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Dmitrovsky, right, and his collaborators—Memoli, left, and Dragnev, center—are buoyed by their trials' results.

The journey is ongoing, but the way is paved

In search of better treatments for patients with advanced cancer, a team of DMS researchers has made repeated journeys from the research lab to the clinic and back again. The results of two recent trials, published in *Cancer Prevention Research*, show that they are drawing closer to their destination.

About 150,000 Americans die each year from lung cancer—more than from any other form of cancer—and the five-year survival rate hovers around 16%. So, says DMS's Ethan Dmitrovsky, M.D., it's critical to develop better treatments. He has led a decade-long effort to do just that.

New: In the new studies, Dmitrovsky and his fellow researchers treated patients with a novel combination of two drugs—erlotinib and bexarotene. Both of these drugs inhibit a protein called cyclin D1, which is involved in the regulation of the cell cycle and is often overexpressed in lung cancer cells.

In one trial, the research team enrolled 10 patients who were soon to undergo surgery to remove tumors in their lungs. About a week before the surgery, biopsy samples were taken from the patients' tumors, and the patients were then treated with the combination therapy until their surgery. After the procedure, samples were again taken from the tumors.

Pathologist Vincent Memoli, M.D., analyzed both the pre- and postsurgery samples to find out if the treatment had made a difference. Eight patients' tumors had lower levels of key proteins in the postsurgery samples, including six with reductions in cyclin D1. And eight of the 10 also showed evidence that tumor cells were dying. "It's an exciting approach to studying cancer," says Memoli. He adds that he is blinded as to which patients the samples are from until his work is done, to avoid bias.

But 11 of the other 22 patients developed an immune response.

At the same time, the researchers conducted a phase II trial involving 40 patients with advanced non-small-cell lung cancer. Their median age was 67, and most had already been through at least one round of chemotherapy. The average survival for such patients would be expected to be about 4 months, but the 40 patients in the trial survived an average of 5.5 months.

There was no group of control patients who didn't get the combination therapy, so it's possible the increase in survival was due to other factors. But these results, along with the earlier trial and previous research, strongly suggest that the treatment helped.

"This is a promising regimen," Dmitrovsky says. "It's not a cure for lung cancer, but we've taken highly refractory patients that normally would not be expected to respond, and some of them have responded."

Some of the patients who responded had tumors with a specific mutation—to a gene called *KRAS*—that is an indicator of a poor prognosis. Oncologist Konstantin Dragnev, M.D., also a member of the team, says that about a third of lung cancer patients have this mutation and that treating such patients has long been a struggle because of a lack of effective options. This combination therapy, he adds, "provides a promising treatment option" for such patients.

Rise: There were some side effects, which was expected. After the treatment, most patients had elevated levels of triglycerides—a type of fat—in their blood, and many suffered a skin rash. If triglyceride levels rise too high, it can lead to pancreatitis, but no cases were seen in the study. There was also a benefit to these side effects: among patients who exhibited a rash or elevated triglyceride levels, the average survival was 6 months.

Dragnev says the two studies confirm earlier work in the lab. They knew that both of the drugs affect the expression of cyclin D1, but each does it in a different way, meaning that patients who might not respond to either drug individually were more likely to respond to the combination.

"To me, this is the most exciting part of cancer research," says Dragnev. "You can see how something happening in the laboratory is actually helping patients."

Tools: "We really do need new tools for treatment," Memoli adds. "The scientific aspect is interesting, but ultimately we really want to do something that helps people."

The next steps in the researchers' journey include testing the combination specifically in patients with *KRAS* mutations and looking for other drugs that target cyclin D1, but even more effectively. AMOS ESTY