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Preclinical results support entinostat's role in targeting the tumor microenvironment

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Syndax Pharmaceuticals, a clinical stage biopharmaceutical company developing entinostat and SNDX-6352 in multiple cancer indications, in collaboration with The Wistar Institute and Indiana University Melvin and Bren Simon Cancer Center, today announced the publication of a preclinical report demonstrating that entinostat, Syndax's oral, Class-I histone deacetylase inhibitor, enhances the antitumor effect of PD-1 (programmed death receptor-1) blockade through the inhibition of myeloid derived suppressor cells (MDSCs).

The article, titled "Entinostat Neutralizes Myeloid Derived Suppressor Cells and Enhances the Antitumor Effect of PD-1 Inhibition in Murine Models of Lung and Renal Cell Carcinoma," was published in *Clinical Cancer Research* and is available online.

Researchers tested the effect of combining entinostat with an anti-PD-1 monoclonal antibody that enhances the T cell-mediated antitumor immune response. The studies were conducted in two mouse models of renal cell carcinoma and lung cancer and included a series of in vitro experiments aimed at characterizing the effects of this combined treatment on the myeloid derived suppressor cells (MDSCs), a highly immunosuppressive population of tumor infiltrating immature myeloid cells. The results indicated that entinostat has an inhibitory effect on MDSC immunosuppressive function both in vivo and in vitro, which results in enhanced anti-tumor activity of the combination.

"The use of PD-1 inhibitors in the treatment of solid tumors has

demonstrated significant benefit, but many patients still present with progressive disease following treatment," said co-lead researcher Dmitry I. Gabrilovich, M.D., Ph.D., Professor and Program Leader, Translational Tumor Immunology Program, The Wistar Institute. "We have previously demonstrated the role of MDSCs as important mediators of resistance to immune therapy approaches. The results from our new study suggest that entinostat may enhance the anti-tumor efficacy of PD-1 targeted therapy through MDSC targeting, potentially providing an effective combination treatment approach for patients with solid tumors, including lung and renal cell carcinoma."

"Our group has previously reported that entinostat enhances the antitumor effect of high dose interleukin 2 in renal cell carcinoma both in mice and patients. These new findings confirm that the combination of entinostat with immunotherapy has significant immunomodulatory activity and may offer increased benefit for a larger population of patients with renal cell carcinoma, non-small cell lung cancer and other solid tumors with an immunosuppressive tumor microenvironment," said co-lead researcher Roberto Pili, M.D., Robert Wallace Miller Professor of Oncology and Professor of Medicine and Urology at IU Simon Cancer Center. "We are pleased to have obtained the same results in two different laboratories and we look forward to translating these preclinical findings into combination approaches with entinostat to enhance the clinical activity of immune checkpoint inhibition."

"We are excited that these current data support and extend initial observations generated at Johns Hopkins," said Peter Ordentlich, Ph.D., Chief Scientific Officer of Syndax. "Entinostat has now been shown to impact MDSCs in multiple preclinical tumor models across several laboratories as well as from blood samples taken from entinostat treated patients. These data collectively provide strong rationale for combining entinostat with immunotherapies for the treatment of solid tumors. We look forward to providing additional updates from the entinostat clinical

development program."

Provided by The Wistar Institute