Discovery report for KRAS Competitive Landscape Analysis

Research Objective

Tell me about the competitive landscape for kras

Summary of Discoveries

Discovery 1: Tissue-Specific KRAS Variant Distribution and Market Segmentation

The KRAS competitive landscape is segmented by strong, tissue-dependent differences in hotspot variant prevalence, which in turn shape market size and development priorities. G12C dominates lung adenocarcinoma and is addressed by approved inhibitors, whereas pancreatic, colorectal, and endometrial cancers are enriched for non G12C alleles that remain largely underserved; co-mutation architectures further define rational combination strategies.

Discovery 2: Current KRAS Therapeutics and Dominant Combination Strategies

The KRAS therapy space is anchored by two FDA-approved G12C inhibitors, sotorasib and adagrasib, while late-stage development remains G12C-heavy and early pipelines are expanding into G12D, panRAS, and pathway-node modulators. Combination therapy is the dominant development paradigm, with EGFR blockade in colorectal cancer, SHP2 inhibition, checkpoint inhibitors, and MEK inhibitors repeatedly selected to preempt or overcome adaptive signaling.

Discovery 3: Unaddressed Combination Opportunities by Tumor Type

The KRAS competitive landscape is heavily concentrated in EGFR-based combinations in colorectal cancer, while several biologically rational spaces remain largely unaddressed by tumor type. Quantitative genomics and clinical data point to clear opportunities in KRAS-mutant colorectal cancer (FGFR1/ERBB2-high), endometrial cancer (KRASPI3K co-mutant), and pancreatic cancer (hypoxia/glycolysis or CDK4/6 co-targeting) that are not being systematically explored.

Discovery 4: Resistance-Defined Subsegments and Metabolic Vulnerabilities in KRAS Cancers

Resistance biology is segmenting the KRAS market beyond allele and tissue into mechanistically distinct subsegments that differ in outcomes and in the liabilities they create for combination therapy. In NSCLC, STK11/KEAP1 co-mutations define a large fraction of the G12C population and couple to mTORC1 activation, profound immune suppression, andwhen KEAP1 is alteredNRF2driven metabolic rewiring; in colorectal cancer (CRC), acquired resistance converges on DUSP loss with RTK reprogramming and suppressed mTORC1 output. Pharmacokinetic resistance via ABC transporters can emerge under drug pressure but is not prognostic at baseline and historical ABCB1 inhibitor toxicities limit nearterm clinical translatability.

Tissue-Specific KRAS Variant Distribution and Market Segmentation

Summary

The KRAS competitive landscape is segmented by strong, tissue-dependent differences in hotspot variant prevalence, which in turn shape market size and development priorities. G12C dominates lung adenocarcinoma and is addressed by approved inhibitors, whereas pancreatic, colorectal, and endometrial cancers are enriched for non G12C alleles that remain largely underserved; co-mutation architectures further define rational combination strategies.

Background

KRAS has re-emerged as a tractable oncogenic driver due to the advent of allele-selective covalent inhibitors, yet its biology is deeply context-dependent. Variant frequencies and co-mutation partners differ across tissues, creating heterogeneous therapeutic opportunities and resistance liabilities. As programs expand beyond G12C in lung cancer toward non G12C variants across gastrointestinal and gynecologic tumors, the most salient questions for competitive strategy are how variant distribution shapes the addressable market and how co-mutation architectures dictate optimal combinations and sequencing.

Results & Discussion

Across a harmonized TCGA PanCancer Atlas dataset (514 KRAS mutations, 503 patients) spanning lung adenocarcinoma, colorectal, and pancreatic cancers, KRAS hotspot distribution is markedly tissue-specific: G12D (24.7%) and G12V (23.7%) exceed G12C (16.7%) overall, but G12C represents 40.7% of KRAS mutations in lung adenocarcinoma, compared with only 6.7% in colorectal and 0.8% in pancreatic cancer [r0]. In pancreatic adenocarcinoma, non G12C alleles dominate (G12D 41.2%, G12V 27.7%, G12R 21.0%), while colorectal cancer is enriched for G12D (26.0%), G12V (22.0%), and uniquely for G13D (16.6%), underscoring that most KRAS-driven gastrointestinal tumors fall outside the current G12C addressable space [r0]. Hotspots were operationally defined as variants occurring 10 times within the dataset, a threshold used to construct a mutation-by-cancer-type matrix for market sizing and to ensure that downstream comparisons emphasized clinically relevant alleles [r0].

These distributions translate directly into competitive positioning and white space. Two G12C inhibitors are already approvedsotorasib (May 2021) and adagrasib (December 2022 for NSCLC; June 2024 for CRC)with the lung cohort anchoring the G12C market opportunity given its 40.7% intra-indication prevalence and corresponding clinical trial density (1,000+ KRAS-related trials; 165 KRAS inhibitor trials; 35% Phase 3, 23% Phase 2, 18% Phase 1; 55% completed, 27% recruiting) [r0]. By contrast, 83% of KRAS mutations across the dataset lack a genotype-matched therapy, led by G12D (24.7%), G12V (23.7%), and G13D (7.8%), which represent substantial unmet need and are the focus of emerging efforts (e.g., MRTX1133 for G12D in Phase 1/2), alongside pathway-centric strategies including SHP2, SOS1, pan RAS, and MEK inhibition [r0]. These data argue that competitive advantage now hinges on expanding beyond G12C into the non G12C-dominant tumor types and on pairing allele-specific inhibitors with context-informed combinations [r0].

Incorporating endometrial carcinoma meaningfully expands the non G12C market segment. TCGA PanCancer Atlas analysis shows a 18.7% KRAS mutation frequency in endometrial carcinoma (99/529), with the most common alleles being G12D (6.0% of all patients), G12V (3.6%), G13D (2.1%), G12A (1.5%), and G12C (1.1%) [r1]. Applying these frequencies to approximate annual US incidence yields an estimated 9,119 endometrial patients per year with targetable KRAS alleles (as defined in the analysis: G12D, G12V, G13D, G12C), corresponding to an 8.4% expansion versus the established lung, pancreatic, and colorectal indications and a 10.5% expansion when combined with additional emerging tumor types [r1]. This analysis used total cohort size as the denominator to reflect population-level frequencies relevant for

market sizing and projected patients by multiplying TCGA-derived prevalence by approximate US incidence for each cancer type, thereby aligning the genetic epidemiology with commercialization decisions [r1].

Co-mutation architecture further stratifies these markets and guides combination strategy. In lung adenocarcinoma, STK11 co-mutations are significantly enriched in KRAS G12C tumors (31.4% in G12C vs 10.015.0% in G12D/G12V; OR = 2.98, p = 0.0209), and KEAP1 alterations occur in 1521% of KRAS-mutant cases, whereas both events are essentially absent in colorectal and pancreatic cohorts, suggesting lung-specific biology that may blunt immunotherapy combinations and favor alternative partners with G12C inhibitors [r2]. Colorectal cancers show high PIK3CA co-mutation rates (41.4% in G12D; 34.7% in G12V; 20.0% in G12C), motivating KRAS plus PI3K/AKT pathway combinations, while pancreatic cancers are characterized by pervasive TP53 co-mutation (approximately 7680%), reinforcing their aggressive biology and the need to consider downstream or synthetic-lethal strategies; BRAF co-mutation remains rare across contexts, consistent with mutual exclusivity [r2]. Together, these features define variant- and tissue-specific resistance liabilities that competitors must address to achieve durable benefit [r2].

