An Open-Label Phase II Study to Evaluate PT2385 for the Treatment of Von Hippel-Lindau Disease-Associated Clear Cell Renal Cell Carcinoma

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BACKGROUND

Patients with von Hippel-Lindau (VHL) disease have an increased risk for developing clear cell renal cell carcinoma (ccRCC) as well as other benign and malignant tumors in multiple organs.

Current treatment of VHL associated ccRCC is based on a program of surveillance and surgical intervention to minimize the risk of metastasis, as no systemic therapies are currently approved for use in the localized setting.

HIF-2α is believed to be a key mediator of oncogenesis in renal tumors with VHL alterations. PT2385 is a first-in-class small molecule inhibitor of HIF-2α which has shown efficacy in advanced sporadic ccRCC.

Here we report on the safety and efficacy of oral PT2385 in VHL patients with localized ccRCC.

METHODS

Eligible patients were required to have at least 1 measurable VHL associated ccRCC tumor confined to the kidney and no solid ccRCC tumor greater than 3.0 cm.

PT2385 was administered orally at a dose of 800 mg twice daily.

The primary endpoint of the study was overall response rate (ORR) in renal tumors, based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1).

Secondary and exploratory endpoints included evaluation of safety, pharmacokinetics, response in VHL-associated non renal tumors, and modulation of erythropoietin (EPO).

The study was halted after enrollment of four patients owing to the inconsistent pharmacokinetic characteristics of the drug, in favor of a second-generation HIF-2α inhibitor with more reliable pharmacologic properties.

PATIENTS

Table 1. Patient Baseline Characteristics and Follow Up by Patient

Pt	Age and Gender	ECOG	Baseline VHL Manifestations	Prior ccRCC Resected	Weeks on Therapy	# of Renal Tumors	Median baseline tumor size (cm)
1	69 F	1	renal tumors, pancreatic cysts, spinal cord hemangioblastomas, bilateral retinal hemangioblastomas	LPN 5.5 cm T1b	28	2	2 (1.6-2.4)
2	60 F	0	renal tumors, pancreatic cysts, cerebellar and spinal cord hemangioblastomas, bilateral retinal hemangioblastomas	RPN x2 LPN all T1a	143	2	2.1 (1.5-2.6)
3	53 F	0	renal tumors, pancreatic cysts and neuroendocrine tumor (distal panc 2010), spinal cord hemangioblastomas, right retinal hemangioblastomas	LPN 3.5 cm T1a	13	1	1.7
4	51 F	0	renal tumors, pancreatic cysts and neuroendocrine tumor, cerebellar hemangioblastoma	R RFA x 2 RPN 5.0 cm T1b	13	1	2.1

Legend. ECOG = Eastern Cooperative Oncology Group; VHL = von Hippel Lindau; ccRCC = clear cell renal cell carcinoma; distal panc = distal pancreatectomy; LPN = left partial nephrectomy, RPN = right partial nephrectomy, RFA = radio-frequency ablation.

RESULTS

Four patients were enrolled on study with median follow-up of 19 weeks (range 13-143).

All patients had stable disease (SD) as their best response at latest assessment, including 1 patient who has remained on study for 2.7 years.

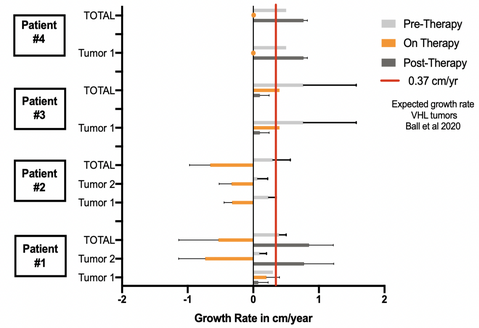
Median growth rate of individual tumors on therapy was -1 mm/yr (range -3 to +4), compared to a median of 3mm/yr (1-7) prior to therapy, and 3mm/yr (2-7) after termination of therapy.

VHL manifestations in other organ systems (hemangioblastoma, pancreatic neuroendocrine tumor) remained stable or improved. 2/3 patients with ocular manifestations had improvement in retinal hemangioblastomas and one had SD as the best response. 3/3 patients with spine hemangioblastomas had SD. 1 patient with 2 pancreatic solid lesions exhibited a 44% decrease in size of each lesion.

All patients had at least one grade 1-2 AE, most commonly a mild impairment in concentration manifested as word-finding difficulties. Dose was interrupted in 3 patients. There were no grade 3-4 AEs related to PT2385.

SUM TOTAL GROWTH RATES

Figure 1. Sum Total Growth Rate of Individual Lesions for Each Patient



Legend. For each patient, the tumor growth rate in cm/year is shown for each individual tumor as well as in sum total. Growth rates based on time intervals pre and post therapy are also shown. The red line at 0.37 cm/year shows the expected growth rate for a VHL ccRCC tumor based on a large natural history study.

SAFETY PROFILE

Table 2. Treatment Related Adverse Events

Adverse Event	# (%) pts affected (G1-4)	# (%) G1	# (%) G2	# (%) G3	# (%) G3 - 4
Nausea	4 (100)	4 (100)	0 (0)	0 (0)	0 (0)
Dysphasia	3 (75)	0 (0)	3 (75)	0 (0)	0 (0)
Fatigue	3 (75)	3 (75)	0 (0)	0 (0)	0 (0)
Insomnia	2 (50)	2 (50)	0 (0)	0 (0)	0 (0)
Headache	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)
Diarrhea	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)
Anemia	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)
Hypophosphatemia	1 (25)	0 (0)	1 (25)	0 (0)	0 (0)
Hypernatremia	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)
Dysguesia	1 (25)	0 (0)	1 (25)	0 (0)	0 (0)
Dysesthesia	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)
Dry Eyes	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)

CONCLUSIONS

In the first study of a novel HIF-2a inhibitor in patients with VHL, PT2385 demonstrated stabilization of disease in VHL-associated clear cell RCC and non renal tumors, and showed an acceptable safety profile. Further evaluation of this class of agents in VHL is warranted, and a second-generation HIF-2α inhibitor (MK 6482) is currently the subject of a phase 2 trial in this population.

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