Abstract #3100: First-in-human Phase 1 Study of Pimicotinib (ABSK021), a CSF-1R Inhibitor, in Patients with Advanced Solid Tumors

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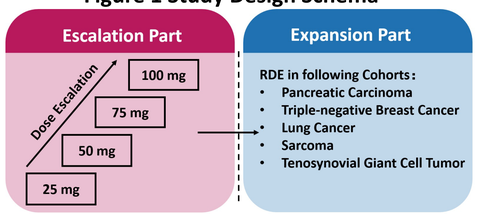
BACKGROUND

- Colony-stimulating factor 1 (CSF-1) pathway is involved in the development of various types of cancer.
- Pimicotinib is an orally-available, selective, potent small molecule CSF-1R inhibitor with significant pre-clinical anti-tumor activity.

METHOD

- The escalation part employed a 3+3 design with a starting dose of 25 mg QD (28-day/ cycle) to determine the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE) of Pimicotinib in Patients with advanced solid tumor.
- The expansion part evaluated Pimicotinib at RDE in patients with pancreatic carcinoma, triple-negative breast cancer, lung cancer, and sarcoma. (ClinicalTrials. gov NCT04192344)

Figure 1 Study Design Schema



RESULTS

Patients

- As of Dec 31, 2022, 74 pts received at least one dose of Pimicotinib at 25 mg (n = 6), 50 mg (n = 58), 75 mg (n = 8), or 100 mg (n = 2) QD.
- Median age was 59 years old; 47.3% were white,33.8% were Asian and 18.9% were African American.85.1% had metastasis; 67.6% had ≥3 lines of prior systemic anti-tumor therapies. (**Table 1**).
- Median duration of treatment was 49.5 days (range 4-377 days).

Safety

- Treatment-related adverse events (TRAEs), TRAEs ≥ Gr 3, and serious TRAEs occurred in 74.3%, 21.6%, and 4.1% patients, respectively. The most common (≥10%) TRAEs were serum enzyme elevations, which were all believed to be Pimicotinib **MOA related. (Table 2).**
- Serious TRAEs included 1 ascites (50 mg), 1 blood bilirubin increase (75 mg), and 1 vaginal hemorrhage (50 mg).

Efficacy

- By cutoff, 12 out of 51 (23.5%) response-evaluable patients achieved stable disease.

CONCLUSION

- ***Pimicotinib*** has tolerable ***safety*** profile in ***patients with advanced solid tumors***. MTD is determined as 75 mg QD and RDE as 50 mg QD.
- Peripheral and tissue PD changes demonstrate Pimicotinib can block CSF-1R activity in patients with advanced solid tumor.
- Favorable PK profile supports exploration on QD dosing. No dose adjustment has been identified based on tested covariates.

Table 1. Demographic Characteristics

	25 mg (N=6)	50 mg (N=58)	75 mg (N=8)	100 mg (N=2)	Total (N=74)
Age (Years)					
Median	54.0	58.0	65.0	66.0	59.0
Min, Max	25, 72	31, 82	33, 76	61, 71	25, 82
Race, n(%)					
Asian	3 (50.0)	22 (37.9)	0	0	25 (33.8)
Black or African American	1 (16.7)	11 (19.0)	1 (12.5)	1 (50.0)	14 (18.9)
White	2 (33.3)	25 (43.1)	7 (87.5)	1 (50.0)	35 (47.3)
ECOG, n(%)					
0	0	18 (31.0)	1 (12.5)	0	19 (25.7)
1	6 (100.0)	40 (69.0)	7 (87.5)	2 (100.0)	55 (74.3)
Metastatic, n (%)					
Yes	4 (66.7)	49 (84.5)	8 (100.0)	2 (100.0)	63 (85.1)
Number of Regimens					
≥3	2 (33.3)	40 (69.0)	7 (87.5)	1 (50.0)	50 (67.6)

Table 2. TRAE with Incidence ≥ 10% by Preferred Term

	25 mg (N=6)		50 mg (N=58)		75 mg (N=8)		100 mg (N=2)		Total (N=74)	
Preferred Term (PT)	Any TRAE n (%)	>=Gr 3 n (%)	Any TRAE n (%)	>=Gr 3 n (%)	Any TRAE n (%)	>=Gr 3 n (%)	Any TRAE n (%)	>=Gr 3 n (%)	Any TRAE n (%)	>=Gr 3 n (%)
Any TRAEs	5 (83.3)	0	42 (72.4)	12 (20.7)	6 (75.0)	2 (25.0)	2 (100.0)	2 (100.0)	55 (74.3)	16 (21.6)
CPK increased	3 (50.0)	0	28 (48.3)	6 (10.3)	3 (37.5)	0	2 (100.0)	2 (100.0)	36 (48.6)	8 (10.8)
AST increased	2 (33.3)	0	15 (25.9)	0	2 (25.0)	1 (12.5)	0	0	19 (25.7)	1 (1.4)
LDH increased	2 (33.3)	0	14 (24.1)	0	0	0	0	0	16 (21.6)	0
HBDH increased	2 (33.3)	0	10 (17.2)	0	0	0	0	0	12 (16.2)	0
Anaemia	2 (33.3)	0	8 (13.8)	2 (3.4)	0	0	0	0	10 (13.5)	2 (2.7)
Hyponatraemia	3 (50.0)	0	6 (10.3)	0	0	0	0	0	9 (12.2)	0
Nausea	1 (16.7)	0	8 (13.8)	0	0	0	0	0	9 (12.2)	0
ALT increased	1 (16.7)	0	7 (12.1)	0	0	0	0	0	8 (10.8)	0
ALP increased	0	0	8 (13.8)	0	0	0	0	0	8 (10.8)	0
Lipase increased	0	0	8 (13.8)	0	0	0	0	0	8 (10.8)	0