Endometrial carcinoma exhibits a distinct and highly actionable co-mutation pattern that converges on the PI3KAKT pathway. Among KRAS-mutated endometrial tumors, PTEN (88.9%), PIK3CA (60.6%), and PIK3R1 (34.34%) are frequently co-altered, with 96% harboring at least one of these events, 54.55% carrying both PTEN and PIK3CA, and 41.41% carrying PTEN, PIK3CA, and ARID1A together; TP53 co-mutation is relatively low at 16.16% compared with colorectal and pancreatic cancers [r7]. This profilePTEN/PIK3CA/PIK3R1-dominated with high ARID1Adiffers from colorectal despite shared PIK3CA enrichment, and it provides unusually strong rationale for KRAS inhibitor combinations with PI3K/AKT/mTOR pathway agents specifically in endometrial carcinoma [r7]. In sum, the KRAS competitive landscape is best understood as a set of tissue- and allele-defined submarkets with distinct combination imperatives: G12C-centered lung disease constrained by STK11/KEAP1 biology, colorectal and endometrial segments enriched for PI3K-pathway lesions, and pancreatic cancer dominated by non G12C alleles and TP53 co-alterations that collectively remain therapeutically underserved [r0, r1, r2, r7].

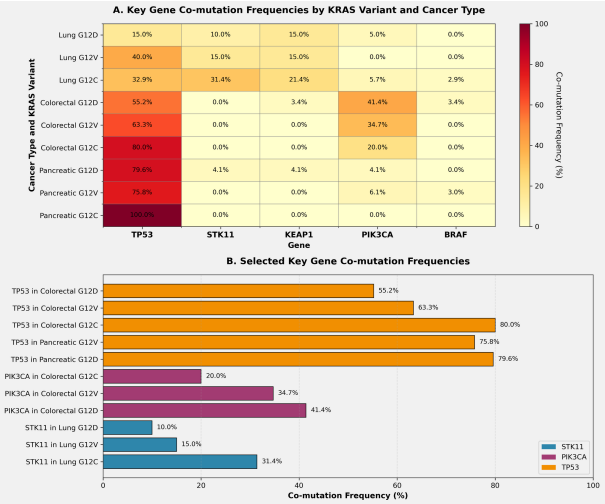

Figure 1: KRAS co-mutation landscapes are highly tissue- and variant-specific. (A) Heatmap showing the frequency of co-mutations in key driver genes across major KRAS variants in lung, colorectal, and pancreatic cancers. (B) Bar chart highlighting selected co-mutation frequencies, illustrating the enrichment of TP53 co-mutations in gastrointestinal cancers, PIK3CA in colorectal cancer, and STK11 in lung cancer. These distinct genetic architectures suggest different therapeutic vulnerabilities and inform rationales for combination strategies. (Source: [r2])

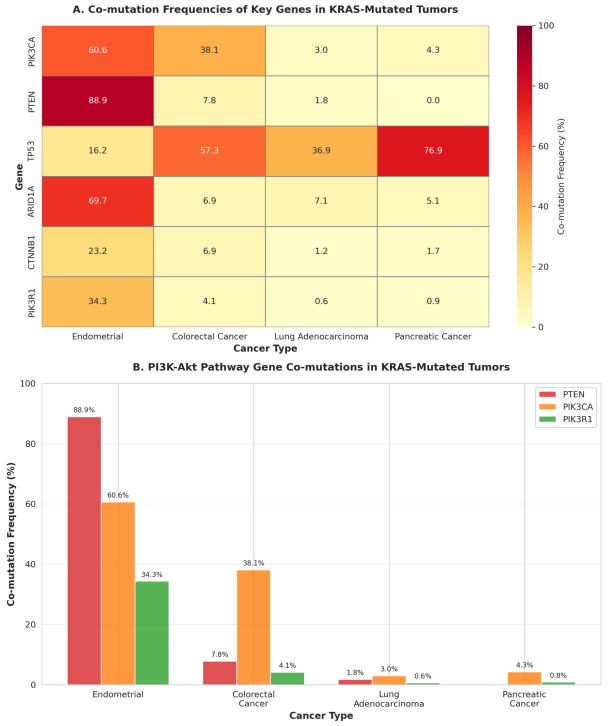

Figure 2: Co-mutation patterns in KRAS-mutant tumors are highly tissue-specific. (A) Heatmap showing the co-mutation frequency of key cancer-related genes across KRAS-mutated endometrial, colorectal, lung, and pancreatic cancers. (B) Bar plot detailing the prevalence of co-mutations in PI3K-Akt pathway genes across the same tumor types. These distinct genomic landscapes, particularly the enrichment of TP53 alterations in pancreatic cancer and PI3K-Akt pathway alterations in endometrial cancer, suggest the need for tissue-specific rational combination strategies. (Source: [r7])

Trajectory Sources

Trajectory r0:

KRAS COMPETITIVE LANDSCAPE: COMPREHENSIVE DATASET DESCRIPTION

Executive Summary

A comprehensive dataset collection has been retrieved and documented for analyzing the KRAS competitive landscape. The collection consists of **27 files totaling 4,146 MB** from five authoritative sources: Clinic...

Trajectory r1: Endometrial carcinoma represents a substantial underserved patient population for KRAS-targeted therapies, with 18.7% KRAS mutation frequency (99/529 TCGA patients) and an estimated 9,119 annual US patients with targetable mutations (G12D, G12V, G13D, G12C), representing 10.5% market expansion beyon...

Trajectory r2:

KRAS VARIANT-SPECIFIC CO-MUTATION ANALYSIS

Analysis Overview I analyzed 331 TCGA PanCancer Atlas samples with the three most common KRAS mutations (G12D, G12V, G12C) across lung adenocarcinoma (n=130), colorectal (n=122), and pancreatic (n=82) cancers. The analysis identified distinct co-muta...

Trajectory r7:

ANALYSIS RESULTS

Key Findings

KRAS-Mutated Endometrial Carcinoma Shows Highly Distinct Co-Mutation Patterns In KRAS-mutated endometrial carcinoma (n=99 samples from TCGA PanCancer Atlas), we identified exceptionally high co-mutation frequencies in PI3K-Akt pathway genes, with a patter...

Current KRAS Therapeutics and Dominant Combination Strategies

Summary

The KRAS therapy space is anchored by two FDA-approved G12C inhibitors, sotorasib and adagrasib, while late-stage development remains G12C-heavy and early pipelines are expanding into G12D, panRAS, and pathway-node modulators. Combination therapy is the dominant development paradigm, with EGFR blockade in colorectal cancer, SHP2 inhibition, checkpoint inhibitors, and MEK inhibitors repeatedly selected to preempt or overcome adaptive signaling.

