First-in-human phase I study of a selective VEGFR/FGFR dual inhibitor sulfatinib with milled formulation in patients with advanced solid tumors

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Introduction

Sulfatinib is a highly selective small molecule dual inhibitor of VEGF receptor (VEGFR1, 2 and 3) and FGF receptor (FGFR1) developed by Hutchison MediPharma. It demonstrated potent in vivo inhibitory effects on a variety of human tumor xenografts. The current study was designed to evaluate safety and tolerability, pharmacokinetics (PK), and preliminary anti-tumor activity of sulfatinib. The data of patients treated with the original formulation dosing from 50 to 300mg once or twice daily has been reported in ASCO 2012. A milled formulation was developed to reduce the PK variability and optimize absorption afterwards. The poster will focus on presentation of the data of the milled formulation.

Objectives

Primary objective

- The primary objective of this phase I dose-escalation study was to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) and safety in patients with advanced solid tumors.

Secondary objective

- To characterize the PK profile of single dose and multiple doses of sulfatinib

Exploratory objectives

- To evaluate preliminary efficacy of sulfatinib in patients with advanced solid tumor

Methods

Eligibility

Eligible patients were adults with locally advanced or metastatic solid malignant tumors for whom standard therapy either does not exist or has proven to be ineffective or intolerable. Patients must have ECOG performance status of 0 or 1, and adequate organ and bone marrow function.

Patients with uncontrolled hypertension, uncontrolled CNS metastasis and recent severe bleeding history (>30ml during the past 3 month) and hemoptysis (>5 ml fresh blood during the past 4 weeks) were excluded.

Study Design and Assessment

This is a phase I, open-label, dose-escalation study of sulfatinib administered orally in patients with advanced solid tumor. The study consists of two stages: a dose-escalation stage and a dose-expansion stage. The dose-escalation stage is designed to determine the MTD and/or RP2D and evaluate pharmacokinetics of sulfatinib. The conventional 3+3 design is applied for dose escalation and MTD determination.

Patients received a single oral dose of sulfatinib followed by a 6-day drug free wash-out period, before receiving the same doses for 28 consecutive days. After the single dose period, patients who were deemed to benefit from sulfatinib treatment may continue the treatment until disease progression or unacceptable toxicity.

Sulfatinib formulation was changed during the trial conduct, with its original formulation dosing started at 50 mg/day. Seven dose levels between 50 mg and 300 mg QD and 2 dose levels of 125 mg and 150 mg BID were evaluated using the original formulation. Sulfatinib milled formulation dosing started at 200 mg QD based on safety evaluation of the original formulation and dog PK comparison between the new and old formulations.

Dose-Limiting Toxicities (DLTs)

A DLT is defined as one of the following toxicities occurring during the DLT assessment window (Cycle 1, Days 1-28) and have a reasonable possibility of being related to sulfatinib:

- Any non-hematological toxicity ≥ Grade 3 according to NCI CTCAE3.0. Fatigue, nausea/vomiting, diarrhea, constipation, pain and hypertension will be considered DLTs only if they reach ≥Grade 3 in severity despite adequate supportive care.
- Grade 4 leukocytopenia
- Grade 4 thrombocytopenia
- Grade 4 anemia (hemoglobin decrease)
- Febrile neutropenia (defined as absolute neutrophil count [ANC] < 1000 cells/mm3 and fever≥38.5℃)
- Grade 3 thrombocytopenia with bleeding tendency

MTD

The MTD is defined as the highest dose at which no more than one of six patients in a single cohort experience DLT in the first cycle (Days 1-28 of Cycle 1).

Results

Patients

Since the original formulation was terminated during the trial and the study conclusion was made on milled sulfatinib, only the milled sulfatinib results are presented here.

As of July 6, 2015, the study enrolled a total of 77 patients amongst whom 34 patients were treated with milled sulfatinib, with a median age of 56 (range: 23-73) years. The most common tumor types of 34 patients included neuroendocrine tumor (NET) and hepatocellular carcinoma (HCC).

