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Resistance to KRAS Inhibitors

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MaTOS
Lake Tahoe, CA
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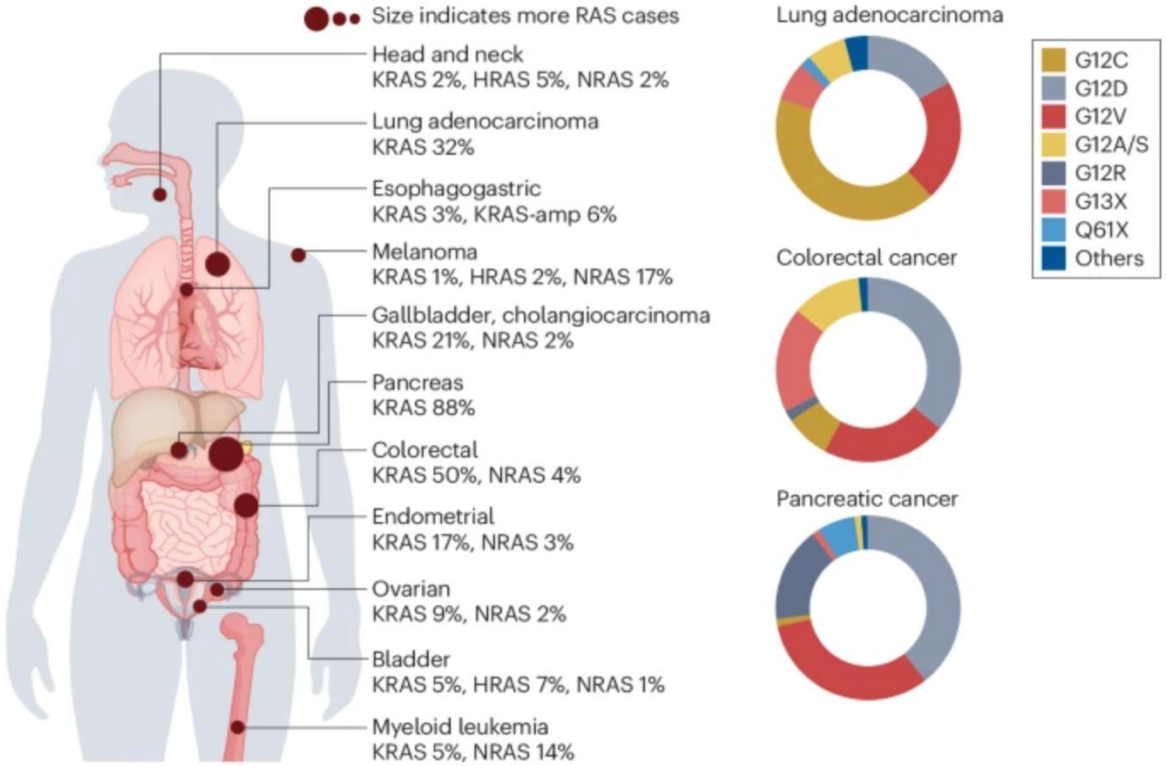
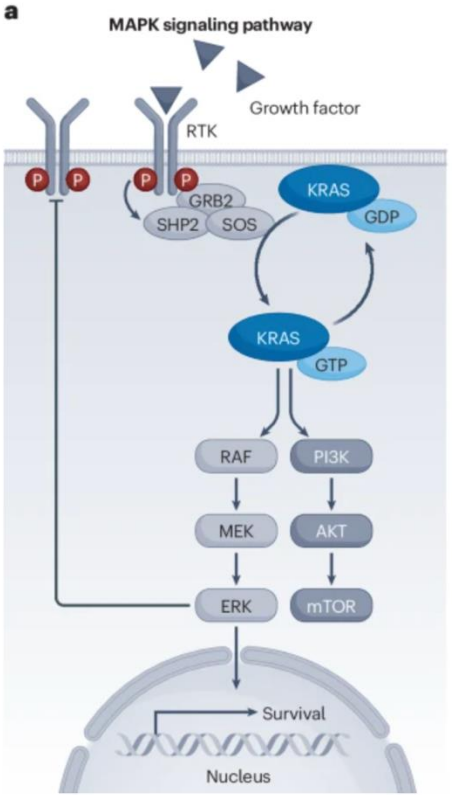
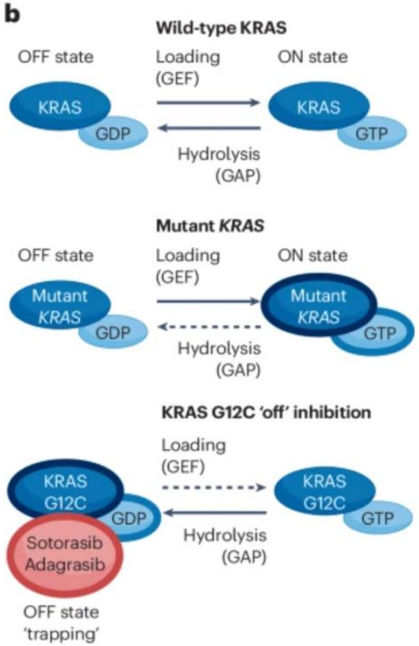
KRAS mutations in NSCLC