Background

KRAS is the most frequently mutated oncogene in solid tumors and a central node of the RTKRASMAPK and PI3KAKT networks that drive proliferation and survival. After decades of challenges in directly targeting RAS, covalent inhibitors for the GDP-bound KRAS G12C variant established clinical proof of concept and secured regulatory approvals. However, KRAS mutation spectra are cancer- and tissue-specific, and most variants are not G12C, which creates segmented target populations and leaves substantial unmet need. Adaptive feedback and pathway cross-talk further limit monotherapy durability, making rational combinations a cornerstone of clinical strategy.

Results & Discussion

The current competitive landscape is dominated by KRAS G12C programs, with two FDA-approved agentssotorasib (Lumakras; May 2021) and adagrasib (Krazati; NSCLC in December 2022 and CRC in June 2024)and a late-stage pipeline concentrated on the same allele [r0]. Across a standardized parse of 1,000 KRAS-related trials, 23 of 26 mutation-selective trials (88.5%) target G12C, led by sotorasib (most mature, including a completed Phase 4 study), adagrasib, and D1553 (two Phase 3 trials), with additional G12C agents such as RMC6291 in Phase 1; diversification beyond G12C includes a G12D program (RMC5127, Phase 1) and a panRAS/multi-selective program (RMC6236, Phase 3) [r3]. Broader pipeline curation corroborates this picture and identifies other G12C agents (GDC6036, JNJ74699157) as well as nonallele-selective or pathway-modulating entrants (SHP2 and SOS1 inhibitors; MEK inhibitors) shaping competitive dynamics [r0].

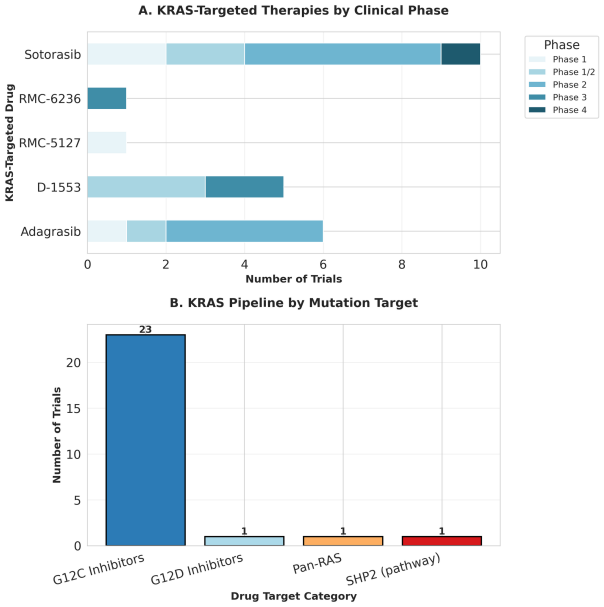

Figure 3: The KRAS clinical development pipeline is dominated by therapies targeting the G12C mutation. (A) The number of clinical trials by development phase for representative KRAS-targeted drugs. (B) The distribution of trials across different drug target categories, including specific KRAS mutations and pathway modulators. This analysis highlights the maturity of G12C inhibitor programs while illustrating the nascent diversification into non-G12C and pathway-directed strategies. (Source: [r3])

Population segmentation based on TCGA Pan-Cancer Atlas underscores why G12C has been the initial beachhead and why nonG12C programs are critical to growth. In a curated dataset of 514 KRAS mutations across lung, colorectal, and pancreatic adenocarcinomas, G12C constitutes 16.7% overall but is enriched in lung adenocarcinoma (40.7%), while being rare in pancreatic adenocarcinoma (0.8%); by contrast, pancreatic cancers are dominated by G12D (41.2%), G12V (27.7%), and G12R (21.0%) [r0]. Colorectal cancer is enriched for G12D (26.0%), G12V (22.0%), and G13D (16.6%), the latter

uniquely common in CRC and not addressed by current drugs; overall, 83% of KRAS mutations in this dataset lack a specific targeted therapy, delineating a substantial white space for G12D, G12V, G13D, and Q61-directed or panRAS approaches [r0]. The resulting market map highlights lung adenocarcinoma as the prime addressable population for approved G12C agents, pancreatic cancer as a largely underserved segment, and CRC as a bifurcated opportunity with both G12C-directed therapy and nonG12C innovation needs [r0].

Combination therapy is the prevailing development strategy. Using a standardized definition of combination trials as those with more than one active therapeutic intervention (excluding placebo/controls and diagnostics), 18 of 26 KRAS drug trials (69.2%) test combinations, and across 263 oncology trials primary partners include EGFR inhibitors (cetuximab in 40 trials, panitumumab in 16), antiVEGF therapy (bevacizumab in 34), checkpoint inhibitors (pembrolizumab in 26, nivolumab in 13, durvalumab in 11), MEK inhibitors (binimetinib in 14, trametinib in 7), and cytotoxic backbones (carboplatin in 21, gemcitabine in 14, cisplatin in 13); KRAS drugspecific combinations are most frequently with checkpoint inhibitors, MEK inhibitors, chemotherapy, and antiEGFR agents, reflecting vertical and nodal blockade strategies [r3]. These partners map to KEGG-defined nodes in RAS/MAPK and PI3K/AKT pathways (e.g., BRAF, MEK1/2, PIK3CA, SHP2, SOS1), providing a pathway-centric rationale for coinhibition [r0]. Mechanistically, SHP2 inhibition blocks RTKRAS feedback that reactivates MAPK after KRAS G12C blockade and increases KRASGDP occupancy to deepen target engagement, with additional immunestimulatory effects; EGFR inhibition is particularly compelling in CRC, where EGFR-driven feedback dominates adaptive resistance; and vertical coinhibition with MEK suppresses residual ERK output and buffers upstream heterogeneity [r4, anastasiou2024, kim2020, liu2021, bteich2023, takeda2025, dunnettkane2021, hofmann2021]. To enable these summaries, trial phases, statuses, and drug aliases (e.g., AMG 510sotorasib, MRTX849adagrasib) were standardized, and while the trial corpus analyzed represents the first 1,000 records, it captures the dominant programs and combination patterns [r3].

Colorectal cancer illustrates the maturation of KRAS combinations, with multiple randomized latestage studies pairing KRAS G12C inhibitors with EGFR blockade: adagrasib plus cetuximab versus chemotherapy (NCT04793958, Phase 3), sotorasib plus panitumumab versus regorafenib/trifluridinetipiracil (NCT05198934, Phase 3), and a firstline study testing sotorasib plus panitumumab plus FOLFIRI versus FOLFIRIśbevacizumab (NCT06252649, Phase 3), alongside additional Phase 2 and Phase 1/1b efforts in resectable and metastatic settings and across sponsors and molecules (e.g., GDC6036+cetuximab) [r45]. The combination space is also diversifying beyond EGFR, exemplified by a KRAS+CDK4/6 study (JDQ443 plus ribociclib; NCT05358249), although not all exploratory programs have persisted and basket/platform designs complicate tumorspecific attribution; EU registry corroboration was not available in the provided material, but the registry evidence supports a robust, CRCfocused KRAS+EGFR track and emergent nonEGFR combinations [r45]. Collectively, these patterns, together with the high proportion of nonG12C variants and the limited pancreatic addressability of G12C, indicate that competitive advantage will hinge on allele expansion (e.g., G12D and panRAS), rational coinhibition of adaptive nodes, and diseasespecific development designs that reflect tissuedependent feedback circuits [r0, r3, r4, r45].

