**Background**

- Renal cell carcinoma (RCC) accounts for ~3% of adult malignancies in the US, with an estimated 61,000 new cases and 13,000 deaths in 2011 (seer.cancer.gov事实表/factshp13p5.dte).
- The 5 year survival rate for metastatic RCC is ~11%, and despite the recent approval of several targeted agents, progress is short-lived and occurs only in a subset of patients.
- Approved drugs for advanced RCC include 2 classes of targeted agents: VEGF (bevacizumab, sunitinib, sorafenib, temsirolimus, everolimus, rapamycin) and mTOR (rapalogs).

**PWT33597 inhibitors cell proliferation**

**Table 1.** Dose values were determined using Kinase-Go (PI3K, alpha, delta), ADP-Go (PI3K beta, gamma), and Lance Ultra (mTOR) assays.

**Figure 3.** A) Bright field microscopy shows presence of cystoidic vacuoles following 72 hour culture. PWT33597 was tested at 1x, 3x or 6x the (second line) concentration. B) Rapamycin was tested at 500 nM (CL), 50 nM (HC), 1 nM and without chloroquine (CEP, left), an autophagy inhibitor. Actin (orange staining) showed positive staining following PWT33597 treatment (data not shown).

**Superior xenograft efficacy than standard of care agents**

**Figure 4.** A) Mean tumor volume (mm^3) in RCC xenografts with rapamycin, sorafenib, and PWT33597. A) Mice with large 786-O tumors (mean 550 mm^3) were treated with PWT33597 (75 mg/kg QD, PO), vehicle only or sunitinib (35 mg/kg QD, PO). B) 786-O xenografts were treated with either vehicle or sorafenib (35 mg/kg, PO) or 16 mg/kg sunitinib (PO) for 14 days respectively, followed by PWT33597 (75 mg/kg, PO) until day 35. A separate group was treated with vehicle only for 18 days.

**Summary**

PWT33597 is a balanced dual inhibitor of PI3K alpha and mTOR, and inhibits in vitro RCC proliferation and mTOR/PI3K signaling.

In the renal 786-O xenograft model, tumor growth inhibition by PWT33597 was superior to that of approved agents rapamycin or sorafenib, or the PI3K inhibitor GDC-0941.

PWT33597 rapidly regressed large 786-O xenografts, and evidence of increased apoptosis was apparent by IHC.

To assess a potential clinical treatment paradigm, PWT33597 was administered after sorafenib treatment, and xenograft tumor regression was observed.

These data provide rationale to test PWT33597 in patients with RCC.

**The PI3K/mTOR inhibitor PWT33597 regresses 786-0 renal xenografts**

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**Abstract #3737**

AACR 2012

**References:** Abou Youssif et al., Cancer 2011, 117(24): 3679-86; Gilroy et al., J. Translational Medicine 2011, 9(123); Westergaard et al., Unpublished 2008, 80(273).

**Figure 1.** Pathway to tumor progression in RCC based on its target profile:

• PI3K/PIK3CA/PIK3R1 (PI3K)
• PIK3R2/3 (PI3K II)
• PIK3R1 (PI3K III)
• PI3K inhibitor screening
• 18F-FDGPET/CT and IHC assays.

**Figure 2.** Effects of PWT33597, GDC-0941 and Rapamycin on cell proliferation/viability in 786-O cells. Rapamycin consistently shows only partial inhibition of cell viability compared to 786-O and RCC cell lines.

**Figure 3.** A) Western blot analysis in 786-O cells following 2 hour treatment with PWT33597 (80 mg/kg QD, PO).