Next Wave of KRAS G12C Inhibitors May Address Limits of First-Gen Drugs, AACR Studies Show

Early studies of KRAS inhibitors from Loxo Oncology, Genentech, and Innovent suggest newer drugs have activity in KRAS G12C-resistant patients.

By Alison Kanski

IN PHASE I TRIALS, KRAS G12C inhibitors under development at Eli Lilly, Genentech, and Innovent benefited patients with difficult-to-treat tumor types and even some who had become resistant to KRAS inhibition.

Researchers at the American Association for Cancer Research's annual meeting presented data from three trials, in which they evaluated these KRAS inhibitors as monotherapy and in combination with other treatments. Lilly's Loxo Oncology evaluated its drug, LY3537982, as a single agent and with Merck's checkpoint inhibitor Keytruda (pembrolizumab) and Lilly's EGFR inhibitor Erbitux (cetuximab) in solid tumors. Genentech also studied divarasib in combination with Erbitux in KRAS-mutant colorectal cancer, while Innovent evaluated IBI-351 as a monotherapy in advanced solid tumors harboring a KRAS G12C mutation.

All three drugs demonstrated promising activity in the trials researchers highlighted at the meeting, including in patients with acquired resistance to KRAS G12C inhibitors, and appeared to be better tolerated by patients than first-generation drugs in the class. However, all the drugs need to be studied further in larger populations before they can truly be pitted against the two KRAS inhibitors on the market: Amgen's Lumakras (sotorasib) and Mirati Therapeutics' Krazati (adagrasib).

Ryan Corcoran, an associate professor of medicine at Harvard Medical School, who was not involved with any of the trials, suggested at the meeting that there is a lot of room to improve upon the approved therapies. In the trials that led to the approval of Lumakras in KRAS G12C-mutant NSCLC, the response rate was 36 percent and the disease control rate was 81 percent. For Mirati's Krazati, the overall response rate was 43 percent and 80 percent of patients achieved disease control.

"This still means that the majority of patients fail to respond," Corcoran said.

"The duration of disease control is limited by acquired resistance, and many groups are now

finding that emerging RAS mutations are driving resistance in 40 percent to 50 percent of patients," he continued. "Tolerability is still an issue, even though these are highly selective inhibitors, and in some instances this is hampering initial combination efforts."

Corcoran is hopeful that some of the newer KRAS G12C inhibitors will mitigate the limitations of first-generation drugs. Therapies that increase KRAS target engagement could "widen the therapeutic index" of these treatments, which he said could improve the tolerability of combination approaches with anti-PD-1 and other treatments. Moreover, drugs that target the "on" state of KRAS, may be more effective than agents that target the "off" state, or GDP-bound state, of KRAS, he suggested.

The question drugmakers and researchers should be asking, Corcoran said, is "have we hit a ceiling with what we can achieve with KRAS G12C inhibition alone or is there more to be achieved by more optimal KRAS G12C inhibition?"

Loxo's LY3537982

In its Phase I study of LY3537982, Loxo enrolled 84 patients with advanced KRAS G12C-mutant solid tumors including non-small cell lung, colorectal, pancreatic, and other cancers in the monotherapy arm. Patients with a variety of tumor types responded to LY3537982. Out of 20 colorectal cancer patients, two responded to the treatment, but the majority, 90 percent, achieved disease control. Among 12 pancreatic cancer patients, 42 percent responded and 92 percent achieved disease control.

The monotherapy cohort also included NSCLC patients who had previously received a KRAS G12C inhibitor and those who hadn't. Among 14 patients who had prior G12C inhibitors, one responded to Loxo's drug, and 54 percent, nine patients, achieved disease control. Among G12C inhibitor-naïve patients, three of eight participants responded, and 88 percent had disease control.

"[LY3537982] is designed to be able to achieve high target occupancy at low concentration," said Yonina Murciano-Goroff, a medical oncologist at Memorial Sloan Kettering, who presented the data at the meeting. "That has potential interest in terms of safety [because] we can give lower amounts of [the] drug, and we may be able to do it more safely and to facilitate combinations."