Table 1. Baseline Patient Characteristics (n=34, treated with milled formulation)

Characteristics	N=34
Median age, years(range)	56（23-73）
Sex n (%)	
Male	24(71%)
Female	10(29%)
ECOG PS n (%)	
0	4(12%)
1	30(88%)
Tumor site n (%)	
NET (G1/G2)*	21(62%)
NET (G3)	1(3%)
HCC	9(26%)
GIST	1(3%)
Leiomyosarcoma	1(3%)
Abdominal Malignancy	1(3%)
Tumor metastasis n (%)	
Yes	34 (100%)
No	0
Median number of prior Systemic Treatment (range)	1(0-4)

*NET was pathologically graded as well differentiated (G1 or G2) and poorly differentiated (G3)

Patient Disposition

Table 2. Summary of Patients Distribution by Dose

Cohort	Does	N*	Patients completed DLT observation (28 days)	Withdraw within the first cycle
1	200mg QD	7	6	1
2	300mg QD	18	17	1
3	350mg QD	9	7	2
Total		34	30	4

Note: One patient in the 200mg QD cohort was replaced due to early withdrawal. Additional HCC or NET patients were enrolled in the 300mg or 350mg QD cohorts to further evaluate the safety and PK of the dose level.

Thirty-four patients who received at least one dose of milled sulfatinib were evaluable for safety as of July 6, 2015. Thirty patients completed the 28-day (first cycle) DLT observation window. Totally 3 dose levels of 200, 300 and 350 mg QD were evaluated. The median treatment cycles for 34 patients were nearly 5 Cycles.

MTD and RP2D

MTD was not reached up to dose of 350mg QD with milled formulation. Sulfatinib exposure plateaued at the dose of 350 mg QD, while preliminary anti-tumor efficacy had been observed at the doses beyond 200mg QD. Based on these observations, dose escalation was stopped at 350mg QD and sulfatinib milled formulation 300 mg QD was determined as RP2D .

Safety and Tolerability

Cumulative safety data as of July 6, 2015 are summarized in Table 3 and 4 below. All the 34 patients experienced at least one adverse event (AE). The most frequently reported AEs were proteinuria (67.6%), diarrhea (64.7%), serum transaminase increased and hypertension (58.8% each), hypocalcaemia (55.9%), blood bilirubin increased (47.1%). Most of the AEs were mild or moderate (NCI CTC AE grade 1/2). (See Table 3). Totally 16 (47.1%) patients experienced treatment related≥Grade 3 AE. The most common treatment related ≥Grade 3 AE was proteinuria that was observed in 5 (14.7%) patients. (See Table 4). Only 1 DLT (G3 serum transaminase increased) occurred in the 200mg QD cohort during sulfatinib milled formulation treatment period.

Table 3. Summary of AEs Reported by >20% Patients Irrespective of Causality (Milled Formulation N=34)

	All schedules (N=34)	
Adverse Event	**All grades n (%)**	**Grade 3/4 n (%)**
Proteinuria	23(67.6%)	5(14.7%)
Diarrhea	22(64.7%)	2(5.9%)
Serum transaminase increased	20(58.8%)	3(8.8%)
Hypertension	20(58.8%)	4(11.7%)
Hypocalcaemia	19(55.9%)	0
Blood bilirubin increased	16(47.1%)	1(2.9%)
Blood albumin decreased	15(44.1%)	0
Fatigue	15(44.1%)	2(5.9%)
Platelet count decreased	14(41.2%)	2(5.9%)
Hypokalemia	14(41.2%)	1(2.9%)
Anemia	13(38.2%)	2(5.9%)
White blood cell count decreased	13(38.2%)	0
Hypertriglyceridaemia	12(35.3%)	0
Neutropenia	12(35.3%)	1(2.9%)
Abdominal discomfort	11(32.4%)	0
Nausea	11(32.4%)	0
TSH increased	10(29.4%)	0
Abdominal distension	9(26.5%)	0
Blood uric acid increased	9(26.5%)	1(2.9%)
T wave change	9(26.5%)	0
Dizziness	7(20.6%)	0

Table 4. Summary of Grade≥3 AEs Related to Sulfatinib (Milled Formulation N=34)

