A phase II study of apatinib, a highly selective inhibitor of VEGFR-2, in patients with metastatic solid tumors without standard treatment options

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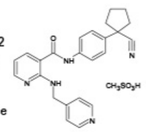
Background



- Apatinib (YN968D1) is an orally administered, highly selective tyrosine kinase inhibitor of VEGFR-2 with suggested efficacy in treating various solid tumors including gastric cancer
- VEGFR-2 signaling has a pivotal role in tumor angiogenesis with many clinical studies demonstrating that selective inhibition of VEGFR-2 can limit tumor growth and disease progression, resulting in improved overall survival
- Apatinib has been studied in China in many clinical trials treating a number of solid tumors and has recently been approved by the Chinese FDA for treatment of advanced gastric cancer
- This study reports the first experience of safety and efficacy of apatinib outside of China including Korean and Caucasian patients

Objectives

Primary Objectives

- To evaluate the safety and tolerability of 28-day cycles of 850 mg apatinib mesylate in subjects who have attempted at least one prior standard chemotherapy

Secondary Objectives

- To evaluate the pharmacokinetics (PK) profile of apatinib after oral administration of a single dose and at steady state
- To obtain information regarding the efficacy of apatinib in human subjects with solid tumors
- To obtain information regarding the pharmacodynamics (PD) of apatinib in human subjects with solid tumors

Methods

Study Design

This clinical trial (NCT01497704) was a 2-part Phase I/IIa, open-label, safety, and preliminary efficacy study of apatinib in subjects with solid tumors who were refractory (or intolerable) to conventional therapy

- Part 1 was a Phase I dose escalation study, enrolling subjects with any solid tumor
- Part 2 was a Phase IIa study, enrolling subjects with gastric cancer, NSCLC, CRC, HCC, neuroendocrine tumor, or mesothelioma
- Study patients were enrolled at 2 sites: Asan Medical Center in Seoul, Korea and Huntsman Cancer Institute in Salt Lake City, UT, USA

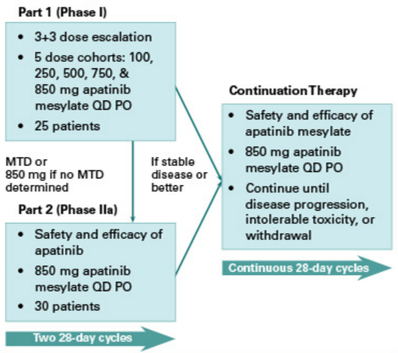
The Part 1 dose escalation study evaluated 5 doses of apatinib mesylate ranging from 100–850 mg over two 28-day cycles and was reported previously.[1] Since no MTD was determined in Part 1, the highest 850 mg dose was selected as the starting dose for Part 2 reported here.

Part 2 patients received 850 mg apatinib orally, in the morning for two 28 day cycles. After 2 cycles, patients were evaluated for disease response according to RECIST 1.1. Patients who had a determination of stable disease or better, were allowed to go into continuation therapy until disease progression, intolerable side effects, or withdrawal of consent (Figure 1).

AEs were assessed per NCI-CTCAE v4.03 at all visits and for 28-days from the last dose of study drug.

Blood samples for pharmacokinetics and pharmacodynamic markers in Part 2 were collected between 3–5 h (approximately C_{max}) on days 1 and 56±2 and before dosing (C_{trough}) on days 2±1, 8±1, 15±2, 29±2, 43±2, and 56±2. Pharmacodynamic markers included VEGF, sVEGFR-1 (Flt-1), sVEGFR-2, sVEGFR-3, sTie-2, PIGF, and sVCAM-1.