Trajectory Sources

Trajectory r0:
KRAS COMPETITIVE LANDSCAPE: COMPREHENSIVE DATASET DESCRIPTION
Executive Summary
A comprehensive dataset collection has been retrieved and documented for analyzing the KRAS competitive landscape. The collection consists of **27 files totaling 4,146 MB** from five authoritative sources: Clinic...

Trajectory r3:
The analysis of 1,000 KRAS-related clinical trials from ClinicalTrials.gov reveals a competitive landscape dominated by G12C inhibitors, with an identifiable emerging pipeline for other KRAS mutations and clear combination therapy strategies.
Key Findings
1. G12C Inhibitor Dominance The cl...

Trajectory r4: The hypothesis is supported: the dominant clinical combinations with KRAS G12C inhibitorsSHP2, EGFR (in CRC), and MEK inhibitorsare each grounded in well-defined feedback reactivation or parallel-pathway signaling mechanisms that limit monotherapy and are mitigated by vertical or nodal co-inhibiti...

Trajectory r45: A multi-field, synonym-expanded ClinicalTrials.gov search identified multiple trials pairing KRAS inhibitors with EGFR inhibitors in colorectal cancer and at least one KRAS+CDK4/6 combination in advanced solid tumors, supporting the hypothesis; EU CTR corroboration was not possible from the provided...

Unaddressed Combination Opportunities by Tumor Type

Summary

The KRAS competitive landscape is heavily concentrated in EGFR-based combinations in colorectal cancer, while several biologically rational spaces remain largely unaddressed by tumor type. Quantitative genomics and clinical data point to clear opportunities in KRAS-mutant colorectal cancer (FGFR1/ERBB2-high), endometrial cancer (KRASPI3K co-mutant), and pancreatic cancer (hypoxia/glycolysis or CDK4/6 co-targeting) that are not being systematically explored.

Background

Direct KRAS inhibition has opened a path to precision therapy in historically intractable RAS-driven tumors, but adaptive signaling and tumor typespecific biology often limit durability. As a result, combination strategies are the focal point of competition, aiming to co-suppress feedback activation and bypass networks that reactivate MAPK or sustain survival. Mapping where combinations are mature versus missingby tumor type and pathwayclarifies near-term differentiation opportunities and helps align development plans with the biological architecture of each disease.

Results & Discussion

The current KRAS combination market is most advanced in colorectal cancer (CRC), where co-targeting EGFR has moved into multiple late-phase programs. A multi-field registry screen enumerated several KRAS+EGFR trials spanning Phase 3 studies (e.g., sotorasib+panitumumab; adagrasib+cetuximab) and additional Phase 2/1b programs, evidencing broad clinical and commercial commitment to this axis; one KRAS+CDK4/6 study (JDQ443+ribociclib) is also progressing in advanced solid tumors, though not pancreas-specific [r45]. In contrast, CRC lacks direct KRAS+HER2 regimens despite recurrent HER2 biology in CRC subsegments, and reviews and registry scans corroborate that no such combinations are registered in CRC cohorts to date [r65, piazza2024]. This patternmature EGFR combinations with sparse exploration beyond EGFRdefines the present center of gravity in CRC [r45].

The underdevelopment of KRAS+FGFR and KRAS+HER2 combinations in CRC is notable given the size and risk profile of targetable subpopulations. In TCGA COADREAD, high expression defined as the top quartile within the KRAS-mutant cohort identified 25.2% FGFR1-high and 25.2% ERBB2-high tumors, with 45.9% high for either gene and only 4.6% concurrently high for both, indicating two largely independent, addressable segments; FGFR1 and ERBB2 expression were uncorrelated (Pearson r = 0.107, p = 0.115; Spearman ρ = 0.009, p = 0.896) [r60]. Prognostically, FGFR1-high status portended significantly worse outcomes in a KRAS-mutant CRC cohort (GSE39582): overall survival HR = 1.88 (95% CI 1.133.12, p = 0.016) and relapse-free survival HR = 1.74 (95% CI 1.032.96, p = 0.040), with multivariable adjustment preserving the OS risk (adjusted HR = 1.89, p = 0.015) [r75]. Despite this prevalence and risk signal, registry and review syntheses identified no Phase II/III trials pairing a direct KRAS inhibitor with a selective FGFR inhibitor in CRC, and likewise no KRAS+HER2 regimens, underscoring a tractable development gap that contrasts sharply with the maturity of KRAS+EGFR [r65, r86, patel2024, piazza2024].

Endometrial cancer (UCEC) represents a second, distinct opportunity defined by an exceptionally high co-alteration rate of KRAS with the PI3K pathway. Across TCGA, 94.95% of KRAS-mutant UCEC patients harbored PTEN, PIK3CA, and/or PIK3R1 alterations versus 43.58% in CRC and 5.36% in lung adenocarcinoma, with large effect sizes (UCEC vs CRC OR = 24.3; UCEC vs LUAD OR = 332.1; all comparisons p 1.17Œ10^{-20}) [r22]. Yet only one KRAS-inhibitor plus mTOR inhibitor combination (adagrasib+nab-sirolimus, KRYSTAL19) was found in the corpus, which enrolled advanced solid tumors/NSCLC, did not select for PI3K-pathway co-mutations, explicitly did not

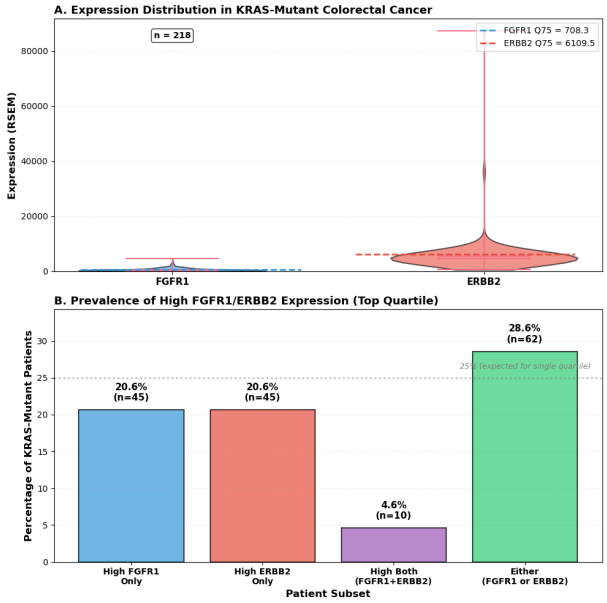

Figure 4: High FGFR1 and ERBB2 expression identify two largely non-overlapping patient populations in KRAS-mutant colorectal cancer. (A) RNA expression distributions for FGFR1 and ERBB2 in KRAS-mutant colorectal cancer (n=218), with dashed lines marking the top quartile (Q75) cutoff used to define high expression. (B) Prevalence of patients with high expression of FGFR1 only, ERBB2 only, or both genes concurrently. The minimal overlap between these groups indicates that FGFR1-high and ERBB2-high tumors represent two distinct and sizable subpopulations for targeted combination therapies. (Source: [r60])

