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New Nanopharmaceutical May Help Overcome Resistance to Certain Anticancer Drugs

BOSTON — The nanopharmaceutical drug CRLX101 is showing promise as a potential new treatment for cancers that develop resistance to antiangiogenic drugs and radiation therapy, according to clinical trial results presented here at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 19 – 23.

Antiangiogenic drugs are anticancer drugs designed to cut off the blood supply that brings tumors the nutrients they need to grow and survive, thereby starving and killing the tumor cells. Over time, however, tumors usually develop resistance to these drugs, often because of the upregulation of a protein called HIF-1 alpha. This protein promotes tumor invasion, metastasis, and cancer stem cell formation, all of which make tumors more aggressive and unmanageable. Antiangiogenesis drugs, as a result, have achieved limited success in the treatment of cancers.

"Reducing or eliminating resistance to antiangiogenic drugs could have meaningful implications for cancer patients. Up until now, HIF-1alpha has been considered impossible to target safely, but CRLX101 may change that," said Scott Eliasof, Ph.D., vice president of Cerulean Pharma Inc., in Cambridge, Mass. "CRLX101 has been shown to inhibit HIF-1alpha, and the clinical data we have obtained to date suggest that it has limited side effects, which may permit it to be effectively combined with other drugs. We believe that CRLX101 may have the potential to manage resistance to antiangiogenic and radiation therapies.

"Based on our preclinical data, we believe CRLX101 may have the potential to have a significant effect on pathological complete response in rectal cancer patients and on overall survival duration in patients with ovarian and kidney cancers," he added.

CRLX101's payload is the toxic anticancer drug, camptothecin, chemically conjugated into nanoparticles of 20-30 nanometers in diameter, using polymeric materials. When CRLX101 is taken up by the tumor cells, preclinical data suggest that the chemical linkers release the payload slowly, ensuring a steady and sustained release of camptothecin over time. This sustained drug release enables durable inhibition of an enzyme called topoisomerase-1, which leads to the inhibition of HIF-1 alpha.

Eliasof and colleagues have initiated four phase II investigator-sponsored clinical trials to test CRLX101 either as a single agent or in combination with an antiangiogenic drug. In one phase Ib/IIa trial, they have recruited nine patients to date with kidney cancer, a cancer that is known to

have high levels of HIF-1alpha. All patients had received prior antiangiogenesis therapy with limited success. When treated in this trial with CRLX101 in combination with the antiangiogenic drug bevacizumab, the researchers observed a 33 percent partial response rate in these patients, which is unprecedented according to Eliasof, because the overall response rate is typically 4 percent with bevacizumab alone and 2% with everolimus, the standard of care in this setting. Of note, the maximum tolerated dose of CRLX101 in combination with bevacizumab is the same as the monotherapy dose, suggesting it has low toxicity and higher tolerability. "Nine patients is a small sample size, but we are cautiously optimistic," he said.

An imaging clinical trial in patients with gastric cancers testing CRLX101 revealed more accumulation of the drug in tumors than in the neighboring healthy tissue, suggesting the compound has the potential to be target specific.

Two clinical trials to test CRLX101 as monotherapy in small-cell lung cancer and ovarian cancer are underway. Before year-end, Cerulean plans to launch two additional combination trials, according to Eliasof. The first clinical trial will combine CRLX101 with bevacizumab in ovarian cancer. The second clinical trial will combine CRLX101 with capecitabine and radiation in neoadjuvant rectal cancer.

"We have generated compelling preclinical data showing synergy when CRLX101 is combined with every antiangiogenic agent we have tested to date. Our focus now is on making a difference in the lives of patients in our various clinical trials."

Scott Eliasof is an employee of Cerulean Pharma Inc., which funded this study.

The 2013 International Conference on Molecular Targets and Cancer Therapeutics is being co-hosted by the American Association for Cancer Research (AACR), the National Cancer Institute (NCI), and the European Organisation for Research and Treatment of Cancer (EORTC).

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About the American Association for Cancer Research

Founded in 1907, the American Association for Cancer Research (AACR) is the world's oldest and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 34,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in more than 90 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 18,000 attendees. In addition, the AACR publishes eight peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the scientific partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and policymakers

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Presenter: Scott Eliasof, Ph.D.

Title: Synergistic activity of CRLX101, a nanopharmaceutical in phase 2 clinical trials, with antiangiogenic therapies mediated through HIF-1alpha inhibition: A translational research program

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Background: Antiangiogenic drugs reduce blood flow to tumors and thereby inhibit tumor growth by starving tumors of oxygen and nutrients. However, antiangiogenic drugs have achieved limited success as monotherapies, in part because of their induction of hypoxia and the concomitant up-regulation of hypoxia-inducible factor 1α (HIF-1α), now well implicated in the promotion of tumor angiogenesis, invasion, metastasis, and cancer stem cell formation. We describe here a translational research program to investigate whether the efficacy of

antiangiogenic drugs can be improved through combination with CRLX101, a camptothecin (CPT) containing nanopharmaceutical that inhibits both topoisomerase-1 and HIF-1α.

Material and methods: We will present preclinical and clinical projects conducted across several major research institutions intended to demonstrate the anti-HIF-1α activity of CRLX101, the capacity of this drug to block the epithelial-mesenchymal transition (EMT) and the formation of cancer stem cells, and the synergistic activity of CRLX101 given in combination with antiangiogenic drugs. We will further describe two ongoing clinical trials evaluating these hypotheses, one at the University of Pennsylvania in advanced renal cell carcinoma (RCC) and one at the Massachusetts General Hospital in relapsed ovarian cancer following progression through prior platinum-containing chemotherapy.

Results: A single dose of CRLX101 durably inhibits HIF-1α protein levels across multiple tumor types. Evaluation of CRLX101 in combination with bevacizumab, aflibercept or pazopanib in the A2780 ovarian xenograft tumor model demonstrates synergistic inhibition of tumor growth inhibition as well as increases in the rate of long-term survivorship. While all three antiangiogenic drugs alone increased HIF-1α protein levels, levels were inhibited in response to combination with CRLX101. In clinical evaluations, a CRLX101-bevacizumab combination appears safe and well tolerated with no dose limiting toxicities observed to date. Notable tumor decreases and long periods of progression free survival have been noted among patients treated with CRLX101-based mono and combination therapy.

Conclusions: Results generated through this translational research program suggest that CRLX101 can overcome HIF-1α-mediated acquired resistance to antiangiogenic drugs, supporting the use of CRLX101 in combination with antiangiogenic drugs as an exciting new paradigm for the treatment of cancer.