Singhal A, Li B, O'Reilly, Nat Med 2024

KRAS signaling





Kevan Shokat
Sjoberg Prize 2023
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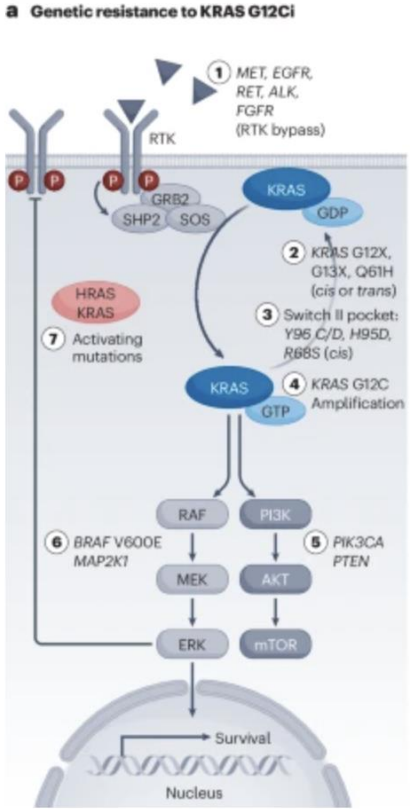
Singhal A, Li B, O'Reilly, Nat Med 2024

KRAS inhibitors in NSCLC: KRAS(OFF)

- Sotorasib
  - CodeBreaK 100 (phase 1/2)
    - n=174, ORR 41%, mPFS 6.3m, mOS 12.5m
  - CodeBreaK 200 (phase3 sotorasib vs docetaxel)
    - n=330, ORR 28.1 vs 13.2%, **mPFS 5.6 vs 4.5m (HR 0.66, p=0.0017)**, mOS 10.6 vs 11.3m
- Adagrasib
  - KRYSTAL-1 (phase 1/2)
    - N=116, ORR 42.9%, mPFS 6.5m, mOS 11.7m
  - KRYSTAL-12 (phase 3 adagrasib vs docetaxel)
    - N=301, ORR 32 vs 9%, **mPFS 5.5 vs 3.8m (HR 0.58, p<0.0001)**
- Divarasib
  - Phase 1
    - N=60, ORR 53.4%, mPFS 13.1m

Skoulidis, NEJM 2021. deLangen Lancet 2023. Janne, NEJM 2022. Mok, ASCO 2024 (LBA8509). Sacher, NEJM 2023.

