PT2977

Hypoxia-inducible factor 2a (HIF-2a), a transcription factor, has been established as an oncogenic driver in clear cell renal cell cancer (ccRCC). The first HIF-2a antagonist being evaluated in clinical development, PT2385, has demonstrated clinical activity in ccRCC patients who had previously been treated with multiple lines of therapy. There is continuing effort to characterize additional HIF-2a antagonists possessing attributes that may contribute to enhanced clinical activity. PT2977 is a novel HIF-2a antagonist with improved potency in preclinical tumor models compared to PT2385. This improvement arises from enhanced biochemical and cellular potency, an improvement in plasma protein binding, and diminished metabolic clearance in vivo relative to PT2385. PT2977 exhibits favorable metabolic stability and pharmacokinetic characteristics when dosed orally in multiple preclinical species. Allometric scaling of the preclinical data predicts PT2977 to be suitable for oral once-daily dosing in humans. PT2977 inhibits expression of HIF-2a target genes in tumor cells and induces complete stasis or regression in ccRCC xenografts.

A strong pharmacokinetics/pharmacodynamics correlation is observed in tumors from xenograft models treated with PT2977. Gene expression analyses of ccRCC xenografts treated with PT2977 reveal extensive modulation of genes in the tumor cells as well as in immune cells. Immune phenotyping of tumors treated with PT2977 confirms that HIF-2a antagonism results in a reduction in the number of immunosuppressive myeloid-derived cells, including neutrophils and macrophages. Treatment with PT2977 also results in an influx of mature dendritic cells. These observations are consistent with HIF-2a exerting an immunosuppressive effect on the tumor microenvironment, in addition to driving angiogenesis and the proliferation and viability of tumor cells. With its favorable preclinical profile, PT2977 is well positioned to further reveal the broader therapeutic potential of HIF-2a antagonism for the treatment of cancer, as a single agent or in combination with other immune-modulating agents.

Peloton has succeeded in creating a series of orally-available small molecules that bind to HIF-2α and inhibit its transcription of disease-promoting genes.

PT2977 is a once-daily, orally-active agent that blocks hypoxia-inducible factor-2α (HIF-2α). It is a structurally-related compound designed to be more potent with less pharmacokinetics variability compared to PT2385.

PT2977 has demonstrated anti-tumor activity with a favorable safety profile in an early-stage clinical study in patients with solid tumors.

Given its superior profile, PT2977 is the lead agent being developed in oncology by Peloton. In addition to the international Phase 2 trial of PT2977 in VHL disease-associated RCC, Peloton is evaluating the agent in a Phase 1 clinical trial for the treatment of advanced RCC.