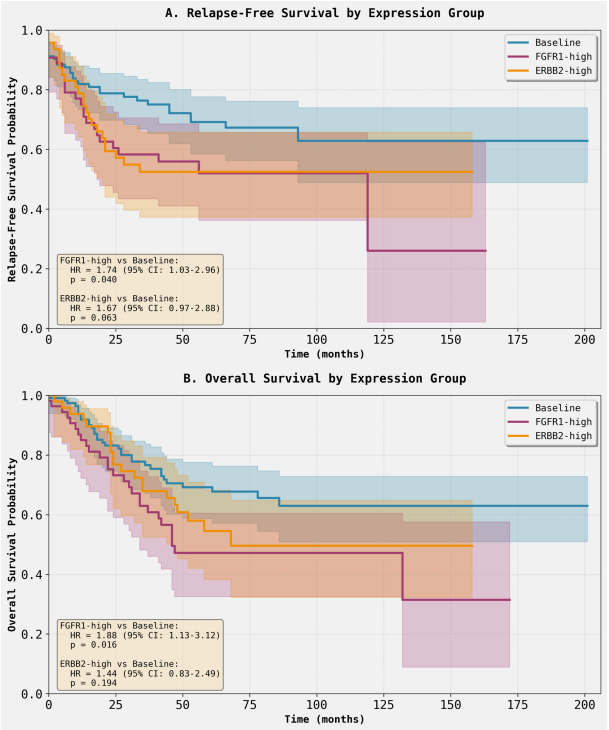

Figure 5: High FGFR1 expression is associated with significantly poorer survival in KRAS-mutant colorectal cancer. Kaplan-Meier curves show (A) relapse-free survival and (B) overall survival for patients from the TCGA cohort stratified by high FGFR1 or ERBB2 expression versus a baseline reference group. The significantly worse outcomes in the FGFR1-high group identify it as a negative prognostic biomarker, supporting the rationale for co-targeting this pathway. (Source: [r75])

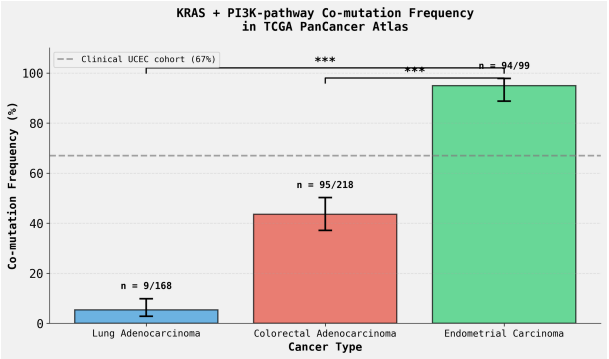

Figure 6: KRAS and PI3K-pathway co-mutations are significantly more frequent in endometrial carcinoma than in lung or colorectal adenocarcinoma. The bar plot shows the percentage of KRAS-mutant tumors with concurrent PI3K-pathway mutations for the indicated cancer types, based on data from the TCGA PanCancer Atlas. The high prevalence in endometrial cancer highlights a rational opportunity for combination therapies co-targeting these pathways. Error bars represent 95% confidence intervals; *** $p < 0.001$. (Source: [r22])

recruit endometrial cancer, and was terminated (business decision) [r12]. Transcriptome-wide comparisons further indicate that KRAS+PI3K co-mutant UCEC differs markedly from CRC, with globally lower immune signatures (e.g., Interferon Gamma Response normalized enrichment score [NES] 1.551, FDR = 0.0126) and lower canonical oncogenic-pathway activity including mTORC1 (NES 1.749, FDR = 0.0016) and KRAS signaling (NES 1.719, FDR = 0.0019), cautioning against naively porting CRC combination assumptions into UCEC without disease-specific validation [r56]. Together, the genetic prevalence and biological distinctiveness argue for focused, biomarker-selected KRAS+PI3K-pathway trials in UCEC, which remain largely unexplored [r12, r22, r56].

In pancreatic ductal adenocarcinoma (PDAC), biologically grounded metabolic and cell-cycle combinations are similarly underdeveloped. Clinically validated hypoxia-pathway agents (e.g., HIF2α antagonists such as belzutifan/MK6482) and indirect HIF modulators

(e.g., mTOR, Hsp90, metformin) provide a feasible toolkit and a strong rationale to blunt KRAS-driven metabolic plasticity, but no confirmed trials were identified that combine a KRAS/panRAS inhibitor with a HIFpathway or GLUT1 inhibitor in PDAC or solid-tumor baskets within the provided evidence [r39, r47, kao2023]. Active panRAS programs (e.g., RMC6236) are advancing as monotherapy and in combinations with PRMT5 or intraRAS agents rather than hypoxia/glycolysis partners, and registry queries similarly returned no pancreatic trials combining KRAS/panRAS with CDK4/6 inhibitors; the KRAS+CDK4/6 space is represented by JDQ443+ribociclib in advanced solid tumors, without pancreatic-specific cohorts confirmed here [r44, r45, r47]. These findings highlight a sizable, mechanism-backed gap in PDAC for KRAS-pathway combinations with hypoxia/glycolysis or CDK4/6 blockade, contrasting with the combination maturity seen in CRC [r39, r44, r45, r47, kao2023].

Altogether, the competitive map shows deep investment and late-phase progress for KRAS+EGFR in CRC, but underdevelopment of KRAS+FGFR or KRAS+HER2 in CRC, KRAS+PI3K-pathway strategies in endometrial cancer, and KRAS+persistent-stress adaptations (hypoxia/glycolysis, CDK4/6) in PDAC. Quantitative segmentation underscores that these gaps are not niche: nearly half of KRAS-mutant CRCs are FGFR1- or ERBB2-high by top-quartile expression and FGFR1-high confers inferior survival, UCEC exhibits near-ubiquitous PI3K-pathway co-alteration among KRAS-mutant tumors, and PDAC has a rich set of actionable metabolic targets without corresponding KRAS combinations in registries [r12, r22, r47, r60, r75]. Prioritizing biomarker-enriched studies in these segments would both diversify the KRAS combination portfolio and align development with disease-specific biology that is currently unaddressed by the dominant EGFR-first CRC paradigm [r45, r65, r86].

Trajectory Sources

Trajectory r12: The hypothesis is supported: within the provided evidence, only one KRAS-inhibitor plus PI3K/AKT/mTORinhibitor trial was identified, and none specifically recruit or stratify endometrial cancer or select for co-occurring PIK3CA/PTEN/PIK3R1 alterations.

