SCIENCE BEHIND THE STUDY

Advances in RAS Therapeutics for Pancreatic Cancer

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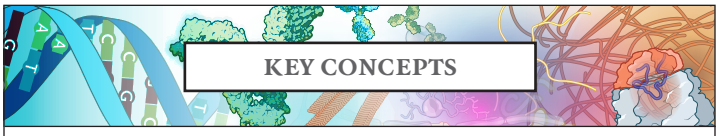
Somatic mutations in the Kirsten rat sarcoma viral oncogene homologue (KRAS) occur in more than 90% of pancreatic ductal adenocarcinomas. In this issue of the *Journal*, Wolpin et al.[1] evaluated the side-effect profile of and response to a first-in-class small-molecule drug called daraxonrasib, which targets the active state of RAS (see Key Concepts) in patients with metastatic pancreatic ductal adenocarcinoma who have received at least one previous line of chemotherapy. In the context of second-line treatment, they reported an objective response according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, in up to 35% of patients and a median response duration of 8.2 months.

HOW IS KRAS RELEVANT TO PANCREATIC CANCER?

Discovered in 1982,[2] *KRAS* is a critical driver of tumor initiation, found in the earliest precursor of pancreatic ductal adenocarcinoma, pancreatic intraepithelial neoplasms.[3] The KRAS protein drives myriad signaling pathways that promote cell growth and survival and alters cellular metabolism and the tumor microenvironment. Preclinical studies in mouse models of pancreatic ductal adenocarcinoma established the critical role of KRAS in tumor initiation and maintenance, supporting KRAS as a key dependency in pancreatic ductal adenocarcinoma.

ISN'T KRAS UNDRUGGABLE?

KRAS encodes a small GTPase that cycles between inactive GDP-bound (OFF) and active GTP-bound (ON) states (Fig. 1A). In pancreatic ductal adenocarcinoma, *KRAS* missense mutations predominantly affect glycine 12 (G12): 42% result in G12D, 31% in G12V, and 15% in G12R. Mutations in other codons such as glycine 13 (G13) and glutamine 61 (Q61) are infrequent, and G12C mutations are found in fewer than 2% of pancreatic ductal adenocarcinomas.[4] These single amino-acid substitutions impair the intrinsic and GAP-stimulated KRAS GTPase activity, favoring the formation of active RAS-GTP.



KRAS signaling

A process in which KRAS, a cytoplasmic molecule, acts like a switch in a cell-proliferation pathway that begins at the cell surface with the binding of growth factors (or other proteins) to receptors and ends with the activation of specific genes that promote cell proliferation. Oncogenic variants in the gene *KRAS* result in versions of the KRAS protein that are permanently switched "on," resulting in uncontrolled cell proliferation and cancer.

Molecular glue

A small molecule that brings together two proteins that would not normally interact and "glues" them together. The binding of molecular glue to a protein creates a new surface that allows it to bind to a second protein, thus forming a complex of the two proteins and the glue. This complex may stabilize existing interactions, show a propensity for degradation, or assume a new function. The glue may confer on one protein the ability to block the activity of the other protein.

RAS

A GTPase that is associated with the inner face of the plasma membrane, from which it relays extracellular signals (that are created through the binding of ligand to a cell-surface receptor) to cytoplasmic signaling networks. The three RAS proteins (HRAS, KRAS, and NRAS) are members of the RAS superfamily of more than 150 small GTPases. In normal quiescent cells, RAS is in an inactive GDP-bound "OFF" state; it becomes transiently activated in response to extracellular growth signals. The active GTP-bound "ON" state activates downstream effectors, including the RAF kinases, which in turn activate the extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase cascade (MAPK). GTPase-activating proteins (GAPs) then return RAS to the GDP-bound state. In cancer cells, mutant RAS is refractory to GAP and is persistently GTP-bound, leading to constitutive effector signaling (i.e., signaling that is independent of extracellular signals) and cell proliferation.

