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DISCOVERIES

First-in-class ERK inhibitor ulixertinib (BVD-523) shows promise in preclinical cancer models

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Kansas City, MO. — A preclinical study indicates that ulixertinib (BVD-523) holds promise as a treatment for ERK-dependent cancers, including those whose tumors have acquired resistance to other treatments targeting the MAPK pathway. A third of all human cancers are driven by mutations in this pathway.

The study, sponsored by BioMed Valley Discoveries, was published online in Molecular Cancer Therapeutics. Supported by these preclinical findings, clinical trials of ulixertinib were initiated. A Phase 1/2a clinical trial was recently completed and additional trials are currently underway.

"Our findings suggest that targeting ERK activity, the most downstream kinases of the MAPK signaling pathway, may be a rational cornerstone therapy for many tumors," said Dean Welsch, Ph.D., Head of Pharmacology at BioMed Valley Discoveries and lead study author. "ERK inhibitors may have the potential to address issues of drug resistance that have plagued other targeted therapies."

The mitogen-activated protein kinase (MAPK) signaling pathway is one of the most well studied pathways in human biology. This pathway behaves like an intracellular series of switches. A signal activates a cell receptor, which in turn activates RAS, which activates RAF, which activates MEK, which then activates ERK. Switched-on ERK activates numerous targets that enable a cell to grow, proliferate, and survive. In this way, ERK plays a key role in communicating extracellular signals that drive key cellular functions. In many types of cancer, this highly coordinated series of cascading events becomes dysregulated, often as a result of mutations. Dysregulation of the pathway causes cells to grow out of control. Because of its established importance in numerous cancers, this pathway has been the focus of drug discovery efforts for many years.

While no compounds have effectively targeted RAS, drugs designed to inhibit RAF or MEK have improved clinical outcomes for patients with metastatic melanoma and other tumor types. Unfortunately, the majority of patients given these targeted therapies eventually develop resistance to the drugs, and their disease progresses. Because ERK resides at the end of the MAPK signaling pathway, ERK inhibition may provide a unique opportunity to extend the duration of response seen with available treatments.

Results in this study characterizing ulixertinib included the demonstration of potential anti-tumor activity in preclinical *in vitro* assays as well as *in vivo* models, including studies designed to exemplify the potential for treating patients who had never received a pathway inhibitor and those that had acquired resistance. The authors showed that ulixertinib could arrest the growth of cancer cell lines in the laboratory. Furthermore, they demonstrated that the drug could inhibit the growth of tumors, and even cause them to regress in *BRAF* and *RAS* mutant xenograft models. Studies investigating ulixertinib in combination with BRAF inhibitors highlighted the potential for using this agent with existing therapies.

Importantly, cells engineered to be resistant to current therapies were found to retain their sensitivity to ulixertinib. This finding with single-agent ulixertinib was confirmed and extended using *in vivo* resistance models.

Finally, the researchers studied the emergence of resistance to ulixertinib. They found that single-agent treatment of cancer cells with ulixertinib was quite durable and that it was more challenging to develop resistance to ulixertinib than other agents targeting upstream components of the MAPK signaling pathway.

"Because the ERK inhibitor targets the last step in this pathway, we think ulixertinib has the potential to effectively address aberrant pathway signaling resultant from upstream dyregulation – including those as a consequence of mutations to RAS, RAF, MEK, or ERK," said Welsch. "These encouraging preclinical studies suggest multiple opportunities for ulixertinib in various cancers. We look forward to the results from ongoing/planned clinical trials to help define how this agent might eventually help cancer patients".

BioMed Valley Discoveries launched and successfully completed a multi-center clinical trial of the drug in

patients with metastatic or advanced-stage cancer. The company also has several investigator-initiated trials planned or underway looking at other indications for ulixertinib, alone and in novel combination therapy regimens.

Ulixertinib received US Food and Drug Administration (FDA) Fast Track designation in September 2015, which allows for an expedited FDA review of drugs and therapies that treat a serious or life-threatening condition and fill an unmet medical need. Vertex Pharmaceuticals Inc discovered ulixertinib. BioMed Valley Discoveries licensed the compound at the clinical candidate stage and has advanced the compound from the late preclinical stage to the completion of Phase 1/2a.

Co-authors of the study include Ursula A. Germann, Brinley F. Furey, William Markland, Russell R. Hoover, Alex M. Aronov, Michael Hale, Diane M. Boucher, Gabriel Martinez-Botella, Matthew Fitzgibbon, and Mark Namchuk of Vertex Pharmaceuticals Inc; Jeffrey J. Roix, Anna Groover, Gary DeCrescenzo, Caroline M. Emery, and Saurabh Saha of BioMed Valley Discoveries; David A. Sorrell of Horizon Discovery Ltd; Paul Shapiro and Ramin Samadani of University of Maryland School of Pharmacy; Michael J. Wick of START; and Kathryn Meshaw of Charles River Discovery Services. The study was funded by BioMed Valley Discoveries.

About BioMed Valley Discoveries (BVD)

BioMed Valley Discoveries is a clinical stage biotechnology company focused on addressing unmet medical needs in a variety of therapeutic and diagnostic areas. In addition to the ERK inhibitor, BVD's portfolio includes an oncolytic bacteria that has completed enrollment for a Phase I study, a selective phosphoinositide 3-kinase gamma inhibitor in late preclinical testing, and two early-stage antibodies targeting the tumor microenvironment.

Operating since 2007, BioMed Valley Discoveries was established by Jim Stowers Jr., founder of the asset management firm American Century Investments, and his wife Virginia, to advance new medical innovations to improve the lives of patients with difficult-to-treat diseases. BVD is owned by a supporting organization of the Stowers Institute for Medical Research, a non-profit, basic biomedical research organization. Since 2000, the Stowers Institute has received over $1.3 billion in dividend payments from American Century. The Institute has invested a portion of its institutional funds in BVD, whose profits accrue to the benefit of the Institute.

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