AE	200mg QD (N=7) n (%)	300mg QD (N=18) n (%)	350mg QD (N=9) n (%)	Total (N=34) n (%)
Proteinuria	0	3(16.7%)	2(22.2%)	5(14.7%)
Hypertension	0	4(22.2%)	0	4(11.7%)
Diarrhoea	0	1(5.6%)	1(11.1%)	2(5.9%)
Serum transaminase increased	1(14.3%)	1(5.6%)	0	2(5.9%)
Anemia	0	1(5.6%)	1(11.1%)	2(5.9%)
Neutropenia	1(14.3%)	0	0	1(2.9%)
Platelet count decreased	0	0	2(22.2%)	2(5.9%)
Hypokalemia	0	0	1(11.1%)	1(2.9%)
Blood bilirubin increased	0	1(5.6%)	0	1(2.9%)
Fatigue	0	0	1(11.1%)	1(2.9%)
Abdominal pain	0	1(5.6%)	0	1(2.9%)
Hypophosphatemia	0	1(5.6%)	0	1(2.9%)
Blood uric acid increased	0	1(5.6%)	0	1(2.9%)
Total	1(14.3%)	10(55.6%)	5(55.6%)	16(47.1%)

Pharmacokinetics

The major PK results of single-dose and multiple-dose sulfatinib are shown in Table 5. Following a single oral dose of sulfatinib, the geometric mean of $t_{1/2}$ in patients was 19.5, 17.8 and 14.1 hours, respectively, at 200, 300 and 350 mg. The long $t_{1/2}$ in plasma supported the dosing frequency of once daily (QD). The geometric mean of sulfatinib $AUC_{0\text{-}72}$ was 2299, 4594 and 3518 ng・h/mL, respectively, and $AUC_{0\text{-}\infty}$ was 2387, 4778, 3643 ng・h/mL, respectively. The coefficient of variation (CV%) for geometric mean was close to 50% for the major PK parameters, indicating an acceptable inter-patient variability. Following multiple dosing at 200, 300 and 350 mg/day (QD), the geometric mean of $AUC_{0\text{-}24}$ on Day 1 was 1691, 2645 and 3075 ng・h/mL, respectively. Following 14 consecutive administrations (on Day 14), the geometric mean values of $AUC_{\tau,ss}$ at 200, 300 and 350 mg/day were 4100, 4737 and 4764 ng・h/mL, respectively. The fluctuation (presented as fluctuation%) remained at approximately 250% at each test dose. Following 28 consecutive administrations of sulfatinib, the geometric mean of $AUC_{\tau,ss}$ on Day 28 was 3167, 5137 and 3460 ng・h/mL, respectively, at 200, 300 and 350 mg/day. The geometric mean of fluctuation% was 216, 205 and 163%, respectively.

Generally, sulfatinib exposure increased when the dose increased from 200 mg to 300 mg, and then plateaued from 300 mg to 350 mg. Following QD multiple dosing, the mean values of fluctuation% ranged from 163 to 259% and were similar at each dose despite the dosing days (Day 14 and Day 28).

Table 5. Pharmacokinetic Parameters of Milled Sulfatinib[a]

Single dose	200 mg	300 mg	350 mg
AUC_{∞} (h・ng/mL) Geomean (GCV%)	N=6 2387 (34.7)	N=7 4778 (30.3)	N=8 3634 (34.1)
$AUC_{0\text{-}72h}$ (h・ng/mL) Geomean (GCV%)	N=6 2299 (35.1)	N=7 4594 (33.2)	N=8^ 3518 (34.1)
C_{max} (ng/mL) Geomean (GCV%)	N=6 332 (32.5)	N=7 702 (51.5)	N=8 511 (30.2)
T_{max} (h) Median (Min, Max)	N=6 2.0 (1.0,2.0)	N=7 2.0 (1.0,2.0)	N=8 2.0 (1.0,3.0)
$t_{1/2}$ (h) Geomean (GCV%)	N=6 19.5 (25.9)	N=7 17.8 (44.7)	N=8 14.1 (38.5)

