# New drug extends survival in patients with drug-resistant prostate cancer

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A new drug, MDV3100, is improving the survival rate in men with advanced prostate cancer, results of a large, phase III clinical trial show. The drug is designed to block a type of cellular receptor that drives progression of prostate cancer. Based on the strength of the data from the phase III trial, it is anticipated that the biopharmaceutical company Medivation, which licensed MDV3100, will file a new drug application with the Food and Drug Administration later this year.

The presentation of the phase III data represents the culmination of a drug discovery project that began in 2004 in the academic research lab of Howard Hughes Medical Institute investigator Charles L. Sawyers. The story behind the development of MDV3100 illustrates the challenges academic scientists face in moving promising drug compounds from the research lab to the clinic. Sawyers collaborated with UCLA chemist Michael E. Jung on the design and development of MDV3100. Although MDV3100 is one of the first drugs to prolong survival in patients whose prostate cancer has become resistant to standard therapy, there was initially much skepticism in the pharmaceutical industry about whether such a drug – if it could be developed -- would work against this particularly difficult cancer.

"It is a highly unusual for a drug discovered in an academic lab to go all the way to FDA approval," Sawyers said. "The more typical scenario, as was the case with Gleevec, is for a drug company to discover a drug and develop it with the academic community." Gleevec is currently considered the front-line therapy for chronic myeloid leukemia.

Howard I. Scher, who is chief of the genitourinary service at Memorial Sloan-Kettering Cancer Center in New York (MSKCC), is reporting today on the results of the phase III clinical trial of MDV3100 at the American Society of Clinical Oncology Genitourinary meeting. He says the data from the study show that men treated with MDV3100 in the phase III trial had a median survival of 18.4 months, compared with 13.6 months for men treated with placebo.

"This translates into a 37% reduction in the risk of death in patients who are treated with MDV3100," said Scher. Scher is co-principal investigator of the AFFIRM clinical trial, a randomized, double-blind, placebo-controlled, multinational trial evaluating MDV3100 versus placebo in nearly 1,200 men with advanced prostate cancer who were previously treated with hormonal therapy and docetaxel-based chemotherapy. Docetaxel therapy interferes with cell division, and was the first drug shown to prolong survival in patients with advanced prostate cancer. The men participating in the AFFIRM study were enrolled because their cancer advanced despite receiving hormone therapy and chemotherapy. Last November, the AFFIRM study was stopped early when an interim analysis indicated that MDV3100 prolonged survival. Medivation plans to submit a new drug application to the FDA requesting approval for MDV3100 later this year. Sawyers, who is also at MSKCC, is a co-inventor of MDV3100 and was not involved in the clinical trials.

"The reduction in mortality in this phase III study was higher than we had anticipated," said Scher. "This drug is prolonging survival in patients with a particularly hard-to-treat cancer."

Scher added: "As a clinical scientist who's own research is focused on prostate cancer drug development, having the opportunity to follow the science and then lead the development of the drug from the treatment of the first patient through the end of phase III has been one of the most

satisfying and exhilarating experiences in my career."

Each year more than 210,000 new cases of prostate cancer are diagnosed in the United States. Male hormones (androgens) spur growth of prostate cancer cells. Current therapy for advanced prostate cancer involves treatment with drugs that block the androgen receptor. Anti-androgen drugs, such as bicalutamide, suppress the growth of cancer cells temporarily, but patients with advanced cancer eventually develop resistance to such drugs. About 32,000 men in the United States die each year from the disease.

## An Academic Path to Drug Discovery

In the mid-1990s, Sawyers, who was then at UCLA, decided to study how androgen receptors stoke the growth of prostate cancer and why men on hormone therapy ultimately relapse. Sawyers says that at that time, the prevailing notion was that the androgen receptor had nothing to with driving progression of advanced prostate cancer.

In Sawyers' mind it was absolutely critical to understand if androgen receptor activity drove the disease. But in the mid-1990s, scientists did not have the research tools to answer these critical questions. For example, researchers did not have the tumor samples they needed for such studies. "In an ideal world, we would examine material from patients who are in the early stages of their treatment and from those at the late stages," Sawyers said. "That's how we discovered Gleevec resistance. In prostate cancer, that's a non-starter. The tissues are just not available." Sawyers notes that it's technically challenging to try to isolate such tumor samples from patients with advanced prostate cancer because the tumor usually spreads into the bone.

So Sawyers' lab first spent time developing mouse models of advanced prostate cancer. In the mid-1990s, his team isolated prostate tumors

from human patients and grew the tumors in mice. They used the mice to study how prostate tumors responded to the presence or absence of androgen hormones. "We learned several important things by studying those mice," Sawyers said. "We could see that the tumors grew better in male mice. And we could see that if you castrated the male mice, the tumors stopped growing or shrunk. But within a month or two, they would grow back."

