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Drugmakers Going After RAS, MAPK Pathway to Tackle Cancers With Variety of KRAS Mutations

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NEW YORK – Less than a year after the first KRAS inhibitor received regulatory approval in the US, numerous drugmakers have jumped into the space and are exploring therapeutic strategies against tumors driven by different types of KRAS mutations and looking to head off resistance through combination approaches.

Amgen's Lumakras (sotorasib) was the first KRAS inhibitor approved by the US Food and Drug Administration in July 2021 for advanced or metastatic KRAS-mutant non-small cell lung cancer and has since been approved in Europe for the same indication. Mirati Therapeutics' KRAS inhibitor adagrasib is following closely behind in the same setting. In February, the FDA accepted Mirati's new drug application for adagrasib for KRAS G12C-mutated NSCLC with an approval decision expected by Dec. 14.

However, some drugmakers are taking a different approach to KRAS-mutant cancers, aiming to target a wider range of KRAS mutations and exploring strategies for overcoming resistance, while others are developing drugs that target genes other than KRAS but in the same RAS/MAPK pathway, such as SHP2, PLK1, or MEK.

The players in this space that have clinical-stage products include Erasca, which has a suite of drugs targeting various RAS/MAPK genes; Cardiff Oncology, which is developing the PLK1 inhibitor onvansertib; and Verastem Oncology, which is studying the RAF/MEK targeted therapy VS-6766.

Aberrant RAS/MAPK pathway activation is "implicated in five-and-a-half million new cases of cancer per year worldwide," according to Erasca CFO David Chacko, making these among the most common oncogenic drivers. While development and commercialization of KRAS G12C inhibitors addresses a portion of these cancers, since KRAS G12C mutations occur in about 13 percent of lung cancers, patients with other KRAS variants are unlikely to benefit from these drugs.

Overcoming resistance

One motivation to develop drugs targeting other genes on the RAS/MAPK pathway is to overcome resistance. After treatment with KRAS G12C inhibitors, including Lumakras and adagrasib, some patients can develop resistance. One study explored resistance to adagrasib and found there are a number of mechanisms of resistance and acquired resistance mutations that can occur. Some patients developed mutations in other KRAS variants, including G12D, G12V, G12R, and Q61H, while others developed mutations elsewhere on the RAS/MAPK pathway including mutations in NRAS, BRAF, MAP2K1/MEK1, and EGFR.

Erasca has a pipeline of drugs targeting several proteins on the RAS/MAPK pathway including KRAS, ERK, SHP2, EGFR, ULK, and SOS1. The firm's goal in treating cancer, according to Chacko, is to "comprehensively shut down the aberrant signaling within the RAS/MAPK pathway."

Toward that end, San Diego-based Erasca is also investigating combination therapeutic strategies that could prevent the emergence of resistance. The company is exploring its lead candidate ERAS-007, an ERK inhibitor, in two trials enrolling patients with KRAS-mutant cancers. One trial, HERKULES-2, is testing ERAS-007 with a number of agents, including Lumakras, in KRAS G12C-mutant NSCLC. Another trial, called HERKULES-3, is enrolling patients with KRAS-mutant colorectal cancer and giving them ERAS-007 plus Bristol Myers Squibb's CDK4/6 inhibitor Ibrance (palbociclib).

Separately, researchers at Massachusetts General Hospital Cancer Center, MD Anderson Cancer Center, and Dana-Farber Cancer Institute are exploring KRAS G12C inhibitor resistance in a trial funded by Mirati and nonprofit Stand Up To Cancer. That trial will combine ERAS-007 with adagrasib to potentially address both primary and acquired resistance to KRAS inhibition.

The lead researcher of that project, Ryan Corcoran, director of the gastrointestinal cancer center program and the scientific director of the Termeer Center for Targeted Therapy at Mass General, said both primary and acquired resistance can occur through other genes in the RAS pathway.

In upfront resistance "we find there are some very rapid adaptations where cells can turn the RAS pathway back on by allowing signals from upstream cell surface receptors to reactivate RAS despite the presence of a KRAS G12C inhibitor," he said.

In acquired resistance Corcoran said there is an "emergence of subclones ... that have each evolved a resistance mutation that can turn the pathway back on in the presence of a KRAS inhibitor." These resistance mutations can vary, he said, but the goal of the research is to intercept all RAS/MAPK resistance mutations by targeting ERK, the most downstream point in the pathway.

Erasca is also exploring a SHP2 inhibitor, ERAS-601, to target another node on the pathway. The company is evaluating this drug with Eli Lilly's EGFR inhibitor Erbitux (cetuximab) in a Phase I study in colorectal cancer (CRC) and head and neck squamous cell carcinoma (HNSCC). "SHP2 is emerging as a backbone of combination therapy," Chacko noted.

"We believe that combinations are what's going to be needed to effectively shut down the RAS/MAPK pathway," Chacko said. "The RAS/MAPK pathway is a wily pathway. Resistance or escape mechanisms frequently get activated in response to monotherapy inhibitors, so we are focused on combinations as the way to further limit the options that cancer cells have to survive."

