K-RAS-tling with Resistance: KRAS^{G12C} Inhibitors and Strategies for Overcoming Resistance

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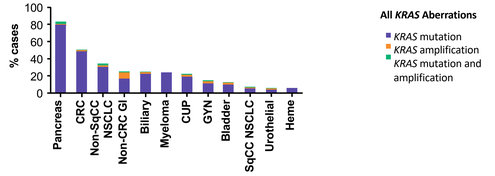
KRAS is the Most Common Driver Oncogene in Humans

- Approximately 30% of all cancers are associated with a RAS mutation, suggesting that a mutation in RAS oncogenes may be a leading cause of carcinogenesis[1]
- Of the RAS oncogenes, a mutation in KRAS is the most frequent, followed by NRAS and HRAS

Figure 1. Frequency in *KRAS* Aberrations by Tumor Type



Distribution of KRAS Variants Differs by Cancer Type

- KRAS^{G12C} mutations are most prevalent in NSCLC; however, they also occur in GI cancers[2]
- The most common KRAS point mutation in all solid tumors is KRAS^{G12D}

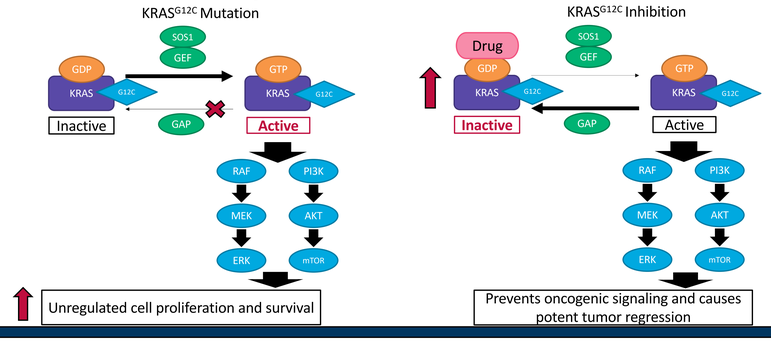
Table 1. Frequency of KRAS Point Mutations in KRAS-Mutated Solid Tumors

Mutation	CRC (%)	Appendix (%)	Pancreatic (%)	Small Bowel (%)	NSCLC (%)	All Solid Tumors (%)
G12C	7	7.4	1.8	6	36.8	11.9
G12D	29.9	50.7	41.8	38.4	14.5	29.5
G12R	1	0	16.1	3.3	1.1	6.2
G12V	20	25.7	31.6	22.5	19.2	23
G13D	15.8	7.4	0.4	11.9	2.7	6.5

KRAS^{G12C} Inhibitors Prevent Oncogenic Signaling

- KRAS^{G12C} mutation impairs GTP hydrolysis, which shifts KRAS to the active GTP-binding state to drive protumorigenic effector signaling[3,4]
- KRAS^{G12C} inhibitors form a covalent bond with cysteine 12 at the switch-II pocket, trapping KRAS in the inactive, GDP-bound state

Figure 2. Mechanism of KRAS^{G12C} Inhibition



KRAS^{G12C} Inhibitors are Only FDA-Approved in NSCLC

- As of March 2023, the FDA has approved two KRAS^{G12C} inhibitors[5,6]

Table 2. KRAS^{G12C} Inhibitor Details

	Adagrasib (Krazati®)	Sotorasib (Lumakras®)
FDA-Approved Indication	Locally advanced or metastatic NSCLC with KRAS^{G12C} mutation	Locally advanced or metastatic NSCLC with KRAS^{G12C} mutation
Dosing	Three 200 mg tablets (600 mg) PO BID	Eight 120 mg tablets (960 mg) PO QD
Pharmacokinetics	98% protein bound Irreversibly binds Half life: 23 hours Metabolized via CYP3A4	89% protein bound Irreversibly binds Half life: 5 hours Metabolized via CYP3A
Drug Interactions	Strong CYP3A4 inhibitors, strong CYP3A4 inducers, CYP3A4 substates, CYP2C9 substrates, CYP2D6 substrates, P-gp substrates, QTc prolonging drugs	Acid-reducing agents, strong CYP3A4 inducers, CYP3A4 substrates, P-gp substrates, BCRP substrates
Warnings	Hepatotoxicity, gastrointestinal bleeding and obstruction, pulmonary toxicity, QTc interval prolongation	Hepatotoxicity, pulmonary toxicity
Common ADE	Edema, prolonged QTc, diarrhea, musculoskeletal pain, elevated creatinine, hypoalbuminemia, hypomagnesemia, hypokalemia	Edema, skin rash, musculoskeletal pain, proteinuria, hypocalcemia, hyponatremia, hypoalbuminemia
Emetic Potential	Moderate to high	Minimal to low