Trajectory r22: The co-mutation frequency of KRAS and PI3K-pathway genes (PTEN, PIK3CA, PIK3R1) in endometrial carcinoma (94.95%; 95% CI: 88.72-97.82%) is significantly higher than in lung adenocarcinoma (5.36%; 95% CI: 2.84-9.87%; p=1.61Œ10^{-54}, OR=332.1) and colorectal adenocarcinoma (43.58%; 95% CI: 37.16-50.22%;...

Trajectory r39: Yesmultiple hypoxia-pathway inhibitors (direct HIF1α, HIF2α antagonists; indirect PI3K/AKT/mTOR and Hsp90 modulators) have reached Phase I with clinical signals in other malignancies and sparse pancreatic-specific data, and their biology provides a strong, testable rationale for synergy with KRA...

Trajectory r44: The hypothesis is not supported by current ClinicalTrials.gov results: targeted API queries returned no registered pancreatic cancer trials combining a KRAS/panRAS inhibitor with a CDK4/6 inhibitor. (Clinical Trial Search: 100719990a70, Clinical Trial Search: dd45eee42c8c)

Trajectory r45: A multi-field, synonym-expanded ClinicalTrials.gov search identified multiple trials pairing KRAS inhibitors with EGFR inhibitors in colorectal cancer and at least one KRAS+CDK4/6 combination in advanced solid tumors, supporting the hypothesis; EU CTR corroboration was not possible from the provided...

Trajectory r47: The available registry evidence in the provided context does not support the hypothesis; no confirmed clinical trials were identified that combine a KRAS/panRAS inhibitor with a HIFpathway (e.g., belzutifan) or GLUT1 inhibitor in pancreatic cancer or solidtumor basket settings.

Trajectory r56: KRAS+PI3K co-mutant endometrial tumors exhibit significantly lower im-

mune infiltration signatures and reduced oncogenic/metabolic pathway activity compared to colorectal cancer counterparts, with all 7 tested immune pathways showing significantly lower expression in UCEC (FDR < 0.25), supporting a d...

Trajectory r60: ## Analysis of High Baseline FGFR1/ERBB2 Expression in KRAS-Mutant Colorectal Cancer
Primary Results
Using the TCGA Colorectal Adenocarcinoma (COADREAD) PanCancer Atlas cohort, I analyzed 218 KRAS-mutant patients with complete RNA-seq data to determine the prevalence of high baseline FGFR1 and...

Trajectory r65: The evidence supports a development gap: no registered or reported trials were identified that combine a direct KRAS inhibitor with a direct HER2 (ERBB2) inhibitor in colorectal cancer or in solid-tumor baskets with explicit CRC expansion cohorts within the provided sources (tria2023thetherapeuticla...

Trajectory r75:
SURVIVAL ANALYSIS OF FGFR1-HIGH KRAS-MUTANT COLORECTAL CANCER PATIENTS
KEY FINDINGS
In the GSE39582 KRAS-mutant colorectal cancer cohort (n=217), **patients with high FGFR1 expression (top quartile) demonstrated significantly worse survival outcomes compared to baseline KRAS-mutant patient...

Trajectory r86: The available registry query and contemporary literature excerpts support the hypothesis that there remain no active or recruiting Phase II/III trials explicitly testing a direct KRAS inhibitor with a selective FGFR inhibitor in a KRASmutant colorectal cancer cohort (Clinical Trial Search: b8c91267...

Resistance-Defined Subsegments and Metabolic Vulnerabilities in KRAS Cancers

Summary

Resistance biology is segmenting the KRAS market beyond allele and tissue into mechanistically distinct subsegments that differ in outcomes and in the liabilities they create for combination therapy. In NSCLC, STK11/KEAP1 co-mutations define a large fraction of the G12C population and couple to mTORC1 activation, profound immune suppression, andwhen KEAP1 is alteredNRF2driven metabolic rewiring; in colorectal cancer (CRC), acquired resistance converges on DUSP loss with RTK reprogramming and suppressed mTORC1 output. Pharmacokinetic resistance via ABC transporters can emerge under drug pressure but is not prognostic at baseline and historical ABCB1 inhibitor toxicities limit nearterm clinical translatability.

Background

KRAS is one of the most frequently mutated oncogenes in solid tumors, and allelespecific inhibitors of KRAS G12C (adagrasib, sotorasib) established the first clinically validated foothold in direct KRAS targeting. Yet durable benefit remains constrained by intratumoral and lineagespecific heterogeneity, adaptive rewiring of growth factor and stress signaling, and cellintrinsic pharmacokinetic defenses. As the field moves from monotherapy to rational combinations and nextgeneration inhibitors, the competitive landscape is being reshaped by resistancedefined molecular subsegments that cut across tissues and alleles, creating distinct therapeutic opportunities and gaps.

Results & Discussion

In KRAS G12C NSCLC, STK11 and KEAP1 co-mutations delineate a quantitatively large and biologically distinct market segment: in TCGA LUAD, STK11-mut/KEAP1-wt, STK11-mut/KEAP1-mut, and STK11-wt/KEAP1-mut subgroups comprise 20.00%, 11.43%, and 10.00% of the G12C cohort, respectively (41.43% combined; n=70) [r20]. Clinically, STK11 co-mutation on adagrasib in KRYSTAL1 associates with similar ORR but markedly shorter PFS (4.2 vs 11.0 months; HR 2.2) and OS (9.8 months vs not reached; HR 2.6), whereas across CodeBreaK sotorasib studies STK11 effects appear largely prognostic with KEAP1 dependence rather than uniformly predictive of reduced drug benefit; KEAP1 emerges as a consistent negative determinant across agents [r19]. Transcriptomically, STK11 and KEAP1mutant G12C tumors display modest mTORC1 activation (e.g., STK11-only NES=+1.553, FDR=0.027; KEAP1-only NES=+1.938, FDR=0.0008) and profound suppression of interferonγ response (NES range 2.0 to 2.7, all FDR<0.001), highlighting a convergent immunecold phenotype [r32]. KEAP1 loss further drives robust NRF2 activation ($\text{HALLMARK}_{\text{XENOBIOTIC\_METABOLISM}}$ NES=2.286, FDR<0.001) with strong upregulation of canonical targets (e.g., AKR1C1/2/3, NQO1, GPX2) [r37], coupled to a striking metabolic program in PPP and glutathione biosynthesis: G6PD 6.01fold, PGD 4.45fold, TKT 2.40fold, GCLC 3.87fold, GCLM 2.81fold, and SLC7A11 3.73fold up in KEAP1mutant vs wildtype tumors (all FDR<0.05) [r42].