Multiple dose	200 mg			300 mg			350 mg		
Day	1	14	28	1	14	28	1	14	28
$AUC_{\tau,ss}$ (h・ng/mL)* Geomean (GCV%)	N=7 1691 (40.0)	N=5 4100 (61.4)	N=5 3167 (59.2)	N=16 2645 (45.4)	N=13 4737 (54.8)	N=5 5137 (60.6)	N=9 3075 (16.7)	N=7 4764 (43.3)	N=6 3460 (50.7)
C_{max} (ng/mL) Geomean (GCV%)	N=7 291 (33.8)	N=6 462 (66.3)	N=5 349 (59.1)	N=16 437 (67.6)	N=13 556 (63.0)	N=5 542 (105)	N=9 482 (17.7)	N=7 599 (38.3)	N=6 323 (90.4)
T_{max} (h) Median (Min, Max)	N=7 2.0 (1.0,2.0)	N=6 1.0 (1.0,2.0)	N=5 2.0 (1.0, 2.0)	N=16 2.0 (2.0,4.0)	N=13 2.0 (1.0,4.1)	N=5 2.0 (1.0, 4.0)	N=9 2.0 (2.0, 2.0)	N=7 2.0 (2.0, 4.0)	N=6 2.0 (1.0, 2.5)
Fluctuation% Geomean (GCV%)	NA	N=5 251 (33.7)	N=5 216 (20.2)	NA	N=13 236 (42.8)	N=5 205 (55.7)	NA	N=7 259 (45.5)	N=6 163 (69.9)

GCV%: Geometric mean CV%; NA: not applicable

[a]: only patients with valid PK data included; ^: n=1 for $AUC_{0\text{-}24h}$ and n=2 for $AUC_{0\text{-}48h}$; *: $AUC_{0\text{-}24h}$ for Day 1

Efficacy

Among 34 patients, 9(26.5%) patients had partial response, including a HCC patient in the 200mg QD cohort, 8 NET patients (5 in the 300mg QD cohort and 3 in the 350mg QD cohort). Seventeen (50%) patients had stable disease (SD) for 8 weeks or longer. In particular, among 18 efficacy evaluable NET patients (who had both valid baseline and post-baseline tumor response evaluation), the best overall response rate (ORR) was 44.4% and disease control rate (DCR) was 100%. Seven NET patients were still on sulfatinib treatment by July 6, 2015, the data cut-off of this report. The tumor origins of the 8 NET patients with partial response include pancreas (3 patients), duodenum (1 patient), rectum (1 patient), thymus (1 patient) and unknown origin (2 patients) (Table 6). Extensive liquefactive necrosis was observed in the tumor lesions in CT images of NET patients who respond to sulfatinib treatment (Figure 2).

Figure 1: Best Response of Efficacy Evaluable NET Patients (N=18)

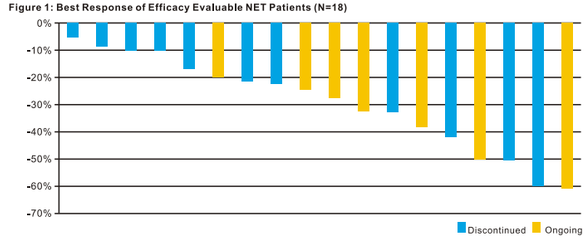
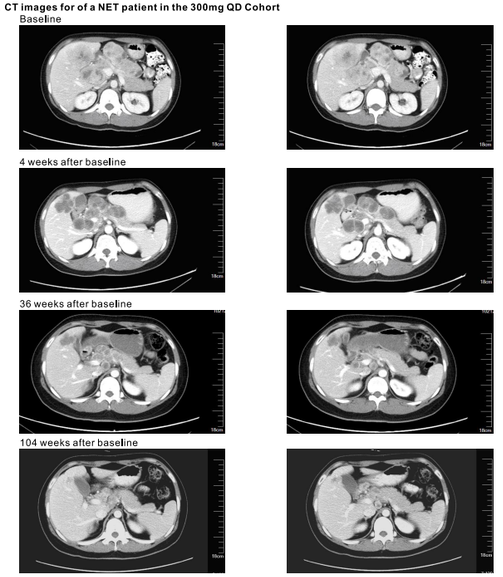


Table 6. Summary of tumor response in NET (G1/G2) subgroup (N=21)

NET subgroup based on primary origin	Total patients N=21	Efficacy evaluable patients N=18	PR patients N=8
Pancreatic NET	7	7	3
Gastrointestinal NET	7	5	2
Other & Unknown origin	7	6	3

Figure 2. CT images for of a NET patient in the 300mg QD Cohort



Conclusions

Sulfatinib was well tolerated at doses up to 350 mg QD. Although MTD was not reached, 300 mg QD was determined as RP2D based on tolerability, efficacy and PK considerations. Sulfatinib showed promising anti-tumor activity, especially in NET patients, and therefore warrants further clinical development.