

# Patient's dramatic response and resistance to cancer drug traced to unsuspected mutations

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The DNA of a woman whose lethal thyroid cancer unexpectedly "melted away" for 18 months has revealed new mechanisms of cancer response and resistance to the drug everolimus, said researchers from Dana-Farber Cancer Institute and the Broad Institute of MIT and Harvard.

The investigators discovered two previously unknown mutations in the [cancer](#)'s DNA. One made the woman's cancer extraordinarily sensitive to everolimus, accounting for the remarkably long-lasting response. The second mutation was found in the DNA of her tumor after it had evolved resistance to the drug 18 months after treatment started, according to the study published in the October 9 issue of the *New England Journal of Medicine*.

The single case study illustrates how repeatedly sequencing a patient's cancer DNA – first prior to treatment and again when the tumor shows signs of resistance – can identify unsuspected "response" and "resistance" mutations that may help guide treatment of other patients.

"This is personalized, precision medicine at its best," said Jochen Lorch, MD, a thyroid cancer specialist at the Head and Neck Treatment Center at Dana-Farber and senior author of the report.

Having identified the mutation – in a gene called TSC2—that caused the patient's dramatic response to everolimus, researchers at Dana-Farber have opened a clinical trial to test the drug's effectiveness in other patients with TSC2 mutations. This type of trial, sometimes called a "basket" trial, is becoming more common as studies of patients who are "exceptional responders" are revealing previously unknown response mutations to a variety of drugs. A basket trial pools patients with a particular response mutation, regardless of the type of cancer they have.

"The study of patients with extraordinary responses can yield critically important insights," said Nikhil Wagle, MD, first author of the report. "These studies could help us develop methods for matching patients to drugs, highlight effective uses for otherwise 'failed' therapies, and design new therapeutic strategies to fight cancer." Wagle is an oncologist at Dana-Farber and is also affiliated with Brigham and Women's Hospital and the Broad Institute of MIT and Harvard.

Everolimus, sold as Afinitor, is approved to treat tumors associated with Tuberous Sclerosis Complex (TSC), a rare genetic disorder caused by mutations in TSC1 and TSC2 genes. It is also approved for use in brain tumors, pancreatic cancer, [kidney cancer](#) and [advanced breast cancer](#). Everolimus targets a protein kinase, mTOR, that regulates important cell functions including growth and proliferation, and which is overactive in some cancers.

The patient whose stunning response to the drug prompted the hunt for mutations was a 56-year-old woman diagnosed in 2010 with [anaplastic thyroid cancer](#). This form of thyroid cancer is almost always fatal within a few months. "No treatment has ever worked," said Lorch. The tumor spread to her lungs despite surgery, radiation and chemotherapy.

Lorch, who was leading a clinical trial of everolimus for a more treatable type of thyroid cancer, decided to include the woman and a handful of other anaplastic patients. To his surprise, after a few months the tumor shrank to a very small size. It remained that way for an unheard-of 18 months until it began to grow again. Using whole-exome DNA sequencing, which scans the protein-coding regions of the genome, the investigators discovered a mutation in the TSC2 gene.

The TSC2 protein normally suppresses mTOR activity; when it is mutated, mTOR is overactivated – making it a prime target for everolimus. None of the other anaplastic patients were so fortunate, which explains their failure to benefit from the drug.

Specimens taken from the tumor after it grew again revealed a mutation in the mTOR protein – not present in the original biopsy sample – that blocked everolimus from binding to it. This mutation – not seen before in humans – explained how the cancer acquired resistance to the drug.

But that was not the end of the story. Laboratory experiments

demonstrated that even the mutated, [resistant cancer cells](#) remained sensitive to a different type of mTOR inhibitor. A new drug of this type is about to enter clinical trials, and the patient described in the report, who is still alive four years after her diagnosis, is in line to receive the treatment, Lorch said.

He added that the case has broader implications, as the same mechanism of resistance to everolimus may be operating in other cancer types such as breast and kidney cancer, for which the drug is FDA-approved and frequently used. "Because we could show that an mTOR inhibitor that is using a different mechanism could overcome resistance in anaplastic [thyroid cancer](#), these findings could provide a rationale for treatment once resistance to everolimus occurs," Lorch said.

Provided by Dana-Farber Cancer Institute

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