Most importantly, the mice become a tool to unravel the cause of resistance to hormone therapy. In 2004, Sawyers' team reported that resistance was caused by a rejuvenated androgen receptor. The team showed that some men with advanced prostate cancer become resistant to hormone therapy because the tumors actually increase production of androgen receptors. Sawyers became convinced that blocking the androgen receptor might be a viable treatment for prostate cancer even at this late stage of the disease. Despite the data emerging from his lab, he was greeted with skepticism from his contacts in the pharmaceutical industry. No one in pharma seemed interested in giving the idea a try, Sawyers said. "Developing new hormone receptor therapy for prostate cancer was just not on anyone's radar anymore," he said.

Sawyers had a decision to make. "I knew if we didn't do something, the idea was just going to sit," he said.

## "Why Don't We Do This?"

Before leading his lab on a leap into the unknown, Sawyers had a series of discussions with his research team about what their next steps should be. Should Sawyers continue to try to interest pharma or should the lab take on the drug discovery project? Sawyers recalls that Charlie Chen and Derek Welsbie -- his two trainees who conducted the mouse studies -- came to him and said, 'Why don't we do this?'" Sawyers was initially skeptical and responded: "Because we don't know how. This is pharma's

territory. We don't know what we're doing."

Sawyers said his skepticism stemmed, in part, from his firsthand experience in understanding how pharmaceutical companies approached cancer drug development. He played a key role in the development of two drugs for chronic myeloid leukemia, Gleevec and Sprycel, for which he shared the 2009 Lasker-DeBakey Clinical Medical Research Award.

Ultimately, Sawyers' experience in chronic myeloid leukemia and belief in what the biology was telling him led to his decision to mount a drug discovery effort in his lab. The goal was bold: Attempt to design a new generation of drugs that could block the androgen receptor where current versions of these drugs no longer worked.

Sawyers knew his HHMI funding would cover the early costs of the research – he could start the project right away without having to ask permission or write a grant application. One of his key early decisions was to ask UCLA synthetic chemist Michael Jung to join the project. "Finding Michael was absolutely key," Sawyers said. Although Jung had never developed a drug himself, he had synthesized some estrogen receptor compounds and was willing to give it a shot. "I think neither of us thought it would go very far," Sawyers said.

Jung scoured the patent literature for chemical compounds that could bind to androgen receptors. Jung noted that bicalutamide – a current drug for prostate cancer – actually bound the androgen receptor rather weakly. Furthermore, Jung found a patent that the French pharmaceutical company Roussel Uclaf had filed in the early 1990s describing a chemical compound that bound to androgen receptor about 100 times more strongly than bicalutamide. "The problem with that compound [RU59063] is that it stimulates – rather than inhibits – the androgen receptor," Sawyers said. "That's why it never went anywhere as a prostate cancer drug."

Jung decided to use RU59063 as a chemical scaffold -- making a series of chemical tweaks to try to convert it from an activator of the androgen receptor to an inhibitor. The researchers synthesized nearly 200 slightly different versions of the drug. They tested each one in the lab on prostate cancer cells that had been engineered to produce high levels of androgen receptor.

Their screens yielded a few new molecules that showed promise -- one of which became MDV3100. The MDV3100 compound bound tightly to the androgen receptor and did not show the cancer-stimulating effect of bicalutamide and other current anti-androgen drugs. After several more months of tinkering, the scientists improved the compound to the point where it was readily absorbed into the blood when taken orally and persisted in the bloodstream.

In early 2005, the researchers tested the new drug's effectiveness in mice with tumors derived from drug-resistant human prostate cancer cells. MDV3100 caused dramatic shrinkage of tumors in the mice. "At that point, I knew we had something. We all did," Sawyers said. "The question became what do we do next?"

Sawyers knew the next logical step was to try to move the compound into clinical trials, but that meant crossing the so-called "valley of death." The term refers to the point in drug development where a large infusion of cash is needed to move a compound from the research and development lab into the clinic. "At most academic research institutions, this is an untenable proposition," Sawyers said. "It's a tremendous step up in procedure, infrastructure requirements and cash, typically several million dollars."

Sawyers showed his group's data to several large pharmaceutical companies – all of them passed. But the promising laboratory studies did pique the curiosity of a much smaller biopharmaceutical company,

called Medivation. Medivation CEO David Hung brought in his team to scrutinize Sawyers' and Jung's lab notebooks, learning their procedures. They hired a lab to try to replicate the findings – which they did. Medivation licensed the compound for commercial development in 2005, and set up the clinical trials, initially at MSKCC and later expanded to other sites.

Looking back over the last decade of work on MDV3100, Sawyers says it's extremely gratifying now to see the drug helping to prolong the lives of those with advanced prostate cancer. He's still focused on the science. There's more to learn about how the drug works and how it ultimately causes the tumors to shrink. "We've been looking hard at those questions," he said. "One of the key questions we're trying to pin down is how does MDV3100 change the structure of the androgen receptor once it is bound to it. We have a ways to go before we know the answer. We also want to know how tumors might escape from MDV3100, so we can be ready with the next drug."

Sawyers and Jung are co-inventors of MDV3100 and could receive royalties if the drug is approved.

Provided by Howard Hughes Medical Institute

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