A phase I study of pazopanib combined with bevacizumab in patients with metastatic renal cell carcinoma or other advanced refractory tumors.

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BACKGROUND

Since previous experiments of bevacizumab with VEGFR tyrosine kinase inhibitors showed overlapping and limiting toxicities, a dose-finding study was designed to explore the safety and feasibility of the combination of a new VEGFR inhibitor pazopanib (PZP) with bevacizumab (Bev), in mRCC treatment-naive patients (pts) or in pts with other advanced refractory solid tumors.

METHODS

An 3 + 3 + 3 design

3 to 9 pts were sequentially enrolled in 3 steps to receive 1 of 4 escalated doses of PZP in combination with Bev.

Study drugs

Dose level (DL)	Bev q2w	PZP/d
DL1	7.5 mg/kg	400 mg
DL2	7.5 mg/kg	600 mg
DL3	10 mg/kg	600 mg
DL4	10 mg/kg	800 mg

The maximum-tolerated dose (MTD) is met if a dose-limiting toxicity (DLT) is observed during the first 8 weeks in at least :

Step 1: 2 out of 3 pts,
Step 2: 3 out of 6 pts,
Step 3: 3 out of 9 pts.

Objectives

- To determine the MTD of the combination, as assessed by the incidence rate of DLT (any grade 4 and/or specific grade 3 toxicities) during the first 8 weeks ;
- To characterize the pharmacokinetic (PK) profile of PZP in combination with Bev.

Main inclusion criteria

- mRCC pts with no previous treatment, others ≤ 2 lines
- ECOG PS ≤ 1
- ALT and AST ≤ 2.5xULN
- Serum creatinine ≤ 1.5 mg/dl or creatine clearance ≤ 50 ml/mn
- Absence of uncontrolled hypertension

Independent Data Safety Monitoring Board

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PATIENTS CHARACTERISTICS

19 pts were enrolled with the following characteristics:

Characteristics		N=19	
Age (median / range)		61 / 41-78	
		n	%
Male		13	68.4
Nephrectomy		7	36.8
Localizations	mRCC	7	36.8
	Melanoma	2	10.5
	Pancreatic cancer	2	10.5
	Adrenocortical carcinoma	1	5.2
	Mesothelioma	1	5.2
	Oesophageal cancer	1	5.2
	Bladder cancer	1	5.2
	Seminoma	1	5.2
	Cervix cancer	1	5.2
	Colorectal cancer	1	5.2
	Breast cancer	1	5.2

PHARMACOKINETICS (PK) RESULTS

Preliminary results of PK analysis showed a **significantly higher PZP AUC at steady-state in pts with DLT**. Moreover, a trend of **lower PZP apparent clearance was observed in nephrectomized pts:** 0.52 +/- 0.14 L/h vs. 0.75 +/- 0.28 L/h for pts without nephrectomy (NS).

DL PZP	400 mg	600 mg
Nb pts	9	6
Mean AUC D15 (µg/mL.h)	749 +/- 259	942 +/- 305
%CV	34	

(%CV for interindividual variability in apparent clearance)

	DLT+ (n = 3)	DLT- (n = 12)
Mean AUC D15 (µg/mL.h)	1112	755
Standard deviation	89	272
One sided Student test	p=0.02	

SAFETY / EFFICACY

N	DOSE LEVEL	DLT	BEST RESPONSE	MEAN RESPONSE DURATION
9	DL1: Bev 7.5 mg/kg + PZP 400 mg	No DLT	1 PR 6 SD 2 PD	> 15 months 4.9 months
10	DL2: Bev 7.5 mg/kg + PZP 600 mg			
	• Step 1 (3 non-nephrectomized pts)	• No DLT	• 1 PR 2 PD	• 7.3 months
	• Step 2 (3 nephrectomized pts)	• 3 DLT : - grade 3 transaminitis - grade 3 pulmonary embolism - grade 3 reversible MAHA**	• 3 SD	• 1.6 months
	• Step 3 (4* non-nephrectomized pts)	• 2 DLT : - grade 3 transaminitis, grade 2 hyperbilirubinemia - grade 3 MAHA	• 1 PR 3 SD	• > 6 months 1.3 months

* 1 pt with early drop out for non authorized reduced dose at week 5

** Microangiopathic hemolytic anemia

⇒ After the end of the Step 2 in DL2:

- IDSMB approved in November 2011 the enrolment of 3 non-nephrectomized pts in the DL2 Step 3.
- MTD of the combination of PZP and Bev is 400 mg/d and 7.5 mg/kg respectively.

CONCLUSION

The MTD of the combination of PZP + Bev is 400 mg/d and 7.5mg/kg respectively, in all pts. All DLT were expected toxicities, 2/5 being linked to VEGF pathway inhibition. Unexpected effect of nephrectomy status was observed on PZP PK. DLT occurrence was correlated with PZP AUC at D15 according to preliminary PK results (n=15). To note, 6-month persistent PR was observed in 3/19 pts in preliminary efficacy analysis. As previously reported with other TKIs combined with Bev, it is impossible to combine full dose PZP with full dose Bev. An extension cohort to validate PK data is of interest.

References

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