Next-Generation TRK Inhibitor Shows Promise for Multiple Cancer Types

Researchers continue to develop new drugs that target cancer with specific genetic mutations anywhere in the body.

April 4, 2019 By Liz Highleyman

An experimental targeted therapy is on track to become a successor to Vitrakvi (larotrectinib) for people who develop resistance to the first "pancancer" drug, according to early study results presented at the 2019 American Association for Cancer Research (AACR) annual meeting this week in Atlanta.

Another report showed that a different site-agnostic therapy with the same target, entrectinib, continues to perform well as it makes its way through the development pipeline, specifically in people with non-small-cell lung cancer (NSCLC).

David Hyman, MD, of Memorial Sloan Kettering Cancer Center in New York presented findings from a Phase I study of BAY 2731954, an investigational selective tropomyosin receptor kinase (TRK) inhibitor that was "purpose built" to work in people who become resistant to Vitraki. Bayer recently acquired both Vitraki (formerly LOXO-101) and BAY 2731954 (formerly LOXO-195) from Loxo Onology.

Vitrakvi is the first approved medication designed to work against all types of cancer that share specific genetic mutations known as TRK fusions, regardless of where they occur in the body.

TRK proteins are encoded by three different neurotrophic receptor tyrosine kinase genes, known as NTRK1, NTRK2 and NTRK3. When one of these genes in a cancer cell fuses with another unrelated gene, it acts as an "ignition switch" that promotes cell growth. Interfering with TRK proteins can halt cancer progression, but because they play a limited role in healthy cells after embryonic development, this causes few side effects, Hyman explained. TRK fusion mutations are rare overall—occurring in less than 1 percent of all cancers—but they are more common in certain cancer types.

As previously reported, in a study of 55 adults and children with 17 cancer types, Vitrakvi demonstrated an overall response rate of 75 percent, and a majority of trial participants had durable responses. However, some people did develop resistance, mostly associated with three different TRK kinase mutations, according to Hyman.

“While responses to TRK inhibition can be dramatic, we have known that acquired resistance may eventually limit the duration of the response," Hyman said in a Memorial Sloan Kettering press release. “As we began to see resistance occur in early larotrectinib clinical trials, we simultaneously began working to provide a next-generation treatment option to this population.”

Hyman and colleagues evaluated BAY 2731954 in children and adults with TRK fusion-positive solid tumors who experienced disease progression while using a prior TRK inhibitor or, in one case, could not tolerate the older drugs.

Twenty participants enrolled in a clinical trial and 11 people who met similar criteria but were not eligible for the formal trial because of medical comorbidities or logistical barriers received the drug though an expanded access program.

Of the 31 total participants, about 70 percent were female and seven were children. About two thirds had previously used Vitrakvi, 28 percent had used entrectinib and the rest had used another investigational drug; the median duration of prior treatment was 11 months. About half each had NTRK1 and NTRK3 fusion mutations, with only one person having NTRK2. Among them, the participants had 15 different tumor types, the most common being sarcomas, gastrointestinal stromal tumors, and pancreas, breast and salivary gland cancers.

Participants were treated with different doses of BAY 2731954 taken by mouth once or twice daily. There was no placebo group. Hyman said the optimal dose and scheduled were still being worked out.

Ten of 29 evaluable patients showed complete or partial tumor shrinkage, for an overall response rate of 34 percent. Another nine people had stable disease. Responses were seen in 45 percent of people with one of the three major NTRK resistance mutations, but not in those with TRK-independent resistance. Several people were still responding after a year on treatment, and one was still responding at nearly two years, Hyman reported.

Treatment was generally well tolerated. The most common side effects were ataxia (loss of muscle control), dizziness, nausea, vomiting and gait disturbances. Hyman noted that the dizziness tends to lessen with time. There were five dose-limiting toxicities but no treatment interruptions.

Based on these findings, the researchers concluded that BAY 2731954 "may provide a continuum of care for patients with TRK fusion cancer who progress on first-generation TRK inhibitors.

“Given how promising our early data are, I would encourage patients who have disease progression after treatment with a first-generation TRK inhibitor to seek out a clinical trial testing a next-generation TRK-inhibitor,” Hyman said.

Entrectinib

In a related presentation during the same session, Robert Doebele, MD, PhD, of the University of Colorado in Aurora, described the latest study findings for entrectinib, an experimental drug from

Genentech that targets both NTRK gene fusions and ROS1 fusions, which play a role in lung cancer. Entrectinib was designed to enter the central nervous system (CNS), meaning it has the potential to treat cancer in the brain, Doebele said.

Doebele reported results from a combined analysis of people with non-small cell lung cancer in three Phase I and II clinical trials known as STARTRK-1, STARTRK-2 and ALKA-372-001. Participants received oral entrectinib once daily.

A larger pooled analysis of all 54 participants in these studies, who had 10 types of locally advanced or metastatic NTRK fusion-positive solid tumors, was presented at the 2018 European Society for Medical Oncology Congress in October.

The full population included people with sarcomas, salivary gland cancer, breast cancer, thyroid cancer and colorectal cancer and other cancers; about one in five had cancer in the brain. The overall response rate was 57 percent, including four people (7 percent) with complete remission. The median duration of response was 10.4 months, the median progression-free survival—meaning patients were still alive without worsening of disease—was 11.2 months and the median overall survival was 20.9 months.

Looking at the 10 lung cancer patients in all three studies, the response rate was 70 percent, including one complete response, Doebele reported. Four of the six people with cancer in the brain saw intracranial improvement. The median duration of response and median overall survival cannot yet be determined because a majority are still responding; the median progression-free survival was 14.9 months.

Here too, treatment was generally well tolerated and most adverse events were mild or moderate. The most common side effects were altered sense of taste (dysgeusia), fatigue and dizziness. Forty percent reduced their dose and 4 percent stopped treatment because of adverse events.

“In this integrated analysis of global multicenter clinical trials, entrectinib induced clinically meaningful, durable systemic and intracranial responses in patients with NTRK fusion-positive tumors,” including those with NSCLC, the researchers concluded.

Click here to read the BAY 2731954 abstract.

Click here to read the entrectinib abstract.
