PT2385: HIF-2α Antagonist for the Treatment of VHL Mutant ccRCC

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Disclosure Information

Eli Wallace

I have the following financial relationships to disclose:

- I am a stockholder and employee of Peloton Therapeutics, Inc.
- and -

I will not discuss off label use or investigational use in my presentation.

HIF-2α : Regulated by O₂ in Concert with pVHL

- 70% of VHL disease patients develop ccRCC
- ccRCC is the leading cause of mortality in VHL patients
- 95% of patients with sporadic ccRCC have defective pVHL
- Loss of VHL results in constitutive activation of HIF-2α

HIF-2α : Driver of VHL-Associated ccRCC

- All pVHL defective ccRCC patients express HIF-2α
- Loss of VHL results in constitutive activation of HIF-2α
- HIF-2α knock-out inhibits tumor growth1,2
- Stabilization of HIF-2α overrides tumor suppressor function of pVHL3

- Hypothesis: Inhibiting HIF-2α will provide therapeutic benefit in the treatment of ccRCC

1Kondo et al. PLoS Biology 2003, 1, 439
2Zimmer et al. Mol Cancer Res 2004, 2, 89
3Yande et al. Cancer Cell 2002, 1, 297
PT2385: A Potent and Selective HIF-2α Antagonist

- PT2385 binds to PAS-B domain of HIF-2α
- Binding blocks HIF-2α:ARNT heterodimerization

**Hypoxia-Inducible Factor-2α and Cancer**

HIF-2α drives the expression of several genes involved in cancer:
- Cyclin D1
  - Cell Cycle Progression
- VEGFA
  - Angiogenesis
- Plasminogen activator inhibitor-1
  - Angiogenesis / Survival
- CXCR4
  - Metastasis
- CD74
  - Immune Response
- GLUT1
  - Cell Metabolism
- TGFα
  - Growth Factor Signaling
- Arginase 1
  - Inflammatory Response

HIF-2α regulates the expression of multiple genes impacting:
- proliferation
- angiogenesis
- metastasis
- immune evasion

**PT2385: Selective Antagonism of HIF-2α Over HIF-1α**

Hep3B cells (Hepatoma, VHL+/+, HIF-1α+/+, HIF-2α+/+)
- Cells treated for 24 h with PT2385 at 21% O₂ (normoxia) or 1% O₂ (hypoxia)

<table>
<thead>
<tr>
<th>Gene</th>
<th>HIF-2α specific genes</th>
<th>HIF-1α specific genes</th>
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<tr>
<td>EPO</td>
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<td>PDK1</td>
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- PT2385 inhibits expression of HIF-2α target genes with no effect on HIF-1α target genes

**PT2385: Efficacious in 786-O Xenograft**

786-O subcutaneous xenograft model of ccRCC (VHL−/−, HIF-1α−/−, HIF-2α+/+)

- Tumor regressions with 3 and 10 mg/kg, p.o., b.i.d. dose
- Similar efficacy in A498 ccRCC xenograft (VHL−/−, HIF-1α−/−, HIF-2α+/+)

All dose groups well tolerated
PT2385: Inhibits Tumor-Derived VEGFA Protein Levels

786-O subcutaneous xenograft model of ccRCC (VHL−/−, HIF-1α−/−, HIF-2α+/+)
Six doses of PT2385 p.o., b.i.d.; plasma protein VEGFA measured 12 h post final dose

- PT2385 has no effect on mouse VEGFA levels (data not shown)
- PT2385 inhibits mouse kidney EPO gene expression (data not shown)

PT2385: Inhibition of the Expression of Multiple Genes

786-O subcutaneous xenograft model of ccRCC (VHL−/−, HIF-1α−/−, HIF-2α+/+)
Six doses of PT2385 p.o., b.i.d.; tumor mRNA measured 12 h post final dose

- Dose-dependent inhibition of HIF-2α regulated genes

PT2385: Inhibits Proliferation and Angiogenesis

786-O subcutaneous xenograft model of ccRCC (VHL−/−, HIF-1α−/−, HIF-2α+/+)
Six doses of PT2385 10 mg/kg p.o., b.i.d.; tumor tissue collected 12 h post final dose

- PT2385 treatment reduces proliferation (Ki67) and angiogenesis (CD-31)

PT2385: Efficacious in Sunitinib Refractory PDX Model

PDX subcutaneous xenograft model of ccRCC (VHL−/−, HIF-1α−/−, HIF-2α+/+)
- Model derived from a patient refractory to both sunitinib and everolimus

- PT2385 efficacious in sunitinib refractory model
- Tumor expresses both HIF-1α and HIF-2α
**Effect of PT2385 and Sunitinib on Blood Pressure**

VEGFR TKIs and VEGFA mAb are associated with hypertension in patients. The effect of sunitinib on blood pressure and heart rate are recapitulated in rats.

- Sunitinib significantly increased blood pressure at its maximally efficacious dose.
- Sunitinib also significantly reduced (10-20%) heart rate.

**PT2385 – 101**

**Objectives & Design**

**Primary Objective:**
- To identify the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose of PT2385 tablets in patients with advanced clear cell renal cell carcinoma (ccRCC).

**Secondary Objectives:**
- To evaluate the safety profile of PT2385.
- To determine the pharmacokinetic (PK) profile of PT2385.
- To assess the pharmacodynamic (PD) effects of treatment with PT2385.
- To assess the anti-tumor activity of PT2385.

**Design:**
- 3+3 Design
- Dose limiting toxicity (DLT) observation period 3 weeks
- Expansion to 25 additional patients at MTD or RP2D

**Effect of PT2385 and Sunitinib on Blood Pressure**

- PT2385 had no effect on blood pressure at 5x the maximal efficacious exposure.
- PT2385 had no effect on heart rate or any other ECG parameter.
- PT2385 has a favorable preclinical safety profile.

**PT2385-101: Pharmacodynamic Response in Patients**

Erythropoietin expression is regulated by HIF-2α.

- In patients, target engagement, as measured by diminution of erythropoietin expression, is exposure related, rapid and pronounced.
PT2385: Novel Therapy for ccRCC

Potent, Selective, Orally Bioavailable, First-In-Class HIF-2α Antagonist

• In preclinical studies:
  • PT2385 binds directly and specifically to HIF-2α — selectively antagonizes HIF-2α over HIF-1α
  • PT2385 inhibits expression of HIF-2α regulated genes in a dose dependent manner in vivo
  • PT2385 inhibits tumor growth and angiogenesis — selectively inhibits tumor derived VEGFA
  • Favorable preclinical safety profile — modest and reversible effect on RBC compartment with no hypertension
• Currently in Phase 1 clinical trial in patients with advanced or metastatic ccRCC
  • Dose escalation stage complete: recommended Phase 2 dose determined
  • Expansion arm recruitment complete

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Patients and their families

www.clinicaltrials.gov: NCT02293980

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