KRAS inhibitor resistance: Genetic resistance



1. Amplifications/mutations of upstream RTK
2. Mutation of the *KRAS* G12C codon to another mutant variant (*cis* G12X) or secondary activating mutation on the *trans* (previously wild type) *KRAS* allele (G12D, G12R, G12V, G13D, Q61H)
3. KRAS switch II pocket mutations that block drug binding
4. *KRAS* G12C gene amplification or copy number gain
5. Bypass via other downstream pathways like *PIK3CA*
6. Bypass via other downstream pathways like *BRAF*
7. Activating mutations in *NRAS* or *HRAS*

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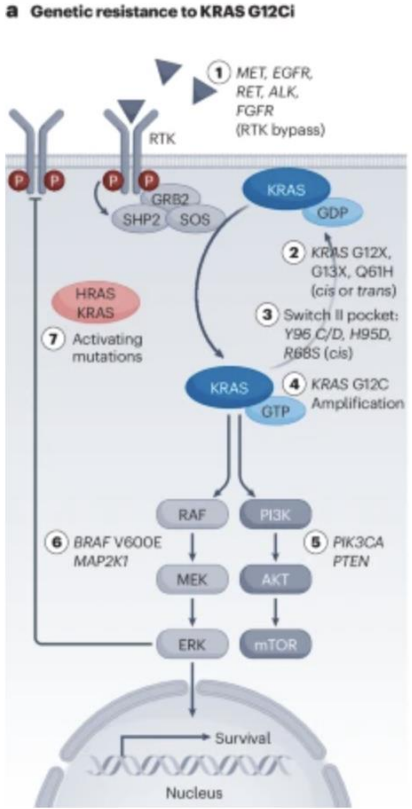
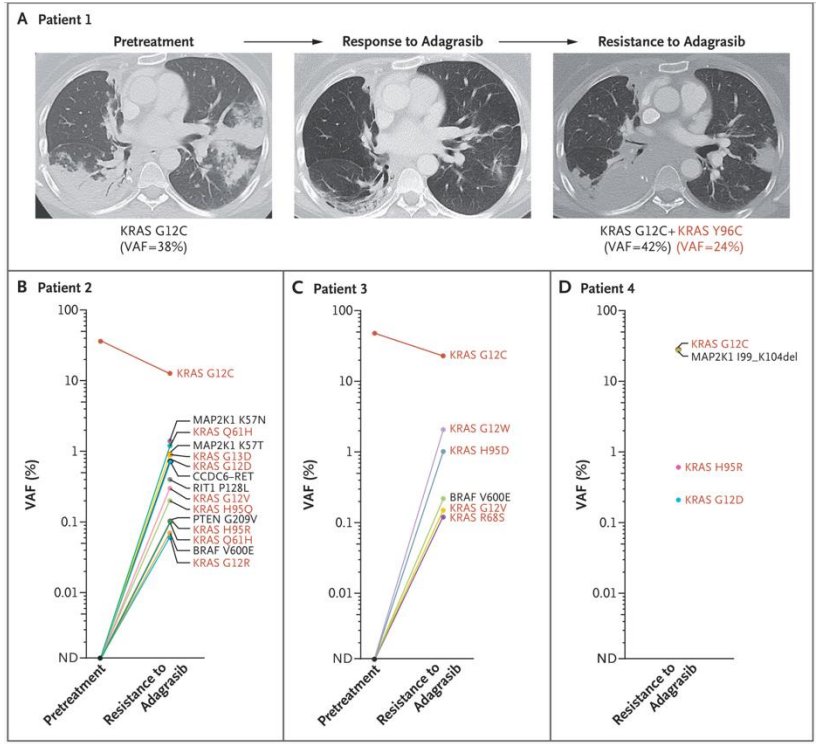
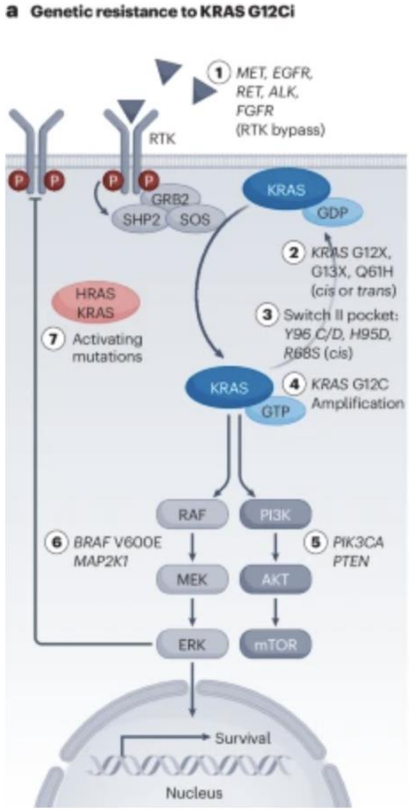
KRAS inhibitor resistance: Genetic resistance



