of patients with advanced KRAS G12C mutant NSCLC following at

least one prior systemic therapy. In China, National Medical Products Administration (NMPA) has also approved fulzerasib, garsorasib, glecirasib and sosimerasib for the same indication.
Currently, multiple other next-generation covalent KRAS G12C off-state inhibitors, as well as mutant-selective KRAS inhibitors (targeting G12D and G12V), pan-KRAS inhibitors and pan-RAS inhibitors, are currently under early phase clinical exploration in NSCLC and other malignancies. Based on compelling preclinical evidence demonstrating synergistic effects between KRAS inhibitors and agents with other mechanisms of action (MOA), multiple clinical trials are currently evaluating combination strategies. A variety of IO-based combination strategies have become the focus of research and development, such as the combination of KRAS G12C inhibitors with immune checkpoint inhibitors (ICI), which have shown promising therapeutic effects in preclinical and clinical explorations.

Rationale For patients with KRAS mutant NSCLC, ICI-based therapy is still the standard of care (SOC) for early-stage and first-line NSCLC. Currently, Allele-specific KRAS G12C inhibitors as monotherapy are changing the treatment paradigm in second-line NSCLC and more novel treatment strategies including KRAS/RAS-targeted monotherapy and combination regimens are under intensive exploration. However, treatment strategies, KRAS mutation detection practice, and novel MOA exploration strategy across different disease stages among different allele/amplification remain unclear. Although KRAS G12C off-state inhibitors have achieved milestone breakthrough in targeted therapy, these agents still face challenges such as uncertainties regarding the optimal treatment strategy, unclear drug resistance mechanisms, safety concerns, and the lack of effective targeted agents for non-G12C KRAS subtypes. Therefore, a scoping review is warranted to systematically summarize treatment strategy and exploration direction to inform status and following research.

METHODS

Strategy of data synthesis This scoping review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search will be performed in the following electronic databases: Medline (PubMed), EMBASE, and the Cochrane Library. A comprehensive search strategy will be developed in collaboration with an information specialist and will be structured around three core concepts: (1) NSCLC; (2) KRAS; (3) clinical trial. Relevant conference abstracts and registered trials may also be supplemented based on expert knowledge to ensure comprehensive coverage of emerging and unpublished evidence.

Eligibility criteria Population(s):
KRAS mutant adult NSCLC patients across all disease stages.
Interventions:
All interventions will be included, such as surgery, radiotherapy, and systematic anti-cancer treatment include monotherapy or combination therapy of target therapy, immunotherapy, chemotherapy, novel therapy (bispecific antibody et al.).
Comparisons: No limitations
Outcomes:
Information needs to focus on:
(1) treatment patterns including regimen and duration of treatment will be analyzed by below stage subgroups:
(1-1) early-stage and locally advanced resectable stage I–III disease;
(1-2) first line of unresectable locally advanced and metastatic disease;
(1-2-1) local advanced unresectable (stage III) with radiotherapy
(1-2-2) local advanced and metastatic unresectable (stage III-IV) without radiotherapy
(1-3) second-line and subsequent therapy for locally advanced and metastatic/stage IIIB-C-IV disease;
(2) monotherapy or combination regimens
(3) research development overview including MOA types, corresponding patient characteristics by different MOA (type of KRAS mutation, stage of NSCLC, treatment-naive/ previously treated, PD-L1 expression level), interventions (drug, treatment regimen).
(3) KRAS testing patterns: sample, testing methods, testing result (corresponding prevalence of multiple allele/ amplification types), region disparities and ethnic differences.
Time: Literature published from 2021
Study Design: Clinical trials.
In addition, we excluded studies involving patients with other diseases or KRAS wild-type NSCLC, articles published prior to 2021, and non-trial publications.

Source of evidence screening and selection After the search and automatic de-duplication, all identified records will be uploaded into Rayyan (https://rayyan.ai/). Two reviewers will screen the literature by reading titles and abstracts of the search results as 1st level screening. All potentially relevant records will be requested and inspected in detail using the full-text version as 2nd level screening. Disagreements between reviewers will

be resolved by discussion, with assistance from a third party if necessary. If the number of eligible trials is excessive, we will first screen candidate trials according to the evidence hierarchy pyramid as recommended by the Cochrane Handbook and then prioritize selecting studies with the most recent publication date, the largest sample size, and the highest methodological quality. This approach will ensure that our synthesis reflects the most robust and up-to-date evidence while maintaining methodological rigor and transparency throughout the selectionprocess.

Data management Multiple reviewers will extract data from each included study using a standardized data extraction form. Any disagreement that arises between the reviewers will be resolved through discussion, or with the final decision from a third reviewer. When multiple reports describe the same underlying study, these reports will be collated and reviewed together to avoid double counting. The most comprehensive and up-to-date report will be used as the primary data source, while additional reports will be consulted to supplement information on study design, outcomes, or follow-up as needed.

Reporting results / Analysis of the evidence We will systematically, descriptively summarize and analyze the extracted data. There will be no meta-analysis in this scoping review.
To visually represent the evidence map on treatment strategy among KRAS mutant NSCLC, bubble plots will be generated to show the treatment landscape. The x-axis represents the category of the treatment regimens and MOA. The detailed drug use will be differentiated by colour. The y-axis represents different KRAS subtypes which will be further divided based on study design. Bubble size represents sample size. Number represents the sum of references.

Language restriction None.

Country(ies) involved China.

Keywords KRAS; NSCLC; MOA; Translational exploration; Testing patterns; Scoping.

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