An illustrated glossary is available at NEJM.org

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Most small-molecule inhibitors target protein kinases by blocking their ATP-binding pocket, which prevents phosphorylation and activation of downstream substrates. Early approaches to block RAS function focused on the design of GTP analogues that block GTP binding to RAS.[5] Unfortunately, whereas ATP binds to protein kinases at low micromolar concentrations, GTP binds to RAS at low picomolar concentrations, which makes the development of small molecules to disrupt this sensitive binding an untenable strategy. Furthermore, early crystal structures of HRAS showed that the surface topology of RAS apparently lacked well-defined pockets that would be amenable to the design of small molecules with sufficient affinity and selectivity. These challenges spurred substantial efforts to develop indirect strategies for targeting RAS, including inhibiting its association with the inner surface of the plasma membrane and blocking downstream RAS effector proteins. Despite encouraging preclinical results, the clinical translation of these approaches has proved more challenging. Consequently, for nearly three decades, RAS has been widely regarded as an undruggable target.

WHAT CHANGED?

Given the critical role of RAS in cancer, these obstacles have not deterred sustained efforts to develop small molecules that disrupt RAS function. A pivotal breakthrough came in 2013 when Shokat and colleagues made the fortuitous discovery of a druggable pocket in RAS.[6] They focused on the *KRAS* mutation resulting in G12C. They reasoned that the highly reactive nature of cysteine could be exploited to develop selective inhibitors of this mutant amino acid. Their development of small molecules that covalently attached to cysteine was transformative, enabling the crystallographic capture of a druggable pocket in KRAS, which they called the switch-II pocket.

In 2021 and 2022, two small molecules (sotorasib and adagrasib) were approved by the Food and Drug Administration for second-line treatment of $KRAS^{G12C}$-mutant non–small-cell lung cancer (Fig. 1B). This new milestone forced a reconceptualization of the therapeutic landscape, because it established RAS as being pharmacologically tractable and motivated efforts to design analogous small molecules to target other KRAS mutant proteins. Sotorasib and adagrasib leverage the binding of the switch-II pocket found in the GDP-bound (OFF) inactive conformation and thus are known as RAS(OFF) inhibitors.

DARAXONRASIB, A RAS(ON) APPROACH

A second, independent approach for the development of RAS inhibitors was based on rapamycin, a natural product isolated from the bacterium *Streptomyces hygroscopicus*.[7] Long used as an immunosuppressive agent for transplantation medicine, rapamycin binds to the FKBP12 protein, forming a binary complex that then binds to the mammalian target of rapamycin (mTOR) protein kinase and forms a tri-complex that inhibits mTOR complex 1. This mechanism, involving a molecular glue (rapamycin), provided the conceptual foundation for the development of RAS(ON) inhibitors.[8,9]

Building on this approach, scientists engineered the cyclophilin A (CYPA)–binding motif of sanglifehrin A (originally isolated from a strain of streptomyces) to enhance its binding to CYPA, a chaperone protein expressed with low variability across cancer types and at higher levels in tumors than in normal tissues, and to generate a neomorphic interface capable of selectively binding the active (ON) state of $KRAS^{G12C}$.[10] The resulting compound, RMC-4998, covalently engages $KRAS^{G12C}$ in the GTP-bound (ON) state by forming a stable complex with RAS and CYPA. The CYPA component of the tri-complex occludes accessibility of $KRAS^{G12C}$ to effectors (e.g., the RAF serine–threonine kinase), blocking the activation of downstream signaling pathways. These studies established the feasibility of RAS(ON) tri-complex inhibitors and catalyzed the development of next-generation compounds, including daraxonrasib.[11,12] Daraxonrasib recognizes all isoforms of RAS (HRAS, KRAS, and NRAS), including RAS mutant and wild-type proteins.[13]

WHAT'S NEXT?

