ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Development of Second-Generation KRAS Inhibitors

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H&O How common are *KRAS* mutations in patients with various types of cancer?

EO Approximately 20% to 25% of patients with cancer will have a *RAS* mutation, with most of these occurring in *KRAS* and far fewer occurring in *NRAS* and *HRAS*.

Moving on to specific diseases, *KRAS* mutations are seen in approximately 90% of patients with pancreatic cancer, 40% to 45% of those with colorectal cancer, and 40% of those with lung cancer. The specificity of the allele, meaning the point on the *RAS* gene where the mutation has occurred, varies among these types of cancer. In pancreatic cancer, *KRAS* mutations occur in G12D in approximately 40% of cases, G12V in approximately 30%, G12R in approximately 15%, and G12C in 1%.

The most common *KRAS* mutations in colorectal cancer are *KRAS* G12D, *KRAS* G12V, *KRAS* G13D, and much less commonly, *KRAS* G12C. The most common KRAS mutations in non–small cell lung cancer (NSCLC) are *KRAS* G12C, *KRAS* G12V, and *KRAS* G12D. The development of RAS inhibitors largely began in lung cancer because these agents were initially designed to target G12C. Sotorasib (Lumakras, Amgen) and adagrasib (Krazati, Mirati Therapeutics) are from the first generation of KRAS inhibitors and target G12C. They were developed after decades of work to devise an effective RAS inhibitor led to the identification of the switch II pocket on G12C.

H&O How often do sotorasib and adagrasib either stop working or fail to produce a response in patients who have a *KRAS* mutation?

EO First-generation inhibitors still play a role as single agents, but the duration of the response is relatively short. In patients with NSCLC, it is common to see a progression-free survival of 5 to 6 months with single-agent sotorasib or adagrasib. The story is a little different in colorectal cancer, in which other signaling pathways are at play, including the mitogen-activated protein kinase (MAPK) pathway and the receptor tyrosine kinase (RTK) pathway. Because of this additional signaling, single-agent RAS inhibitors do not work as well in colorectal cancer as they do in lung cancer. As a result, they are approved in colorectal cancer only in combination with anti-epidermal growth factor receptor (EGFR) therapy and in patients with previously treated disease. RAS inhibition is currently being examined in combination with chemotherapy in the frontline setting.

RAS inhibitors do not have US Food and Drug Administration (FDA) approval for use in pancreatic cancer, although National Comprehensive Cancer Network (NCCN) guidelines endorse the use of sotorasib or adagrasib as a single agent for patients who have previously been treated for pancreatic cancer with *KRAS* G12C. These agents produce response rates of approximately 20% to 30%, with resistance developing after approximately 4 to 6 months. We expect that resistance will develop later with second-generation RAS inhibitors than with first-generation RAS inhibitors because the newer pan-RAS inhibitors may block some of the resistance mechanisms and have greater potency against the target.

H&O What other targeted therapies and targets are available in pancreatic cancer and other RAS-dependent cancers?

EO Approximately 5% to 6% of patients with cancer have a germline mutation in *BRCA1*, *BRCA2*, or *PALB2* and are eligible for treatment with platinum drugs and poly(ADP-ribose) polymerase (PARP) inhibitors. In addition, a small subset of patients with somatic homologous repair deficiency (1%-2%) can benefit from these approaches. Approximately 15% of people with colorectal cancer and a much smaller percentage with localized lung cancer have mismatch repair–deficient tumors and are eligible for single and dual immune checkpoint blockade. Patients who have pancreatic cancer or NSCLC with a wild-type *KRAS* mutation and have *NRG1* fusions are eligible for treatment with the bispecific antibody zenocutuzumab (Bizengri, Merus), and patients who have *RET*-positive metastatic NSCLC are eligible for treatment with selpercatinib (Retevmo, Lilly).

H&O What advances are being made with second-generation RAS inhibitors?

EO Several new types of RAS inhibitors are being developed. Pan-RAS inhibitors, which are designed to target all known *RAS* alleles, are the first type; pan-KRAS inhibitors, which are designed to target selected *KRAS* alleles, including *KRAS* G12D and *KRAS* G12V, are a variation on this type. Mutant or allele-selective inhibitors targeting G12D or G12V are a second type. Other variations include agents that target the "on" state, covalent agents, noncovalent agents, and agents that target at the protein level (known as degraders). Early research is showing higher response rates and better durability of response with second-generation than with first-generation agents, in addition to activity in patients who have developed resistance to first generation agents.