Note:

- CPK=Blood creatine phosphokinase; AST=Aspartate aminotransferase; LDH=Blood lactate dehydrogenase; ALT=Alanine aminotransferase ; ALP= Blood alkaline phosphatase; HBDH=Alpha hydroxybutyrate dehydrogenase
- DLT:One patient (75 mg QD, breast cancer with liver and bone metastases, and abnormal liver function test at baseline) with blood bilirubin increase (Grade 2/3/4). One patient (100 mg QD) with Grade 4 CPK increase. One patient (100 mg QD) with Grade 3 CPK increase leading to less than 75% planned dose administration.

Pharmacokinetics

- Pimicotinib is rapidly absorbed after oral administration, with $t_{1/2}$ from 43.6 to 63.5 h. In the 25 -75 mg dose range, exposure increases slightly less than dose proportional and exposure showed 2-3-fold accumulation at steady state under QD dosing (**Table 3**);
- Population PK model indicated no dose adjustment is required based on the covariates investigated including body weight, ethnicity, age and etc.

Table 3. PK Parameters

	PK Parameters	25 mg QD (N=6)	50 mg QD (N=16)	75 mg QD (N=8)	100 mg QD (N=2)
Single dose	C_{max}(ng/ml)	175 (48.2)	288 (56.7)	508 (49.3)	375 (144.6)
	AUC_{last} (h*ng/ml)	1976 (31.5)	3182 (36.9)	4567 (27.0)	8402 (54.0)
	t_{max}(h)	0.87 (0.45, 3.62)	0.93 (0.50, 6.00)	0.97 (0.45, 2.07)	1.52 (0.93, 2.10)
	$t_{1/2}$(h)	52.7 (35.1) [b]	43.6 (33.5) [c]	49.3 (64.0) [d]	63.5 (NC) [a]
Steady state	$C_{max,ss}$(ng/ml)	385 (52.8)	566 (65.8)	745 (43.3)	NC
	$C_{min,ss}$(ng/mL)	117 (51.7)	192 (47.0)	143 (204.4)	NC
	$AUC_{last,ss}$ (h*ng/ml)	3537 (43.2)	5886 (45.8)	6568 (46.8)	NC
	AR_{Cmax}	2.21 (102.6)	1.96 (44.0)	1.62 (50.0)	NC
	AR_{AUC}	3.25 (28.7)	3.33 (21.7)	2.80 (40.0)	NC

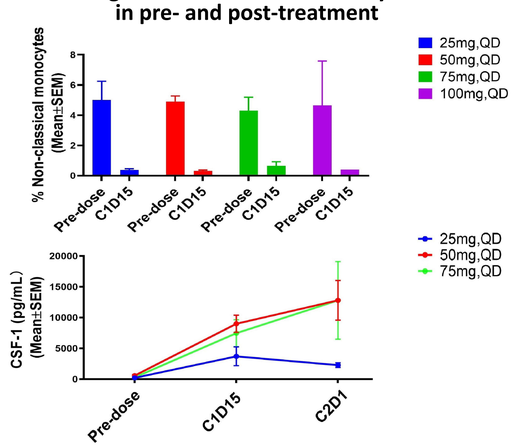
Note:All PK parameters were reported using Geomean (%CV), except t_{max} was reported as median (Min ~ Max); a: n = 1; b: n=3; c: n=10; d: n =6;

Peripheral Pharmacodynamics

In patients with advanced solid tumors, Pimicotinib treatment led to significant PD changes.

- Average of 85%-92% decrease of non-classical monocytes was observed in patients treated with all dose levels. **(Figure 2A)**
- Plasma CSF-1 levels were significantly increased from 25mg QD to 50mg QD, and reached the plateau at 50mg QD. **(Figure 2B)**

Figure 2. Changes of non-classical monocytes and CSF-1 in pre- and post-treatment

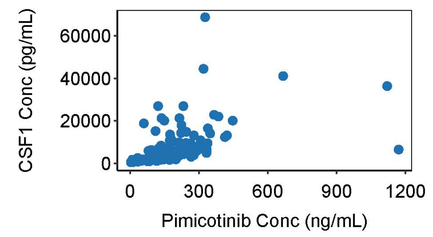


Note: CSF-1, colony stimulating factor-1; C, cycle; D, day. Cut-off data 30 October,2022.

PK/PD Correlation

- CSF-1 concentrations showed a positive correlation with Pimicotinib plasma concentration increase (**Figure 3**).

Figure 3. CSF-1 vs Pimicotinib concentration



Tissue Pharmacodynamics

- Baseline and on-treatment skin biopsy and tumor samples from patient with lung cancer showed a marked reduction in CD163+ macrophages in post-treatment at 50mg QD. **(Figure 4)**

Figure 4. Changes of CD163+ macrophages in skin and tumor samples