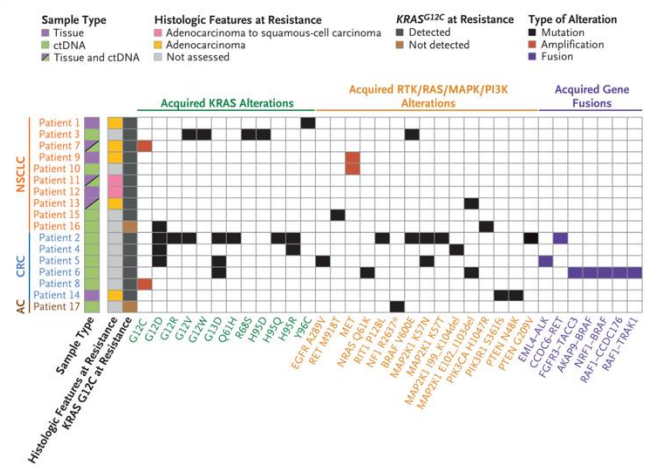


Singhal A, Li B, O'Reilly, Nat Med 2024. Awad, NEJM 2021.

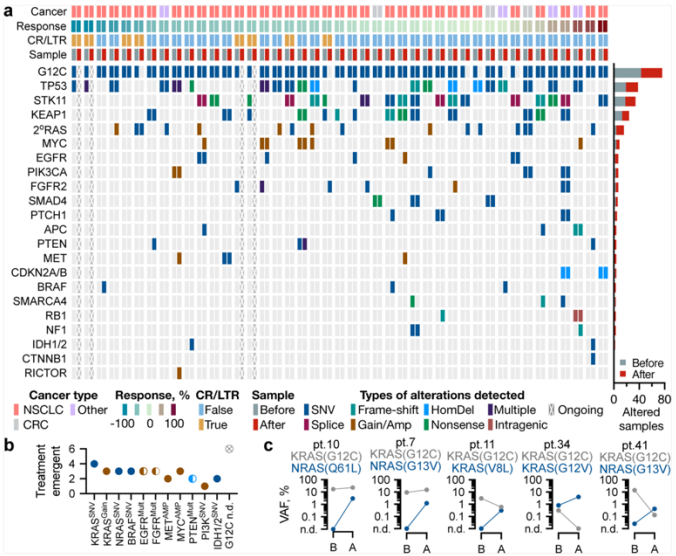
KRAS inhibitor resistance: Genetic resistance



Tumor and/or liquid biopsy with NGS at adagrasib resistance

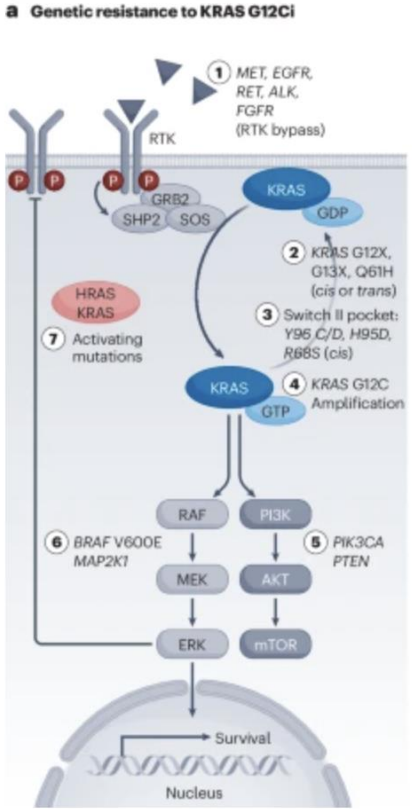


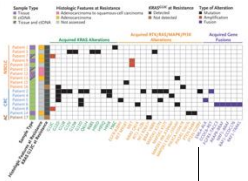
Tumor and/or liquid biopsy with NGS at sotorasib resistance

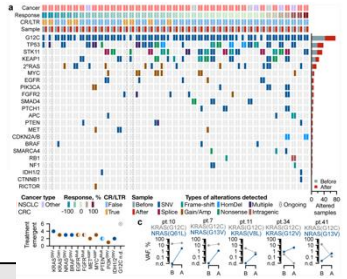


Singhal A, Li B, O'Reilly, Nat Med 2024. Awad, NEJM 2021. Zhao, Nature 2021.