Figure 1. Study Overview



Results

Patients

- Among the 30 patients, 21 patients (70.0%) were male and the median age was 56.5 years. Twenty-three patients (76.7%) were Asian and the remaining 7 patients (23.3%) were Caucasian
- 97% of all patients were treated with apatinib as 3rd line therapy or later and 62% were treated as 4th line or later therapy
- Most subjects had prior experience with fluoropyrimidines (80%), and platinum-based agents (83%). Notably, 31% of subjects had prior anti-angiogenesis therapy (Table 1)

Table 1. Patient Characteristics

Characteristics		All Subjects		Gastric Cancer	
Total Subjects		30		15	
Sex	Male	21	(70%)	9	(60%)
	Female	9	(30%)	6	(40%)
Age, Years	Median (Range)	56.5	(32–82)	58	(32–66)
Race	Caucasian	7	(23%)	0	(0%)
	Asian	23	(77%)	15	(100%)
ECOG PS at Baseline 0/1/2 (N)		2/23/2		0/14/0	
Prior Chemotherapy Regimens (%)	≥1	100%		100%	
	≥2	97%		100%	
	≥3	62%		40%	
	≥4	31%		13%	
Prior Chemotherapy Agents (%)					
	Fluoropyrimidine	80%		93%	
	Platinum	83%		87%	
	Taxane	43%		80%	
	Irinotecan	40%		27%	
	Anti-angiogenic	37%		13%	
Tumor Type	Gastric	15	(50%)		
	Colorectal	9	(30%)		
	NSCLC	3	(10%)		
	Neuroendocrine	2	(7%)		
	Mesothelioma	1	(3%)		

Safety

The overall incidence of AEs can be considered low given the late stage of the patient population and the study duration, with a total of 142 AEs reported across 30 subjects. The toxicities that occurred were generally well tolerated, and there was no toxicity-related death

Table 2. Adverse Event Summary

Adverse Events	Patients N=30	%
Any AEs	30	100.0%
Related AEs	25	83.3%
SAEs	5	16.7%
Deaths	4 *	13.3%
AEs Leading to Discontinuation	2 †	6.7%
AEs Leading to Dose Reduction	6 ‡	20.0%

*Deaths were due to the following causes:

- » Malignant neoplasm progression, unrelated to study drug
- » Acute cholangitis secondary to disease progression, unrelated to study drug
- » Dyspnea secondary to rapidly progressing lung metastases, unlikely related to study drug
- » Gastric obstruction secondary to disease progression, unlikely related to study drug

†Of the 2 AEs leading to discontinuation of drug, one AE was due to rapidly progressing disease and the patients deteriorating status. ‡4 of the 6 AEs that led to dose reduction were also likely related to disease progression.

Table 3 summarizes all AEs and grade ≥3 AEs that occurred in at least greater than 5% of patients.

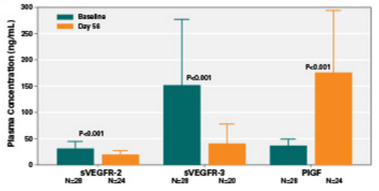
Table 3. AEs Occurring in ≥5% of Patients

AE Term	Any AE (%)		Grade ≥3 (%)	
AEs of Special Interest				
Hand-Foot Skin Reaction	9	(30.0%)	2	(6.7%)
Hypertension	16	(53.3%)	7	(23.3%)
Proteinuria	2	(6.7%)		
Laboratory Abnormalities				
Alanine Aminotransferase Increased	2	(6.7%)		
Aspartate Aminotransferase Increased	2	(6.7%)		
Blood Bilirubin Increased	4	(13.3%)	4	(13.3%)
Hypokalemia	3	(10.0%)	3	(10.0%)
Hypophosphatemia	4	(13.3%)	1	(3.3%)
Hematological AEs				
Platelet Count Decreased	4	(13.3%)	1	(3.3%)
Non-Hematological AEs				
Abdominal Pain	2	(6.7%)		
Asthenia	2	(6.7%)	1	(3.3%)
Back Pain	2	(6.7%)		
Constipation	2	(6.7%)		
Cough	5	(16.7%)	1	(3.3%)
Decreased Appetite	2	(6.7%)		
Dental Caries	2	(6.7%)		
Diarrhea	6	(20.0%)		
Dysgeusia	2	(6.7%)	1	(3.3%)
Dysphonia	3	(10.0%)		
Dyspnea	2	(6.7%)	1	(3.3%)
Fatigue	2	(6.7%)		
Headache	2	(6.7%)		
Hypothyroidism	3	(10.0%)		
Nausea	4	(13.3%)		
Oral Pain	2	(6.7%)		
Pain in Extremity	2	(6.7%)		
Peripheral Sensory Neuropathy	2	(6.7%)		
Pneumonia	3	(10.0%)		
Stomatitis	3	(10.0%)	1	(3.3%)

