On Cancer

When a Cancer Therapy Stops Working: Experimental Drug Addresses Resistance

By Julie Grisham, **Monday, April 1, 2019**

Results from the first phase I clinical trial of a new drug were presented by MSK's David Hyman at the American Association for Cancer Research annual meeting.

Summary

> Early findings from the first phase I clinical trial of a drug called LOXO-195 were presented at the American Association for Cancer Research's annual meeting in Atlanta.

In November 2018, the US Food and Drug Administration **approved the targeted therapy larotrectinib** (Vitrakvi®, also called LOXO-101) for cancers caused by a molecular change called a TRK (pronounced "track") fusion. About 75% of people with this type of mutation initially benefit from the drug. Unfortunately, some of these people eventually stop responding to the drug, and their tumors start to grow again.

On April 1, 2019, at the annual meeting of the American Association for Cancer Research, an international team of researchers led by Memorial Sloan Kettering's David Hyman presented results from the first phase I clinical trial of a related drug, LOXO-195 (also called BAY 2731954). LOXO-195 was developed specifically to treat people whose tumors have developed resistance to existing TRK inhibitors, like larotrectinib. Nearly half (nine of 20) of the people treated with LOXO-195 who had developed resistance to prior TRK inhibitors because they had acquired new TRK mutations responded. In another six, the tumors didn't shrink but also didn't grow.

"Responses to drugs that target TRK fusions, like larotrectinib, can be dramatic. But we know that acquired resistance can develop later, meaning that these patients will need new treatment options," says Dr. Hyman, Chief of MSK's **Early Drug Development Service**.

Blocking Cell Growth Driven by Gene Mutations

TRK fusions occur when a TRK gene and an unrelated gene become abnormally linked together. The result is uncontrolled cell growth. Although TRK fusions are rare, collectively they affect thousands of people who are diagnosed with cancer each year.

Precision oncology is based on the concept that drugs can be designed to target specific gene mutations that drive cancer growth. With this approach, the same drug may work against many tumor types. Larotrectinib was approved for any type of cancer that has a TRK fusion, in both adults and children. LOXO-195 appears to work on many kinds of TRK fusion-positive cancers as well: People with 15 different tumor types were treated in the trial.

LOXO-195 was designed by the company Loxo Oncology based, in part, on research from Dr. Hyman and his colleagues. This prior research found that in people who

initially responded to drugs targeting TRK but who later stopped responding, two kinds of changes led to this acquired resistance. For some people, new mutations in the TRK fusion gene had developed, causing these tumors to be insensitive to prior TRK inhibitors. For others, the tumors found a way to grow without the continued need for the TRK fusion. LOXO-195 is designed to work with tumors that develop new mutations in the TRK fusion gene.

Longer-Lasting Results for Some People

In addition to the 20 people who were treated as part of the trial, another 11 received the drug through the FDA's Expanded Access Program, which allows people who don't have other treatment options and who cannot participate in clinical trials to receive experimental drugs. In total, 24 adults and seven children received the drug.

None of the people who had developed resistance to a prior TRK inhibitor and who didn't have the additional mutations in the TRK fusion gene that LOXO-195 targets responded. "These findings were generally consistent with what we expected based on our biological understanding of how the drug works," Dr. Hyman says. "While it is too early to say for sure whether LOXO-195 could be a meaningful treatment option for patients whose tumors don't develop these new TRK mutations, these very early data suggest that more research is needed to determine the optimal treatment approach for these people."

The most common side effects observed in the trial were dizziness, nausea, anemia, muscle and abdominal pain, fatigue, and a reduced number of lymphocytes (a type of white blood cell). Most side effects seemed to vary with the amount of drug given, with LOXO-195 being very well tolerated at lower to moderate doses. The side effects were reversible.

"This research shows the value of continuing to focus on precision oncology," Dr. Hyman adds. "By studying patients after they develop resistance, we've been able to quickly develop additional drugs to extend the total benefit of this approach."

This study was funded by Loxo Oncology and Bayer, the companies that are developing LOXO-195. Dr. Hyman has received compensation from Bayer for consultancy work and research funding from both companies.

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