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Beyond a single KRAS inhibitor: China-originated therapeutics and the rise of resistance-directed combinations

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For decades, KRAS was the archetype of an "undruggable" oncogene. The success of covalent KRAS G12C inhibitors overturned that paradigm, but it also exposed the limitations of simply matching one mutation with one drug. Responses are often incomplete, resistance emerges through pathway reactivation and tumor-microenvironmental adaptation, and therapeutic sensitivity differs across alleles and tumor lineages[1-5]. The next phase of KRAS therapeutics will therefore depend on both new inhibitors and mechanism-based, biomarker-informed combinations. China-originated drug discovery and clinical translation are increasingly contributing to this shift.

Garsorasib (D-1553) provides a useful starting point and exemplifies this transition. Developed in China, this selective KRAS G12C inhibitor moved from preclinical discovery into phase 1 and phase 2 studies in Chinese patients with non-small-cell lung cancer (NSCLC), and was subsequently approved in China[6-8]. The program matured through international presentations, including AACR and WCLC, before longer-term publication. In a pooled analysis of 189 patients led by Zhengbo Song and colleagues, garsorasib achieved an objective response rate (ORR) of 48.1%, a median duration of response of 12.45 months, and a median progression-free survival (PFS) of 9.07 months[8]. These results established more than another active G12C inhibitor: they created a China-originated clinical platform on which combination strategies could be built.

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The most distinctive example is garsorasib plus ifebemtinib, an oral focal adhesion kinase (FAK) inhibitor. Ifebemtinib should not itself be described as a de novo China-discovered molecule; the innovation is the China-led translational and clinical strategy of pairing FAK inhibition with a China-developed KRAS inhibitor. Preclinical work underpinning the program suggested that FAK inhibition could enhance KRAS G12C blockade through downregulation of FAK-YAP signaling, attenuation of cancer-associated fibrosis, increased T-cell infiltration, and enhanced immunogenic cell death. FAK can therefore be viewed as a candidate adaptive-resistance node rather than a canonical KRAS effector. This program progressed from preclinical observations to ASCO 2024, ESMO 2024, ASCO 2025, and ASCO 2026, and ultimately to peer-reviewed clinical evidence. In treatment-naive KRAS G12C-mutant NSCLC, ifebemtinib plus garsorasib produced a confirmed ORR of 82% in 33 patients after a median follow-up of 21.5 months[2]. Importantly, this was a dual-oral, chemotherapy-free first-line regimen. An additional advantage of this dual-oral targeted regimen is its potential to improve treatment convenience and support long-term adherence. The *Lancet Respiratory Medicine* report described it as the first study to investigate an orally bioavailable FAK inhibitor combined with a KRAS G12C inhibitor in KRAS G12C-mutant solid tumors[2]. A randomized phase 3 study is now evaluating the regimen against immunotherapy plus chemotherapy as the standard-of-care first-line therapy (NCT07174908), which may yet offer some unexpected insights-and perhaps even a few welcome surprises.

The colorectal cancer experience is equally instructive. In previously treated KRAS G12C-mutant metastatic colorectal cancer, the randomized phase 1b/2 study reported confirmed ORRs of 38.9% with ifebemtinib plus garsorasib and 16.7% with garsorasib alone. The prespecified ORR comparison did not reach statistical significance (one-sided $P = 0.068$), but exploratory circulating cell-free DNA analyses showed deeper and more sustained KRAS G12C suppression with the combination[9]. Thus, the importance of this program extends beyond a response rate. It provides a clinically testable framework in which a resistance mechanism is identified, pharmacologically intercepted, and interrogated through molecular monitoring-a translational loop that KRAS drug development increasingly requires.

This strategy is also expanding beyond FAK. A phase 1b/2 study led by Song of GH21 plus D-1553 is being studied in KRAS G12C-mutant advanced solid tumors, including a dedicated setting after prior KRAS G12C inhibition (ChiCTR2600124637). Together, these programs shift combination development from empirical drug pairing toward deliberate interception of adaptive signaling.

China-led innovation is simultaneously moving beyond G12C. RNK08954, developed in Hangzhou, is a selective oral KRAS G12D inhibitor whose development integrates medicinal chemistry, tumor pharmacokinetics, patient-derived models, immune biology, and first-in-human investigation. In *Cancer Discovery*, our team linked prolonged tumor retention and preclinical tumor regression with preliminary clinical activity while also demonstrating synergy with immune checkpoint blockade[3]. GFH375, developed in Shanghai, has independently advanced the G12D field as a dual ON/OFF-state inhibitor; its phase 1 study in 74 heavily pretreated patients with KRAS G12D-mutant solid tumors was published in *Nature Medicine* in 2026[4]. These programs indicate that Chinese KRAS research is not simply reproducing the G12C template but is contributing distinct pharmacologic solutions to previously inaccessible alleles.

These developments reinforce another lesson: "KRAS-mutant cancer" is not a single biological entity. Our team has investigated real-world treatment patterns and therapeutic strategies in patients with KRAS-mutant NSCLC[10]. In a 95-patient retrospective NSCLC cohort, first-line immune checkpoint inhibition plus platinum chemotherapy was associated with longer PFS and OS than platinum chemotherapy alone[5]. A later 129-patient analysis found shorter PFS and OS for patients with KRAS G12D versus non-G12D mutation after the first-line chemoimmunotherapy[11]. These retrospective observations require prospective

validation, but they support integrating allele, co-mutations such as TP53, PD-L1 status, tumor lineage, and serial ctDNA into clinical development[10]. The goal should be not merely to detect KRAS, but to define the biological state in which KRAS operates.

The field is already moving toward broader RAS targeting. At AACR 2026, Song and colleagues reported the first-in-human study design of BPI-572270, a China-developed, cyclophilin A-dependent RAS(ON) multi-inhibitor intended to target a broader spectrum of RAS-mutant tumors[12]. This direction aligns with a broader research agenda led by Song on precision diagnosis, targeted treatment, and resistance mechanisms in advanced KRAS-mutant lung cancer. The trajectory is therefore becoming coherent: G12C monotherapy provides the foundation; FAK and other rational combinations address adaptive resistance; G12D programs expand allele coverage; biomarker studies refine patient selection; and RAS(ON)/pan-RAS strategies attempt to move beyond allele-by-allele drug development.

Looking ahead, KRAS research will extend beyond increasingly potent allele-specific inhibitors toward broader RAS(ON)/pan-RAS targeting and mechanism-driven combinations designed to intercept adaptive resistance. Serial ctDNA profiling and molecular characterization may further enable an evolution-informed therapeutic framework, in which treatment is adapted to emerging resistance rather than guided solely by baseline mutations. Meanwhile, new therapeutic modalities are expanding the boundaries of KRAS targeting, including targeted protein degradation and molecular-glue approaches, as well as immune-based strategies such as KRAS-directed vaccines, TCR-engineered T-cell (TCR-T) therapy, and rational combinations with immune checkpoint blockade. Ultimately, the future of KRAS precision oncology may lie not simply in developing the next inhibitor, but in integrating direct targeting, resistance interception, immune engagement, and dynamic molecular monitoring to anticipate and prevent tumor escape.

DECLARATIONS

Authors' contributions

Involved in manuscript preparation: Hao Y, Song Z

Both authors approved the final version.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI website (https://aizex.net/plusPool) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content the final version.

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