KRAS inhibitor resistance: Genetic resistance



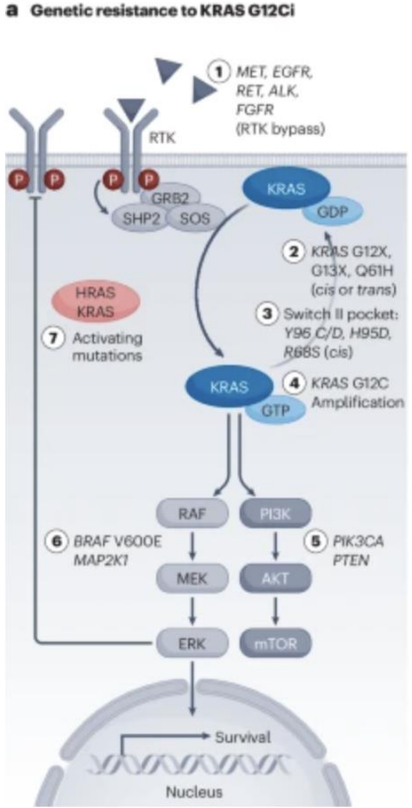




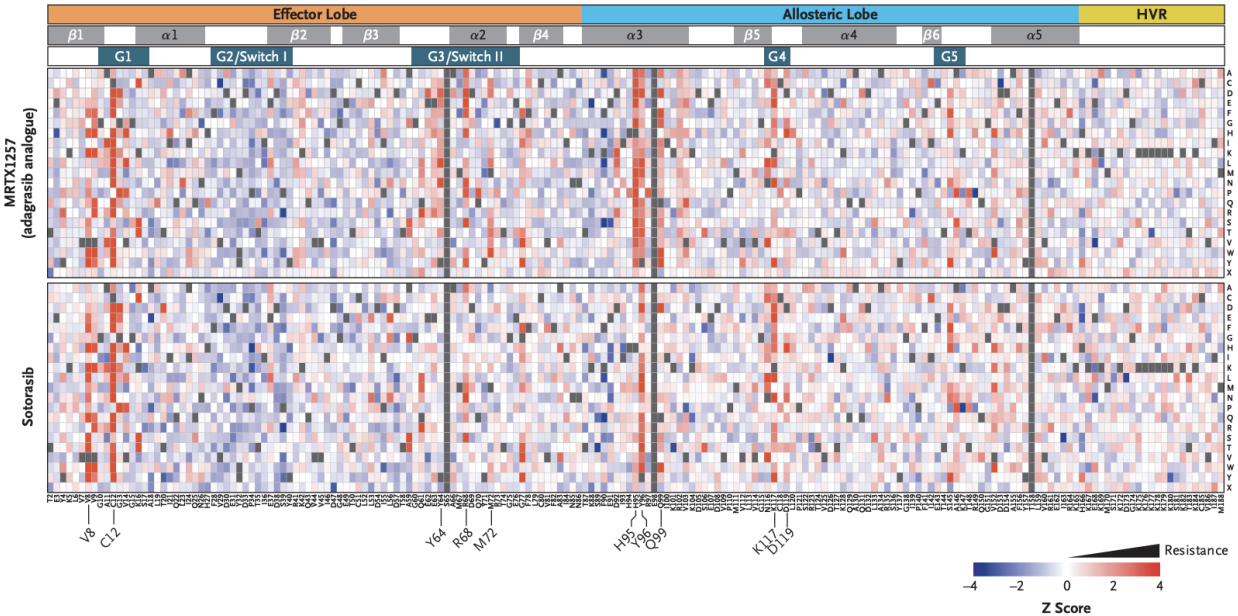
	Awad et al [1]	Zhao Y et al [2]
Drug	**adagrasib**	**sotorasib**
Tumor Type	NSCLC dominant (+CRC)	NSCLC dominant (+CRC)
# of patients evaluated	38	43
# of patients with any resistance alteration	17	27
KRAS allele (G12X, G13X, Q61H) (cis or trans)	35.3%	14.8%
Switch II pocket (R68, H95, or Y96) (cis)	23.5%	0.0%
KRAS G12C gene amplification	11.8%	11.1%
upstream RTK (amplification, fusion, mutation)	35.3%	25.9%
activating mutations in NRAS/HRAS	5.9%	11.1%
BRAF/MEK (fusions, mutations)	23.5%	11.1%
downstream PIK3CA/PTEN	17.6%	11.1%