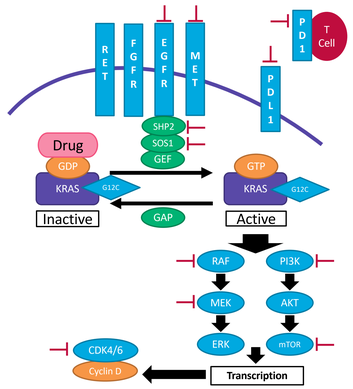
Acquired Resistance Frequently Occurs

- Resistance to KRAS^{G12C} inhibition can occur through several on-target and off-target mechanisms
- Acquired resistance has been shown in a small histologic analysis of KRAS^{G12C}-mutated cancers to occur at a rate of 45% with the use of a KRAS^{G12C} inhibitor[7]

Potential Strategies for Overcoming Acquired Resistance

- Inhibition of proteins downstream of KRAS[8]
  - RAF, MEK, PI3K, CDK4/6, and mTOR
- Inhibition of proteins or targets upstream of KRAS[8]
  - EGFR, MET, SHP2, PD-L1, PD-1, and SOS1
- KRYSTAL-01 CRC cohort receiving cetuximab with adagrasib had longer progression-free survival and higher objective response rate compared to adagrasib monotherapy[9]
- CodeBreaK 101 CRC cohort receiving panitumumab with sotorasib had an objective response rate of 30%[10]
- CodeBreaK 101 CRC cohort receiving trametinib with sotorasib had an objective response rate of 28%[11]

Figure 3. Potential Targets in KRAS^{G12C} Inhibitor Resistance



Ongoing Trials

Table 3. Ongoing Trials Involving KRASG12C Inhibitor Combination Therapy

KRAS^{G12C} Inhibitor (Manufacturer)	Combining Agent	Phase Trial and Setting
Sotorasib (Amgen)	AMG 404 (PD-1 inhibitor) or pembrolizumab Trametinib +/- panitumumab RMC-4630 or TNO155 (SHP2 inhibitors) Everolimus Palbociclib BI 1701963 (SOS1/pan-KRAS inhibitor) Afatinib Panitumumab +/- FOLFIRI Atezolizumab Carboplatin, pemetrexed, docetaxel Bevacizumab + FOLFIRI or FOLFOX	Phase 1b/2 CodeBreaK 101 trial (NCT04185883) in advanced solid tumors, NSCLC, CRC
Adagrasib (Mirati Therapeutics)	Cetuximab Pembrolizumab, Afatinib, Cetuximab	Phase 3 KRYSTAL-10 trial (NCT04793958) in CRC Phase 1/2 KRYSTAL-1 trial (NCT03785249) in NSCLC, CRC
JAB-21822 (Jacobio)	Cetuximab	Phase 1/2 trial (NCT05002270) in CRC
GDC-6036 (Genentech)	GDC-1971 (SHP2 inhibitor), Atezolizumab, Erlotinib, Cetuximab, Bevacizumab	Phase 1 trial (NCT04449874) in advanced solid tumors, NSCLC, CRC

Discussion

- Recent approvals of KRAS^{G12C} inhibitors in NSCLC are a milestone in cancer therapy, as this mutation was previously dubbed “undruggable”
- The prevalence of KRAS^{G12C} mutation is ~13% in lung adenocarcinomas, ~3% of colorectal cancers, and ~1-2% of pancreatic cancers[13]
- KRAS^{G12C}-inhibitors prevent oncogenic signaling in KRAS^{G12C}-mutated cancers by binding to GDP-bound KRAS and locking it in its inactive form. This mechanism can be referred to as KRAS-”off” inhibition. Drugs that target KRAS-”on” inhibition are being studied.[12]
- Resistance to KRAS^{G12C}-inhibitors can occur through many mechanisms, including increased feedback signaling, acquired point mutations, and histologic transformation. Resistance leads to short-lived responses, highlighting the need for combination therapy
- Additional KRAS targeting therapies are being developed for solid tumors, including KRAS^{G12D} inhibitors[12]

Conclusion

- Acquired resistance is a challenge in treating KRAS^{G12C}-mutated cancers, leading to short-lived responses
- To overcome resistance, trials are investigating various therapies in combination with KRAS^{G12C} inhibitors

References

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Abbreviations: BCRP, breast cancer related protein; CRC, colorectal cancer; CUP, carcinoma of unknown primary; FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan chemotherapy; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin chemotherapy; GAP, GTPase-activating protein; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GI, gastrointestinal; GTP, guanosine triphosphate; GYN, gynecologic; Heme, hematologic; KRAS, Kirsten rat sarcoma gene; NSCLC, non-small-cell lung cancer; P-gp, p-glycoprotein; SqCC, squamous cell carcinoma