The pan-RAS agent that is furthest along in development is the tricomplex inhibitor daraxonrasib, also known as RMC-6236. This drug works by binding the intracellular chaperone protein cyclophilin and binding RAS in the GTP-bound "on" state, curtailing downstream RAS signaling. In patients with previously treated pancreatic cancer, response rates to daraxonrasib are somewhere between 29% and 35%, which is really striking.[1] Seeing a single-agent nonchemotherapy option produce that degree of tumor shrinkage, with good durability for some patients, has paved the way for accelerated development.

The results of the first planned analysis of the phase 3 RASolute 302 trial, which is examining the use of daraxonrasib in the second-line setting in metastatic pancreatic cancer, were presented as a late-breaking abstract at the plenary session of the 2026 American Society of Clinical Oncology Annual Meeting (receiving a standing ovation) and simultaneously published in the *New England Journal of Medicine*.[2] In this open-label study, 500 patients with pretreated metastatic pancreatic cancer and an Eastern Cooperative Oncology Group performance status of 0 to 1 were randomly assigned to second-line treatment with daraxonrasib or physician's choice of chemotherapy. At a median follow-up of 8.5 months, all of the study's primary and key secondary endpoints were met. Strikingly, the median overall survival was 13.2 months for daraxonrasib vs 6.6 months for standard-of-care chemotherapy among the 91.8% of patients with *RAS* G12 mutations and nearly identical (13.2 vs 6.7 months, respectively) in the overall group (hazard ratio in both populations, 0.4; $P<.0001$). Grade 3 or higher treatment-related adverse events occurred in 43.6% of those in the daraxonrasib group and 57.5% of those in the chemotherapy group, with the most common grade 3 or higher treatment-related adverse events in the daraxonrasib group being rash (13.7%) and stomatitis (12.0%).

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These results are anticipated to imminently change practice, and daraxonrasib is expected to receive regulatory approval in the United States in an expedited fashion. Furthermore, single-agent daraxonrasib and the combination of daraxonrasib with gemcitabine and nab-paclitaxel have shown promise in the first-line untreated metastatic setting.[3,4] On the basis of these data, RASolute 303 is looking at the first-line treatment of pancreatic cancer, with patients randomized to chemotherapy, single-agent daraxonrasib, or daraxonrasib plus chemotherapy (NCT07491445).

The phase 3 RASolve 301 study is looking at the use of daraxonrasib in patients with previously treated, locally advanced or metastatic *RAS*-mutated NSCLC (NCT06881784).

The combination of a G12C-targeting RAS inhibitor and an anti-EGFR agent plus chemotherapy is in development as a first-line treatment for colorectal cancer (NCT06252649, NCT06997497). In addition, trials in lung cancer are comparing the combination of

an allele-specific inhibitor and immunotherapy with and without chemotherapy or with standard chemoimmunotherapy (NCT06119581, NCT06793215).

The field is moving very rapidly. As recently as the first half of 2025, only a few phase 3 trials were underway at one time in pancreatic cancer, but now I see that at least 12 studies have been announced or activated to evaluate RAS inhibitor therapy in these patients. Therapy options have been limited for patients with *RAS* mutations, so it is exciting to see this wave of development.

The allele-specific RAS inhibitor that is furthest along in development in gastrointestinal cancer is zoldonrasib, also known as RMC-9805, which received Breakthrough Therapy Designation in January 2026 from the FDA for the treatment of *KRAS* G12D–mutant NSCLC. A phase 2 study is examining the use of zoldonrasib, daraxonrasib, or elironrasib (RMC-6291) in NSCLC (NCT06162221). Early results with zoldonrasib have been promising, with a response rate of 30% in patients with previously treated *KRAS* G12D–mutated pancreatic cancer[5] and a response rate of nearly 55% in those with lung cancer.[6] Trials of zoldonrasib combined with standard-of-care regimens are underway (NCT06162221). The favorable safety profiles of allele-specific RAS inhibitors vs those of pan-RAS inhibitors make them suitable for use in combination with a broad array of therapeutics.