Verastem Oncology, a biotech in Needham, Massachusetts, is also looking to address resistance with various combinations of its RAF/MEK inhibitor VS-6676. The company has several trials exploring VS-6676 with its FAK inhibitor defactinib, as well as combination trials with other drugs, such as Lumakras and adagrasib in NSCLC patients who have progressed after single-agent KRAS G12C inhibitor treatment.

"The problem we're trying to solve for is when you're signaling down through the MAP kinase pathway, resistance develops either directly in the pathway or in a parallel pathway," Verastem CEO Brian Stuglik said. "To be successful in managing these tumors, the more nodes that you can block in the vertical MAPK pathway or parallel pathways, the more likely you are to get a deeper, more durable response. Our value proposition with VS-6766 is we're blocking both RAF and MEK, which leads to a more complete blockade within the signaling pathway."

Addressing non-lung, non-G12C tumors

Lumakras and adagrasib, the most advanced drugs targeting KRAS mutations, are both KRAS G12C inhibitors that are initially addressing NSCLC. In the previously treated advanced or metastatic KRAS G12C-mutant NSCLC setting, the two drugs have shown promising activity in a group of patients who previously lacked targeted treatment options.

In the Phase I/II CodeBreaK 100 basket trial that led to the US and European approval of Lumakras in this setting, the drug demonstrated a 40.7 percent response rate with a median progression-free survival of 6.3 months and overall survival of 12.5 months.

Mirati's adagrasib showed similar efficacy in this setting, with about half of patients responding to treatment in the Phase I/II KRYSTAL-1 trial. Mirati also recently reported data showing adagrasib had efficacy in KRAS G12C-mutant NSCLC patients with both treated and untreated brain metastases.

While both Amgen and Mirati are exploring these drugs in non-lung cancers, those studies are not as advanced as their lung cancer programs.

In February, Amgen expanded its cohort of KRAS-mutant pancreatic cancer patients in the CodeBreaK 100 basket trial after seeing promising efficacy in a small number of patients. However, in a cohort of KRAS G12C-mutated advanced colorectal cancer patients, Lumakras monotherapy showed poor efficacy, with only 9.7 percent of patients responding to treatment. After reporting that data, Amgen pivoted to combination strategies in this setting in the hopes of increasing its activity and overcoming resistance.

Similarly, Mirati is also studying adagrasib in combination with Eli Lilly's Erbitux (cetuximab) in KRAS G12C-mutated colorectal cancer in the Phase III KRYSTAL-10 trial.

One drawback of these two drugs is they only target KRAS G12C mutations and, therefore, won't work with patients with other KRAS alterations, such as G12D, G12V, G13D, and G12R. One study that analyzed KRAS variants in more than 13,000 tumor samples across 14 tumor types found G12C mutations showed up in about 12 percent of cases. KRAS G12D mutations occurred in 29.5 percent, G12V in 23 percent, G13D in 6.5 percent, and G12R in 6.2 percent of tumors, while other less common KRAS variants made up the remaining 22.8 percent.

San Diego-based Cardiff Oncology is going after some of these other KRAS variants in non-lung tumors with its PLK1 inhibitor onvansertib. Its most advanced program is exploring onvansertib plus chemo in KRAS-mutant metastatic colorectal cancer patients.

Early results from a Phase Ib/II trial of the combination showed a 34 percent response rate. The responses were seen among colorectal cancer patients with seven types of KRAS mutations including most commonly in those with KRAS G12D, G12V, and G13D mutations. Based on this data, Cardiff is planning a pivotal Phase III trial that can produce data supporting accelerated approval.

Cardiff is going after KRAS-mutant colorectal cancer with a "one-two punch," according to CEO Mark Erlander. First, Cardiff is betting that colorectal cancers harboring KRAS mutations will be more vulnerable to inhibition of PLK1, which is downstream of KRAS; and second, by inhibiting PLK1, the firm is hoping to hobble tumor cells' ability to survive by repairing their DNA.

By combining onvansertib with chemo, specifically irinotecan, Cardiff's strategy is for the chemo to damage the tumor cell DNA. Then, onvansertib comes in and stops the cell from repairing that DNA damage by inhibiting PLK1 and causing cell death, Erlander explained.

Cardiff is similarly going after DNA damage and repair mechanisms in exploring onvansertib plus chemo in a Phase II trial involving pancreatic cancer patients. While this study is in an all-comer

population, Erlander noted that more than 90 percent of pancreatic cancers are driven by KRAS mutations.

"What makes us different is that inhibiting PLK1, in essence, inhibits the entire axis of the tumor cell from being able to survive and to proliferate," Erlander said. "We also know these tumors are more vulnerable [to PLK1 inhibition] because they have a KRAS mutation. Not only does PLK1 facilitate DNA repair, but it's also intricately involved in the cell division of a tumor cell, so you're really hitting it right where it counts."