Singhal A, Li B, O'Reilly, Nat Med 2024. Awad, NEJM 2021. Zhao, Nature 2021.

KRAS inhibitor resistance: Genetic resistance

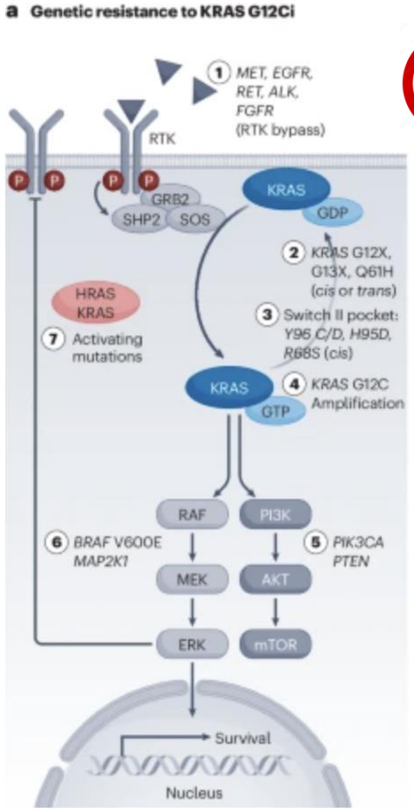


Deep mutational scanning from a lentiviral library: positive-selection screen in Ba-F3 cell line for mutations that cause resistance to two KRAS G12C inhibitors



Singhal A, Li B, O'Reilly, Nat Med 2024. Awad, NEJM 2021.

KRAS inhibitor resistance: Genetic resistance

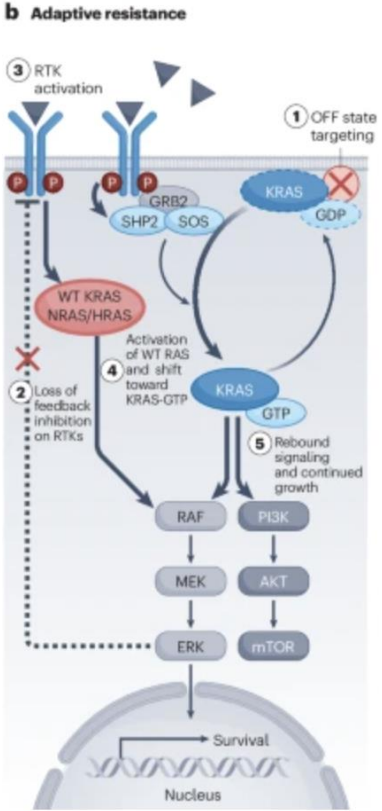


How to target?

- Target secondary alterations
  - Multi-RAS inhibitors
  - RAS degraders
- Rely on binding outside the switch II pocket
  - RAS-ON inhibitors

Singhal A, Li B, O'Reilly, Nat Med 2024

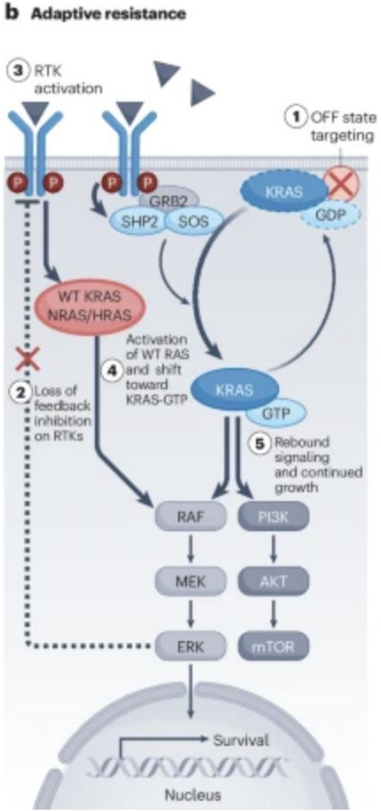
KRAS inhibitor resistance: Adaptive resistance