- The most frequently occurring AEs were the class-based side effects hypertension (53.3%), and hand-foot skin reaction (30.0%)

Pharmacodynamics

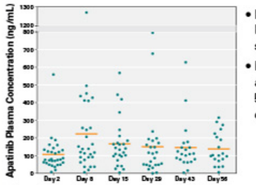
Figure 2. Change in PD Biomarkers from Baseline



- sVEGFR-2 decreased 37% from baseline
- sVEGFR-3 decreased 73% from baseline
- PIGF increased 374% from baseline
- Changes in VEGF, sVEGFR-1, sTie-2, and sVCAM-1 did not reach a statistically significant level

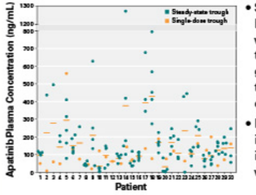
Pharmacokinetics

Figure 3. Trough Plasma Levels



- Plasma levels plateaued by Day 8 when steady-state was achieved
- No indication of accumulation after 56-days of continuous daily dosing

Figure 4. Trough Patient Variability

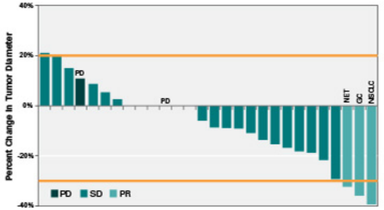


- Steady-state trough levels were measured weekly from Day 8 to Day 56 and were generally higher than the single dose trough on Day 2
- Levels of both intrapatient and interpatient variability were high

Efficacy

Twenty-eight patients were evaluable for disease response at the end of 2 cycles (Figure 5).

Figure 5. 2-Cycle Best Response (All Tumor Types)



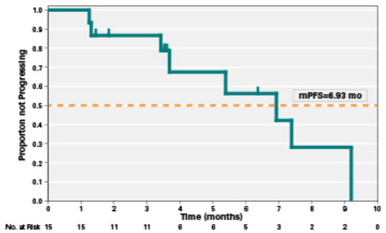
- There was no tumor growth above 20% but 2 patients developed new lesions resulting in PD determinations
- Disease response among gastric cancer patients is in Table 4

Table 4. 2-Cycle Response Rate

	All Tumor Types (%)		Gastric Cancer (%)	
Enrolled Patients	30		15	
Evaluable Patients	28		15	
PR	3	(10.7%)	1	(6.7%)
SD	23	(82.1%)	12	(80.0%)
PD	2	(7.1%)	2	(13.3%)
Objective Response Rate	10.7%		6.7%	
Disease Control Rate	92.9%		86.7%	

- Nine of the 28 evaluable patients had prior anti-angiogenic therapy. Of these patients, 1 patient (GC) had a partial response and 8 patients had stable disease
- In Part 1 of the study[1], an additional 5 GC patients were evaluable with 1 PR at 500 mg, and 2 SD at 500 mg and 850 mg, highlighting the potential for efficacy at doses lower than 850 mg

Figure 6. PFS in Gastric Cancer Patients (preliminary data)



Conclusions

- Apatinib was well tolerated with manageable toxicities and the majority of AEs were mild to moderate in severity
- Apatinib demonstrated promising anti-tumor activity in advanced solid tumors (including gastric cancer mPFS=6.93 months; 95% CI, 3.68–9.20) after failure of standard treatment
- This study reports the first experience of apatinib in Caucasian patients and supports further investigation of apatinib in solid tumors – especially in gastric cancer, where efficacy and safety of apatinib has been reported in a Chinese Phase 3 study

References and Acknowledgements

[1] Sharma S, et al. J Clin Oncol 33, 2015 (suppl:abstr 2525)

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