Durable responses to RAS(OFF) inhibitors have been limited, with multiple resistance mechanisms reported.[14,15] Although the tri-complex formed by daraxonrasib neutralizes RAS effector engagement and downstream signaling, resistance does occur. Wolpin et al. report that treatment was discontinued in most patients for disease progression, which highlights the need

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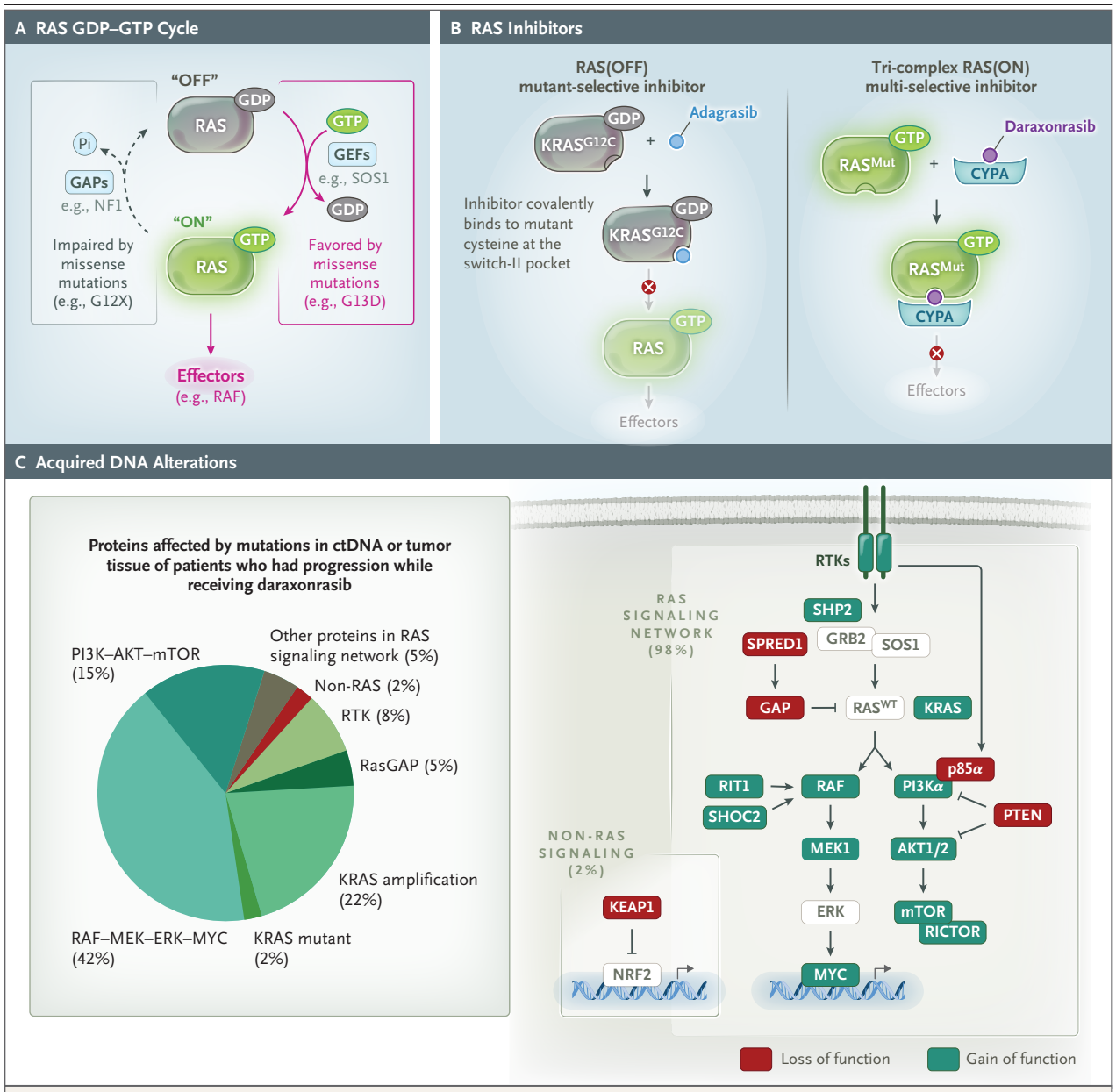

Figure 1. Daraxonrasib Mechanism of Action and Resistance Mechanisms.