1. OFF state targeting leads to…
2. MAPK pathway suppression and loss of feedback inhibition leading to…
3. Upregulation of RTKs
4. Shift of RAS into an ON state mediated by SOS and SHP2 and activation of WT RAS isoforms
5. Rebound signaling feedback

Singhal A, Li B, O'Reilly, Nat Med 2024

KRAS inhibitor resistance: Adaptive resistance



How to target?

- Targeting upstream RTK targeting along with KRAS
- Targeting convergent signaling nodes
  - SHP2
  - SOS1
- Targeting of wild-type RAS isoforms

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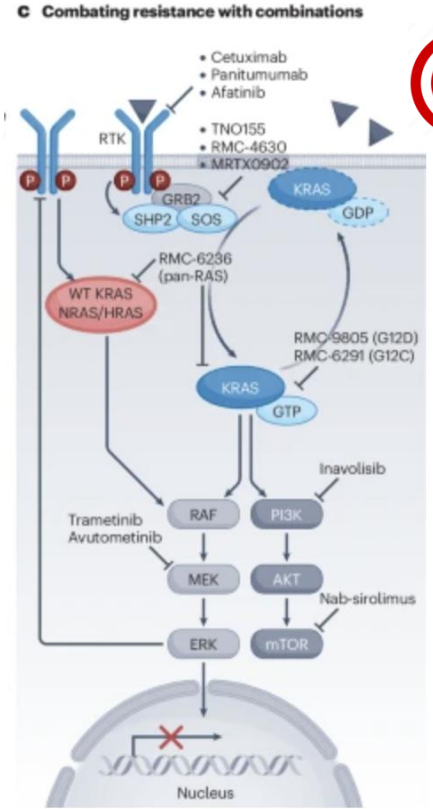
KRAS inhibitor resistance: Other mechanisms

- Primary resistance
  - Eg 36% of patients on CodeBreaK 100
  - Co-mutations in KEAP1, SMARC4, CDKN2A may be implicated
- Histologic/cell-state transformation
  - Akin to SCLC transformation in EGFR resistance
  - Eg transition to a squamous p40+ state noted especially in STK11-mediated tmors
  - EMT states may confer KRAS independence

Singhal A, Li B, O'Reilly, Nat Med 2024

KRAS inhibitor resistance: Combination strategies



How to target in combination?

- With standard therapy
  - Immunotherapy
  - Chemotherapy

- CodeBreaK 202
  - Carbopatin/pemetrexed with sotorasib vs with pembrolizumab in PD-L1<1%
- KRYSTAL-7
  - Pembrolizumab +/- adagrasib in PD-L1>=50%
- SUNRAY-01
  - Pembrolizumab +/- olomorasib in PD-L1>=50%
  - Pembro and chemo +/- olomorasib in PD-L1 0-100%

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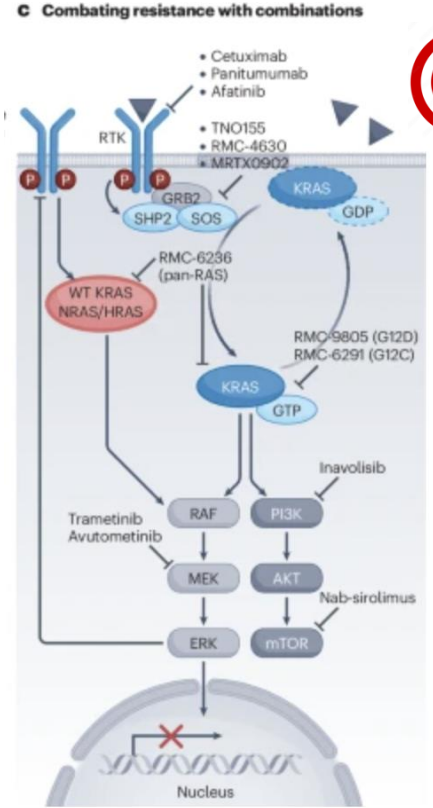
KRAS inhibitor resistance: Combination strategies



How to target in combination?