H&O What toxicities are seen with second-generation RAS inhibitors?

EO The allele-specific inhibitors such as zoldonrasib are generally very well tolerated, with low rates of gastrointestinal toxicity, minimal rash, and low rates of diarrhea, nausea, and mucositis. We see much less toxicity with the allele-specific inhibitors than with the pan-RAS inhibitors because they are more narrowly focused.

The pan-RAS agents tend to produce more toxicity, especially cutaneous toxicity. Rash is a significant factor for many patients; it is mostly low-grade but can be significant and dose-limiting in some cases. We are getting better at managing this type of rash by using measures that include prophylactic topical antibiotics and the avoidance of significant sun exposure. Patients who have higher-grade rashes can require dose interruptions or reductions, however. Pan-RAS agents can also cause nausea.

H&O What other approaches are being developed to overcome resistance to sotorasib and adagrasib, such as combining them with other chemotherapy or EGFR inhibition?

EO Another potential strategy is to combine an allele-specific agent and a pan-RAS inhibitor. For example, a person with a *KRAS* G12D mutation might have a choice in the future of an allele-specific drug, a pan-RAS inhibitor, or a combination approach; all of these are nonchemotherapeutic options. Phase 2 studies are examining the use of daraxonrasib and zoldonrasib in pancreatic cancer and NSCLC (NCT06922591) and in gastrointestinal cancer (NCT06445062). Another approach that is in development is to combine RAS inhibitors with chemotherapy. Chemotherapy can block some of the mechanisms of resistance to RAS inhibition, potentially producing an augmented effect when added to RAS inhibitors; this strategy is supported by compelling preclinical data.[7] We already have proof of principle for this approach when we look at the combination of BRAF inhibition and chemotherapy for *BRAF*-mutated colorectal cancer[8] and the combination of EGFR inhibition and chemotherapy for *EGFR*-mutated lung cancer.[9]

Many patients with pancreatic cancer, colorectal cancer, or lung cancer are older and have comorbidities, so they may not be good candidates for chemotherapy. The use of single-agent RAS inhibition has the potential to provide a valuable treatment option for these patients.

H&O Biomarker selection has become increasingly important in this space. Beyond the specific *KRAS* mutation subtype, what other molecular features do you think will guide treatment decisions as these newer agents move through trials?

EO We currently have the ability to select a specific allele, but selection beyond that is an open story. As we learn more about the mechanisms of resistance to specific agents, we may find that certain co-mutations can predict response to treatment or resistance. For example, we know that *KRAS* G12C–mutated lung cancer in a patient with a co-mutation in *STK11*/*KEAP1* is more likely to be resistant to immunotherapy. Could we identify co-mutations that might predict a response to RAS inhibition? A subset of people have multiple copies of mutant *RAS* (a mutant allele dosage), which might identify a subgroup who are either more sensitive or more resistant to RAS inhibition. Downstream signaling in the RAS/MAPK/ERK pathway, manifested by multiple genomic alterations, might also affect the potential for a response. Another potential factor in response is *RAS* amplifications, which are emerging as an important resistance mechanism.

Another potential biomarker is *MTAP* deletion, which affects approximately 25% of people with pancreatic cancer and somewhat fewer people with lung cancer. Preclinical data suggest that the combination of RAS inhibitors and PRMT5 inhibitors, which are the class of drugs that target *MTAP* deletion, may be promising

in the clinic, and we look forward to seeing early clinical readouts soon.

H&O If second-generation agents obtain approval in the near future, how do you see the treatment-sequencing landscape changing, and will first-generation inhibitors still play a role?

EO It is clear from the preliminary readout of RASolute 302 that the first pan-RAS inhibitor, daraxonrasib, is going to be approved for patients with previously treated pancreatic cancer. Moving forward, it is speculated that next-generation inhibitors will have even greater potency with delayed resistance and will be bioengineered to optimize the therapeutic index and reduce cutaneous and gastrointestinal toxicity. We will need to determine the best way to sequence these agents, which I expect to be informed by preclinical testing and early clinical readouts.

Major priorities for the short term include moving these agents to earlier-stage disease and identifying the most promising combinations in pancreatic cancer. I do not see chemotherapy disappearing entirely, but we may see a day when first-line therapy for certain patients does not include chemotherapy.

Disclosures

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