These NSCLC subsegments carry concrete therapeutic implications and visible white space. mTORC1 activation and interferonγ pathway depression nominate combinations that address metabolic growth signaling and Tcell exclusion, while KEAP1mutant disease presents a coherent NRF2linked redox/NADPH dependency centered on PPP and glutathione enzymes [r32, r37, r42]. However, the translational toolkit is immature: there are no selective, clinically advanced NRF2 inhibitors, and reported antagonists (e.g., ML385, brusatol) are preclinical or pleiotropic, limiting their immediate repurposing with KRAS G12C inhibitors [r38]. Likewise, for the NRF2upregulated metabolic nodes most likely to confer fitnessG6PD, GCLC, SLC7A11no selective clinicalstage inhibitors exist; the most advanced agents are either preclinical tools (e.g., imidazole ketone erastin for SLC7A11) or nonselective/repurposed drugs with limited oncology utility (e.g., sulfasalazine

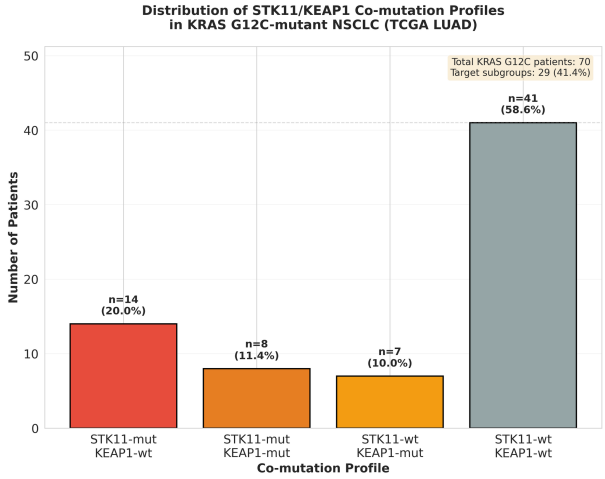

Figure 7: Co-mutations in STK11 and KEAP1 are prevalent in KRAS G12C-mutant non-small cell lung cancer (NSCLC). The bar plot shows the distribution of STK11 and KEAP1 mutational profiles in a cohort of 70 KRAS G12C-mutant lung adenocarcinoma patients from The Cancer Genome Atlas (TCGA). Cumulatively, tumors harboring a mutation in either STK11 or KEAP1 account for 41.4% of the cohort, defining a quantitatively significant patient subpopulation. (Source: [r20])

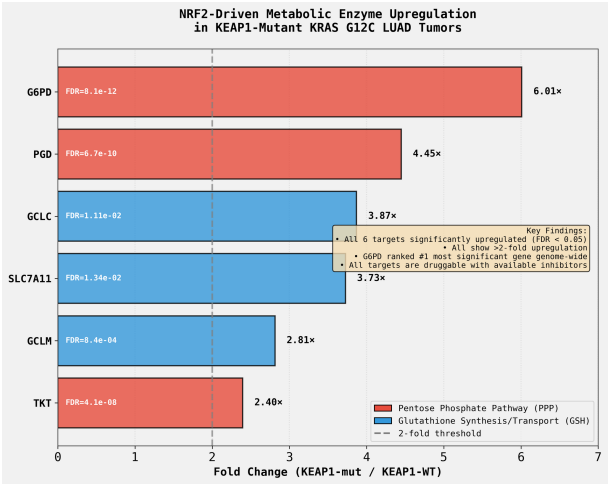

Figure 8: KEAP1 co-mutation in KRAS G12C lung adenocarcinoma drives significant upregulation of NRF2-target metabolic enzymes. The bar plot quantifies the fold change of key enzymes in the pentose phosphate pathway (red) and glutathione synthesis/transport pathway (blue) in KEAP1-mutant versus KEAP1-wild-type tumors, with false discovery rates (FDR) indicated on each bar. The robust induction of these druggable enzymes, such as G6PD, highlights a potential metabolic vulnerability for therapeutic intervention in this patient subsegment. (Source: [r42])

for xCT, buthionine sulfoximine for GCLC), leaving a clear development gap for precision combinations in KEAP1mutant KRAS G12C NSCLC [r57]. Together, these data argue for nearterm testing of KRAS G12C plus mTOR pathway modulation in STK11/KEAP1mutant disease and parallel investment in firstinclass, selective inhibitors of NRF2 or its key metabolic effectors to unlock this highprevalence, poorprognosis segment [r32, r38, r42, r57].

In CRC, resistance to KRAS G12C inhibition segments the market along different mechanistic axes. In adagrasibresistant SW837, bulk RNAseq shows upregulation of bypass RTKs (FGFR1 log2FC=1.47, KIT 2.80, ERBB2 0.67), coupled with suppression of PI3KAkt signaling and loss of MAPK negative feedback (DUSP4 log2FC=0.96, DUSP6 2.35); unbiased enrichment pinpoints mTORC1 signaling as specifically downregulated (NES=1.935, FDR=0.0046), more so than the broader PI3K/AKT/mTOR hallmark (NES=1.386, FDR=0.077) [r6, r30, Thatikonda2023SciAdv]. These patterns nominate FGFR or KIT cotargeting with KRAS G12C inhibitors and caution against default PI3Kinhibitor combinations in this resistance state [r6]. Crossmodel comparison underscores context dependence: ERK inhibitorresistant SW620 exhibits FGFR1 upregulation and DUSP4/6 loss but downregulates ERBB2/ERBB3 (rather than upregulating them), indicating that RTK liabilities are lineage and drug specific [r40, Nussbaum2024]. Collectively, a CRC subsegment emerges in which sustained ERK output is maintained via DUSP loss and selected RTK rewiring, while mTORC1 output is attenuatedan actionable map that differs materially from the KEAP1/NRF2driven NSCLC segment [r6, r30, r40].

Mechanistically, the DUSP4/6deficient state creates two therapeutic entry points: pushing ERK signaling beyond a toxic threshold (e.g., with DUSP6 blockade or ERKhyperactivating schedules) and neutralizing unrestrained HER2/HER3 signaling that can follow DUSP6 loss; preclinical studies show that tool compounds like BCI induce ERKhyperactivationmediated cytotoxicity rescued by MEK/ERK inhibitors, and that combining KRAS/MAPK inhibitors with panHER TKIs or HER2directed ADCs yields strong synergy in KRAS/MAPKdriven models [r26]. While there are no clinicalgrade DUSP inhibitors, these convergent vulnerabilitiesERK overdose and

HER2/HER3 codependenceprovide translatable hypotheses for CRC resistance subsegments defined by DUSP loss and RTK rewiring [r26].