- With standard therapy
  - Immunotherapy
  - Chemotherapy
- With upstream RTK inhibition
  - EGFR, pan-ERBB
- With inhibition of convergent signaling nodes
  - SOS1 and SHP2 inhibitors
- With downstream RTK inhibition, cell cycle, etc
  - MAPK blockade (eg trametinib. RAF/MEK clamp, FAK inhibitor)
  - YAP-TAZ inhibitors
  - CDK inhibitors

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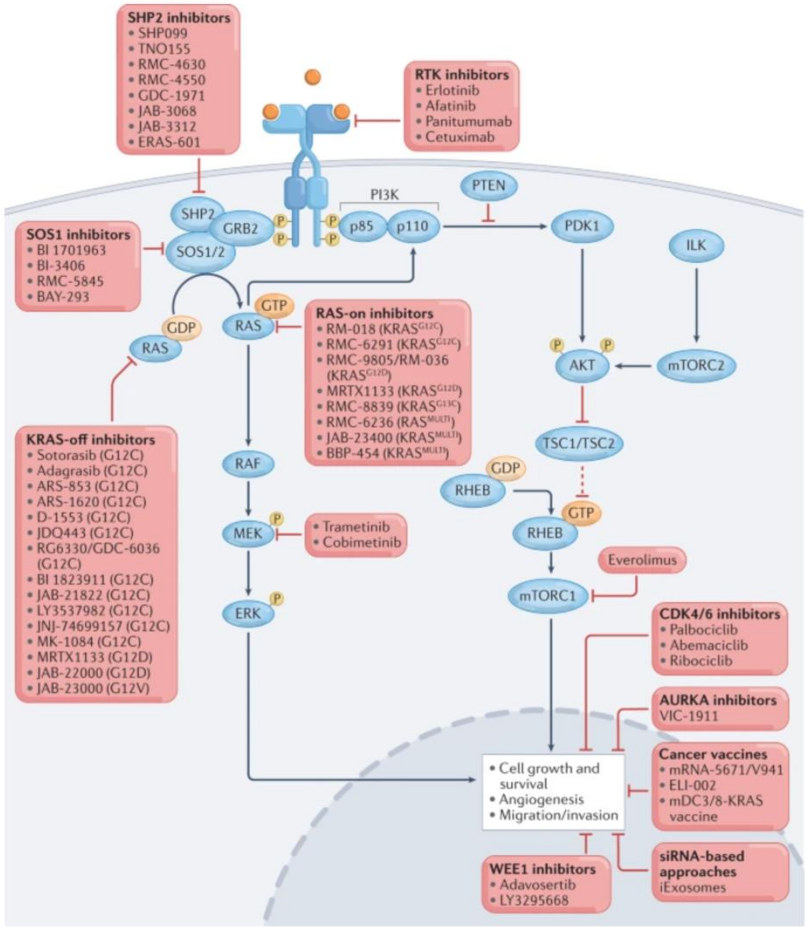
KRAS inhibitor resistance: Compounds in development

How to target?



Punekar, Nat Rev Clin Onc 2022

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KRAS inhibitor resistance

- 1st generation KRAS G12C inhibitors have shown benefit, but efficacy limited by acquired (and primary) resistance
- Mechanisms of resistance include
  - Genetic resistance
  - Adaptive resistance
  - Primary resistance
  - Histologic/cell-state transformation

🎯 Phase 3 trials in combinations with immunotherapy and chemoimmunotherapy soon to read out

🎯 KRAS next generation agents include RAS-ON inhibitors, RAS degraders, and multi-RAS inhibitors

🎯 Combinations with inhibitors of other RTKs and novel agents are coming

Thank you!