Verastem, meanwhile, has a focus on KRAS-mutant low-grade serous ovarian cancer. The company has an ongoing, potentially registrational Phase II study of VS-6676 alone or with defactinib in patients with recurrent low-grade serous ovarian cancer, enrolling both KRAS-mutant and KRAS-wild type patients. Once results from the expansion phase of that study come in, expected in late 2022, the company hopes to discuss with the FDA the possibility of seeking accelerated approval for the agent in ovarian cancer.

"What's important for low-grade serous ovarian cancer is about 70 percent of cases have a mutation in the RAS pathway," Verastem's Stuglik said.

Early data presented last year from a study of VS-6676 and defactinib in ovarian cancer demonstrated that half of all patients (52 percent) responded to treatment, and 70 percent of KRAS-mutant patients responded. In that small trial, the median progression-free survival was 23 months in the overall study population.

"We started out thinking that we would just see responses in KRAS-mutant patients, but now we understand that the tumors we're calling KRAS-wild type are still mutant in other drivers of the RAS pathway," Stuglik said. The results "say that we can help not just 30 percent of low-grade serous ovarian cancer patients with KRAS mutations, but a larger of a set of these patients."

Along with ovarian cancer, Verastem is also exploring the RAF/MEK inhibitor in advanced pancreatic, KRAS-mutant endometrial, and other RAS-mutant solid tumors in a Phase I basket study.

As a dual RAF/MEK inhibitor, VS-6676 has the unique ability to block two nodes of the RAS pathway, said Verastem Chief Scientific Officer Jonathan Pachter. Combining VS-6676 with defactinib and other drugs, such as Lumkras and adagrasib, makes that blockade even deeper and addresses different escape mechanisms.

"In this pathway there is a need for vertical blockade," Pachter said. "If you block any single node in the pathway, you don't get the maximum depth and duration. That's part of why RAF and MEK inhibitors are often used together with the G12C inhibitors blocking KRAS."

The company is also considering the benefits of blocking parallel pathways. "If you block RAF or MEK, you get activation of FAK as a potential resistance mechanism," Pachter explained. "That's important because it can drive various other pathways, like the AKT pathway, to drive tumor growth and potentially bypass the value of blocking the RAS pathway."

Because KRAS mutations occur across tumor types, there's been an open question in the field as to whether tissue-agnostic therapies could eventually be developed that will work in tumors as long as they are being driven by common oncogenic drivers.

However, tissue-agnostic studies in tumors with KRAS mutations can be tricky. John Strickler, associate professor of medicine at Duke Cancer Institute and an investigator for Lumakras clinical

trials, noted that some tumor types have greater opportunity to acquire bypass mutations to escape KRAS inhibition.

"It has to do with the oncogenic pathways driving tumors, and there's heterogeneity in that respect," Strickler explained. "[KRAS inhibitors are] doing the exact same thing. They're reaching their target, but that wiring of the tumors can be different. There may be more genomic or molecular heterogeneity in certain tumor types, or there may be certain types of proteins that are overexpressed in certain tumor types that lead to greater opportunity for rescuing a tumor cell from single-agent KRAS inhibition."

Toward regulatory submissions

Cardiff, Erasca, and Verastem are all beginning to explore either registrational studies or potential accelerated approval filings with the FDA as their drugs advance.

Cardiff is perhaps the farthest along the path to approval. In January, the company expanded its Phase II trial in KRAS-mutant colorectal cancer to generate more survival data that it could share with the FDA. The firm is also planning a pivotal Phase III study of onvansertib plus standard-of-care treatments in the colorectal cancer population, which will begin later this year. The Phase III pivotal study could support accelerated approval based on an interim analysis, the company said on a call with investors in January.

While Erasca has not announced plans for any discussions with regulators for its programs, Chacko noted they hope to quickly identify signals of efficacy from early-stage trials and "potentially move towards registration-enabling studies."

Verastem is also beginning to consider pathways to accelerated approval for VS-6676. Last year, the FDA granted breakthrough therapy designation to VS-6676 plus defactinib for previously treated patients with recurrent low-grade serous ovarian cancer regardless of KRAS status based on an early readout from the Phase I/II FRAME study.

Verastem said it designed the expansion phase of the registration-directed RAMP-201 trial in ovarian cancer based on discussions with regulators. Once the expansion phase is fully enrolled, expected later this year, and that data is reported, it should be "sufficient for accelerated approval," Stuglik said.

The company's other registration-directed trial, RAMP-202, is evaluating VS-6766 alone or combined with defactinib in recurrent KRAS G12V-mutant and/or KRAS- and BRAF-mutant NSCLC.

"We're trying to improve upon the around 35 percent response rate and current duration of therapy that you see with the KRAS G12C inhibitors," Stuglik said. "While the G12C inhibitors are an advance [in treatment], there's still room for improvement, both in terms of the percent of patients who respond and the duration of response given the resistance mechanisms that develop while on therapy."

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