The trial also included 13 patients who received LY3537982 with the immunotherapy Keytruda. Among nine NSCLC patients who hadn't gotten a prior KRAS G12C inhibitor, seven (78 percent) responded to the combination treatment. Of these patients, three had PD-L1 expression scores greater than 50 percent. Four patients in this arm had prior G12C inhibitor therapy, of which one responded to treatment and three out of four patients achieved disease control.

In a third arm of the trial, Loxo explored the activity of LY3537982 with Erbitux in KRAS G12C-mutant colorectal cancer. Among 11 evaluable patients, the response rate was 45 percent and the disease control rate was 100 percent.

LY3537982, both as a single agent and in combination with other drugs, was well tolerated, "even in those patients with prior intolerance to other KRAS G12C inhibitors," Murciano-Goroff said. Her team is continuing to explore the activity of LY3537982 in patients previously treated with a KRAS G12C inhibitor.

Genentech's divarasib

Genentech's KRAS inhibitor divarasib, when combined with Erbitux in a Phase Ib trial, led to a confirmed response in 62 percent of patients with KRAS G12C-mutant advanced or metastatic colorectal cancer.

These results represent a "new benchmark" for this combination in colorectal cancer, according to Jayesh Desai, a medical oncologist at the Peter MacCallum Cancer Center in Australia who presented the data. The activity of the divarasib-Erbitux combo is also an improvement on the previously reported single-agent activity of divarasib in KRAS-mutant colorectal cancer. Desai cited an earlier study, in which there was a 24 percent overall response rate to divarasib in patients with these types of tumors.

"We know that patients with colorectal cancer have generally lower response rates to KRAS G12C inhibition than what we see, for example, in non-small cell lung cancer," Desai said. "A number of resistance mechanisms have been identified. The most important of those is thought to be via signaling through the EGFR pathway, leading to a rationale to combine [divarasib] inhibition with EGFR inhibition."

The researchers also allowed colorectal cancer patients who had prior KRAS G12C inhibitor treatment to enroll in this study. Among five such patients, three responded to the divarasib-Erbitux combination.

Corcoran, who wasn't involved with this trial, said that this combination is yielding "registrational-level activity" in colorectal cancer, even though the data remains too early to make comparisons to other KRAS inhibitors or combination treatments.

Going forward, Genentech is evaluating divarasib with other therapies in addition to EGFR inhibitors in KRAS-mutant colorectal cancer, Desai said. In this same Phase I trial, Genentech is studying divarasib with its anti-PD-L1 drug Tecentriq (atezolizumab), anti-angiogenic drug Avastin (bevacizumab), and its EGFR inhibitor Tarceva (erlotinib), as well as with chemotherapy, an investigational SHP2 inhibitor, and a PI3K-alpha inhibitor.

Innovent's IBI-351

Innovent's IBI-351 also demonstrated promising activity in a Phase I trial involving Chinese patients with advanced KRAS G12C-mutated NSCLC at AACR.

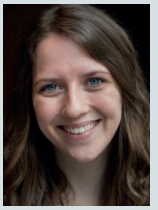
KRAS mutations are much rarer in Chinese patients, according to Chongrui Xu, an assistant professor at Guangdong Provincial People's Hospital in Guangzhou, China, who presented the results of this trial. He estimated that around 3 percent of Chinese patients have KRAS-mutated NSCLC compared to 13 percent of patients globally.

Of 30 NSCLC patients who received the recommended Phase II dose of IBI-351, the response rate was 66.7 percent, and 96.7 percent achieved disease control. Three-fourths of the study population responded for at least six months, but the median duration of response was not reached in the study.

At a median follow-up of 8.1 months, the median progression-free survival on IBI-351 was 8.2 months. The six-month progression-free survival rate was 58.9 percent.

Innovent is also exploring IBI-351 with other drugs, including in a Phase I trial with Erbitux in patients with KRAS G12C-mutated metastatic colorectal cancer and in another Phase I trial with Lilly's investigational PD-1 inhibitor sintilimab in KRAS-mutant NSCLC.

These presentations at AACR on next-generation KRAS inhibitors forecast a crowded market in coming years. That's even more reason, researchers said, to design and conduct trials that elucidate the activity of each drug and to explore combination strategies that increase the benefit to patients across tumor types. "Maximizing this [space] and thinking about how we get our best drugs to patients earlier is going to be important as things evolve," Murciano-Goroff said. PMQ



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