Finally, pharmacokinetic resistance via drug efflux and metabolism appears as a partially conserved, pressureinduced class effect rather than a baseline determinant. Across sotorasibresistant lung and adagrasibresistant CRC models, multiple ABC transporters (ABCA5, ABCA7, ABCB1, ABCB8, ABCC5, ABCF3) and CYP enzymes (CYP27A1, CYP2U1, CYP4B1, CYP2T1P) are upregulated in both contexts, yet pathwaylevel enrichment did not reach significance in the sotorasib model, and ABCB1 upregulation was notably stronger with adagrasib (log2FC 4.31 vs 0.90), indicating drug and tissuespecificity [r61, Hafner2023NatureCancer, Thatikonda2023SciAdv]. Importantly, a ninegene pharmacokinetic resistance score (geometric mean of ABCA5, ABCA7, ABCB1, ABCB8, ABCC5, ABCF3, CYP27A1, CYP2U1, CYP4B1) applied to treatmentnaïve TCGA KRASmutant tumors showed no adverse prognostic association; in LUAD, the topquartile group even had better PFS (logrank p=0.0357), underscoring that these signatures likely arise under therapy rather than at baseline [r67]. Historically, potent ABCB1 inhibitors (zosuquidar, tariquidar, elacridar) failed to deliver a workable therapeutic index and introduced drugdrug interaction risks; combined with known Pgp liabilities of KRAS G12C inhibitors, this helps explain why effluxinhibitor combinations have not advanced competitively in this space [r62, Santarpia2023]. Together, these data argue for biomarkerguided monitoring of transporter induction during therapy, while steering combination development toward the mechanistic subsegments above rather than broad ABC blockade [r61, r62, r67].

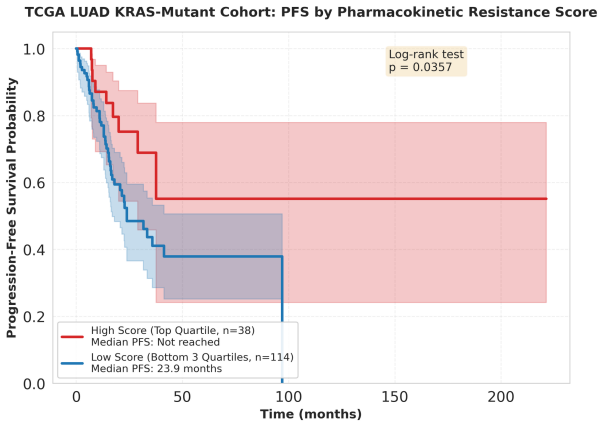

Figure 9: A baseline pharmacokinetic resistance score is not a negative prognostic marker in KRAS-mutant lung adenocarcinoma. Kaplan-Meier analysis of progression-free survival (PFS) is shown for the TCGA KRAS-mutant LUAD cohort, comparing patients with a high score (top quartile, n=38) to those with a low score (bottom three quartiles, n=114). The high-score group exhibits significantly longer PFS (median not reached vs. 23.9 months; p=0.0357, log-rank test), indicating this signature is not associated with poor outcomes at baseline. (Source: [r67])

Trajectory Sources

Trajectory r6: Gene expression analysis of adagrasib-resistant versus sensitive KRAS G12C colorectal cancer cells revealed significant upregulation of receptor tyrosine kinases (FGFR1, KIT, ERBB2) supporting the bypass signaling hypothesis, but unexpectedly showed downregulation rather than upregulation of the PI3...

Trajectory r19: The hypothesis is partially supported: STK11 co-mutation is associated with markedly shorter PFS/OS on adagrasib (KRYSTAL-1) but shows no consistent detriment with sotorasib across CodeBreaK trials, where effects appear prognostic and KEAP1-dependent rather than uniformly predictive of reduced drug ...

Trajectory r20: ## Analysis Results: STK11/KEAP1 Co-mutation Profiles in KRAS G12C-mutant NSCLC

Study Context Using the cBioPortal API, I queried the TCGA Pan-Cancer Atlas Lung Adenocarcinoma cohort ($luad_{tcga\_pan_{can}\_atlas_{2018}}$, n=566 samples) to identify patients with KRAS G12C mutations and characterize thei...

Trajectory r26: Yesmultiple preclinical lines of evidence show that loss of DUSP4/DUSP6 creates targetable liabilities that can be exploited either by forcing toxic ERK hyperactivation (e.g., DUSP6 inhibition or MAPK-hyperactivating strategies) or by co-targeting adaptive HER2/HER3 signaling that becomes unrestrai...

Trajectory r30: The hypothesis is strongly supported: mTORC1 signaling pathway is more specifically and significantly downregulated (NES = -1.935, FDR q = 0.0046) than the broader PI3K/AKT/mTOR pathway (NES = -1.386, FDR q = 0.077, not significant) in adagrasib-resistant SW837 colorectal cancer cells.

Trajectory r32: In KRAS G12C-mutant lung adenocarcinoma from TCGA, STK11 co-mutations are associated with modest but significant mTORC1 pathway activation (NES=+1.624, FDR=0.005), while both STK11 and KEAP1 co-mutations are strongly associated with immune-suppressed tumor microenvironments evidenced by marked downr...

Trajectory r37: KEAP1-mutant KRAS G12C tumors in the TCGA LUAD cohort demonstrate robust transcriptional activation of the NRF2 pathway, with HALLMARK$_{\text{XENOBIOTIC_METABOLISM}}$ showing a Normalized Enrichment Score (NES) of 2.286 and FDR q-value <0.001, confirmed by multiple independent NRF2 gene sets.

Trajectory r38: Based on the provided evidence, there are no selective, clinically advanced NRF2 inhibitors suitable for immediate repurposing in combination with KRAS G12C inhibitors for KEAP1mutant NSCLC; available agents are largely preclinical or pleiotropic modulators with limited or unsuitable safety/clinica...

Trajectory r40: ## Analysis of ERK Inhibitor Resistance in SW620 Colorectal Cancer Cells
Using pre-processed differential expression data from GSE237177 (Nussbaum et al., 2024), I extracted log2 fold changes and p-values for five target genes comparing ERK inhibitor-resistant vs. sensitive SW620 cells:
Quanti...

Trajectory r42: ## Analysis of NRF2-Driven Metabolic Enzyme Upregulation in KEAP1-Mutant KRAS G12C LUAD
Summary of Key Findings
Hypothesis Status: CONFIRMED
All six examined metabolic enzymes in the pentose phosphate pathway (PPP) and glutathione (GSH) synthesis pathways show statistically significant an...

Trajectory r57: The hypothesis is supported: across G6PD, GCLC, and SLC7A11, the most advanced agents identified in the provided sources are either preclinical tools or nonselective repurposed drugs, with no selective clinical-stage inhibitor for any of the three targets; only sulfasalazine (xCT) reached a small ea...

Trajectory r61: The pharmacokinetic resistance signature characterized by ABC transporters and cytochrome P450 enzymes shows partial but incomplete conservation across KRAS G12C inhibitors, with individual genes (6 ABC transporters and 4 CYP450 enzymes) significantly upregulated in both sotorasib-resistant lung can...

Trajectory r62: Available evidence shows that potent ABCB1 inhibitors have a poor therapeutic index and problematic pharmacology, whichtogether with drugdrug interaction riskshas curtailed development and plausibly explains their absence from current KRAS inhibitor combination trials.

Trajectory r67:
ANALYSIS SUMMARY
Main Conclusion The baseline expression of the 9-gene pharmacokinetic resistance signature in treatment-naive KRAS-mutant tumors does NOT correlate with poor survival outcomes as hypothesized. In the only significant finding (LUAD progression-free survival), high baseline exp...