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Genomic testing links 'exceptional' drug response to rare mutations in bladder cancer

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A patient with advanced bladder cancer in a phase I trial had a complete response for 14 months to a combination of the targeted drugs everolimus and pazopanib, report scientists led by a Dana-Farber Cancer Institute researcher, and genomic profiling of his tumor revealed two alterations that may have led to this exceptional response.

This information can help identify cancer patients who may respond to everolimus, according to the report published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Studying exceptional responders can help us understand the specific reasons why some tumors are highly sensitive to certain anticancer agents," said Nikhil Wagle, M.D., of Dana-Farber Cancer Institute, the report's first author. "We can use that information to identify patients whose tumors have genetic alterations similar to those found in exceptional responders, and treat them with those same agents."

Exceptional responders are rare cancer patients whose cancers are extremely sensitive to drugs and who have long-lasting responses to therapy.

"We conducted a phase I clinical trial to test the efficacy of two anticancer agents—the mTOR inhibitor everolimus, and pazopanib, another drug that are approved for treatment of kidney cancers and sarcomas —and one of our patients developed near complete remission of his bladder cancer which lasted for 14 months," said Wagle, who is

also an Associate Member of the Broad Institute of MIT and Harvard. A complete response to a drug is when all signs of a tumor disappear.

"We performed whole-exome sequencing of the patient's tumor, and to our surprise, we identified two mutations in the gene mTOR, which is the target for everolimus," said Wagle. The protein made by this gene plays a role in many cell functions, and has been found to be mutated in a number of cancers. MTOR inhibitors such everolimus have been approved for treatment of some cancers, including breast and kidney.

In this phase I trial, the investigators recruited nine patients with advanced solid tumors, including five with bladder cancer, whose diseases had progressed despite treatment with standard therapies. Patients received one to 13 cycles of everolimus and pazopanib.

One of five patients with bladder cancer had a complete response, as evaluated by imaging, which lasted for 14 months. To understand why his tumor responded dramatically, the investigators performed complete sequencing of the coding regions of his tumor genome, which included about 25,000 genes, and identified two mutations in mTOR.

The two mutations, mTOR E2419K and mTOR E2014K, had never been identified in humans, according to Wagle, although one of the mutations had previously been well studied by scientists in yeast and in human cell lines.

Wagle and colleagues conducted further laboratory studies to understand the nature of the two mutations, and found that they activated the mTOR-mediated cell signaling pathway, leading to sustained cancer cell proliferation. These mutations likely rendered the patient's cancer dependent on the mTOR pathway to survive, which is the likely reason the cancer became exquisitely sensitive to the mTOR inhibitor everolimus, explained Wagle.

"Results of our study suggest that we should make a catalogue of activating genome alterations in the mTOR pathway," said Wagle. "Patients with tumors that harbor these alterations might be particularly suitable for treatment with drugs like everolimus and other mTOR inhibitors.

"This is yet another example of how therapies targeted toward the genetic features of a tumor can be highly effective, and our goal moving forward is to be able to identify as many of these genetic features as possible and have as many drugs that target these genetic features as possible, so we can match the drugs to the patients," said Wagle. "There are many more patients out there with extraordinary responses to a variety of anticancer therapies, and it will be of great scientific and clinical value to study them."

Provided by Dana-Farber Cancer Institute