As shown in Panel A, RAS binds and hydrolyzes guanosine-5′-triphosphate (GTP) to guanosine-5′-diphosphate (GDP). The GTP-bound (ON) state transitions to the GDP-bound (OFF) state as GTPase-activating proteins (GAPs) stimulate the RAS-intrinsic GTPase activity. Growth-factor stimulation of receptor tyrosine kinases (RTKs) activates guanine nucleotide exchange factors (GEFs) that accelerate intrinsic RAS exchange activity and the formation of RAS-GTP. RAS-GTP preferentially binds to downstream effectors, predominantly RAF, which leads to activation of the ERK mitogen-activated protein kinases. Panel B shows two types of RAS inhibitors. In contrast to the approved OFF-state $KRAS^{G12C}$-selective covalent inhibitors (e.g., adagrasib), daraxonrasib is a noncovalent RAS(ON) multiselective inhibitor that recognizes the ON state of wild-type and mutant RAS proteins. Daraxonrasib alone cannot bind RAS and first forms a binary complex with cyclophilin A (CYPA), which then forms a tri-complex with RAS-GTP, in which the CYPA–daraxonrasib complex prevents effector binding. Panel C shows genomic alterations in circulating-tumor DNA (ctDNA) or tumor tissue of patients who had tumor progression while receiving daraxonrasib monotherapy.[16,17] Acquired mutations and putative resistance mechanisms include missense mutations, deletions, truncations, fusion genes, and amplifications (amp). A total of 84 patients were evaluated (44 with pancreatic ductal adenocarcinoma, 17 with non–small-cell lung cancer, 15 with colorectal cancer, 4 with *NRAS*-mutant melanomas, and 4 with other cancers), with acquired DNA alterations detected in 44 (52% overall and 59% with pancreatic ductal adenocarcinoma). Percentages may not total 100 because of rounding.

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Table 1. Trials of Combination Therapies Involving Daraxonrasib.*

Trial and Drug	Targets	Cancers
NCT06040541: phase 1–1b		
Zoldonrasib (RMC-9805)	$KRAS^{G12D}$	Solid tumors
NCT06128551: phase 1b–2		
Elironrasib (RMC-6291)	$KRAS^{G12C}$	Solid tumors
NCT06162221: phase 1b–2		
Elironrasib + pembrolizumab with or without chemotherapy	$KRAS^{G12C}$, PD-1, DNA	Solid tumors
Pembrolizumab with or without chemotherapy	PD-1, DNA	NSCLC
Zoldonrasib + chemotherapy	$KRAS^{G12D}$, DNA	NSCLC
NCT06360354: phase 1b		
Anvumetostat (AMG 193)	PRMT5	*MTAP*-deleted GI cancers
NCT06445062: phase 1–2		
5-Fluorouracil–based regimens	Thymidylate synthase	Colorectal cancer, PDAC
Cetuximab with or without mFOLFOX6†	EGFR, DNA	Colorectal cancer, PDAC
Gemcitabine + nab-paclitaxel	DNA, tubulin	PDAC
Zoldonrasib + 5-fluorouracil–based regimens	$KRAS^{G12D}$, thymidylate synthase	Colorectal cancer, PDAC
Zoldonrasib + cetuximab with or without mFOLFOX6†	$KRAS^{G12D}$, DNA, others	Colorectal cancer, PDAC
Zoldonrasib + gemcitabine + nab-paclitaxel	$KRAS^{G12D}$, DNA, tubulin	PDAC
NCT06922591: phase 1–2		
Vopimetostat (TNG462)	PRMT5	*MTAP*-deleted PDAC, NSCLC

* This table was compiled from ClinicalTrials.gov. EGFR denotes epidermal growth factor receptor, GI gastrointestinal, MTAP methylthioadenosine phosphorylase, NSCLC non–small-cell lung cancer, PD-1 programmed cell death protein 1, PDAC pancreatic ductal adenocarcinoma, and PRMT5 protein arginine methyltransferase 5.
† The modified FOLFOX6 (mFOLFOX6) chemotherapy regimen includes fluorouracil, oxaliplatin, and leucovorin.

to understand the primary and adaptive mechanisms of resistance.

Reactivation of RAS pathway signaling through genomic alterations has been reported in preclinical models and tumor-derived cell-free DNA of patients treated with daraxonrasib (Fig. 1C); combination strategies are being evaluated (Table 1).[16,17] Identifying predictive biomarkers of response and rationally designing combination strategies to overcome resistance mechanisms to daraxonrasib will be essential to improving on the unprecedented responses to this single-agent small-molecule inhibitor in pancreatic ductal adenocarcinoma.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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