Drug Shows Activity in Men with Advanced Prostate Cancer

A new multi-center study shows that an experimental drug lowers prostate specific antigen (PSA) levels - a marker for tumor growth - in men with advanced prostate cancer for whom traditional treatment options have failed. The study, led by researchers at Memorial Sloan Kettering Cancer Center (MSKCC), is published today in *Science Express*, the online version of the journal *Science*. [PubMed Abstract]

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Most men with metastatic prostate cancer eventually build up resistance to the drugs that lower or block male hormones and develop a more aggressive form of the illness called castration-resistant prostate cancer (CRPC), or hormone-refractory disease. According to the study's findings, investigators studied two novel compounds, RD162 and MDV3100, and not only gained an understanding of their novel mechanism of action, but found that these agents showed activity in CRPC cells in culture and in mice.

The study also reports on a Phase 1/2 trial of MDV3100 in 30 patients with advanced CRPC and found that 22 out of 30 men showed declining PSA levels, and 13 out of 30 men (43 percent) had PSA levels fall by more than half.

Several years ago, the senior author of the study, Charles Sawyers, MD , and his colleagues at the University of California, Los Angeles (UCLA), uncovered a potential reason why metastatic prostate cancer patients eventually relapse with CRPC. This insight was used to discover RD162 and MDV3100.

"It's gratifying to know that our hypotheses about why men develop resistance to currently available treatments are confirmed and, most importantly, that there are already patients who are benefiting from our research," said Dr. Sawyers, Chair of the Human Oncology and Pathogenesis Program at MSKCC and a Howard Hughes Medical Institute investigator.

Current treatments for men who have advanced prostate cancers inhibit the activity of male hormones that help drive tumor growth. Many of these drugs disrupt the androgen (male hormone) receptor, which helps regulate cell proliferation, but tumors eventually become resistant to the drugs by expressing higher levels of the receptor. Preclinical studies by Dr. Sawyers and others have demonstrated that CRPC cells have increased expression of the androgen receptor and that overexpression of this receptor may contribute to the progression of disease.

Based on this information, Dr. Sawyers initiated a collaboration with Michael Jung, PhD, Professor of Chemistry at UCLA, that led to the discovery of a number of nonsteroidal, small molecule antiandrogen compounds, including MDV3100, which has been shown to retain its anticancer activity, even when the receptor's expression is elevated.

"The discovery and initial development of this drug was a collaborative effort all done in the academic setting, without reliance on the engine of the pharmaceutical industry that typically drives drug development," said Dr. Sawyers. Dr. Jung's group synthesized the compounds, which Dr. Sawyers' team then evaluated using prostate cancer mouse models engineered to highly express the androgen receptor, mimic progression to castration-resistant disease, and reflect the biology of clinical drug resistance.

According to the new study, the team of researchers tested various compounds to block the androgen receptor in CRPC cells. They chose to further evaluate the drug RD162 and a closely related compound, MDV3100. According to their findings, both drugs inhibit the androgen receptor function by impairing the receptor's ability to enter a CRPC cell's nucleus (called nuclear translocation), blocking it from binding to the DNA of its target genes, and preventing the cell from growing. They found that both compounds worked well in cells in culture, shrank tumors in mice, maintained tumor shrinkage for months, and prevented the androgen receptor from activating additional genes later in the process, or "downstream." Other currently approved drugs cannot disable the receptor in such a way.

The biopharmaceutical company Medivation, Inc., licensed RD162 and MDV3100 from UCLA in 2006 and has already completed enrollment in the first human trial of oral MDV3100 - a Phase 1/2 clinical trial, which was led by investigators at MSKCC and conducted through the Prostate Cancer Clinical Trials Consortium. The Consortium is sponsored by the Department of Defense and the Prostate Cancer Foundation. The trial enrolled men with metastatic, castration-resistant prostate cancer who relapsed after treatment with conventional hormone therapy and demonstrated anti-prostate cancer effects beginning with the first patient treated with MDV3100 at the lowest dose. Further positive results from an additional 110 patients who received the drug at higher doses were recently reported at the ASCO Genitourinary Cancers Symposium in February 2009.

"The declines in PSA levels observed thus far and the general tolerability of this treatment are encouraging," said Howard Scher, MD , a study co-autho and Chief of the Genitourinary Oncology Service at MSKCC. "I am looking forward to continuing the study of this drug, which has the potential to be a powerful tool in a limited arsenal of treatments against this deadly form of the disease." A Phase 3 trial is planned to begin later this year.

Researchers at MSKCC, UCLA, Oregon Health and Science University, University of Washington, Seattle, and Medivation, Inc., contributed to the research. Dr. Sawyers and several of the study's authors are co-inventors on patent applications covering RD162, MDV3100, and related compounds.

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