A Phase I Study of HM781-36B, a novel pan-Her inhibitor in patients with advanced solid tumor

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Introduction

- The EGFR family plays an important role in the mediating growth factor signaling. The mutation or overexpression of EGFR and HER-2 are observed in many human solid tumors. A strong correlation has been found between solid tumors with high levels of EGFR and HER-2 and poor prognosis.[1]
- Current EGFR targeted agents are limited by the development of drug resistance. In particular, resistance to EGFR inhibitors is mainly caused by an acquired mutation (T790M), which is detected in 50% of clinically resistant patients.[2,3]
- HM781-36B is a potent pan-Her inhibitor which shows potent in vitro and in vivo activities for EGFR related cancer models including mutant EGFR and mutant Her-2 model.[4]

■ Table 1. Inhibition of EGFR family kinases

Enzyme (IC_{50}, nM)	EGFR			HER-2	HER-4
	WT	T790M	L858R/T790M		
Erlotinib	>1,000	>1,000	>1,000	>1,000	>1,000
BIBW-2992	8.0	9.8	24.0	24.9	26.6
HM781-36B	3.2	1	2.2	5.3	23.5

■ Table 2. Inhibition in EGFR expressing cancer cells and normal cells

Cell line (GI_{50}, nM)	HCC827	H358	H1975	Hs-27	Balb/c 3T3
	$EGFR^{\Delta E746-A750}$ (Lung)	$EGFR^{WT}$ (Lung)	$EGFR^{L858R/T790M}$ (Lung)	Normal	Normal
Erlotinib	2.4	286.7	>1,000	>10,000	>10,000
BIBW-2992	1.2	37.8	42.0	2,835	2,105
HM781-36B	1.2	4.8	5.7	3,830	2,409

■ Table 3. Inhibition in HER-2 expressing cancer cells

Cell line (GI_{50}, nM)	SK-Br3	BT-474	MDA-175	N87	Calu-3	H1781
	$Her\text{-}2^{WT}$ Amp (Breast)	$Her\text{-}2^{WT}$ Amp (Breast)	$Her\text{-}2^{WT}$ (Breast)	$Her\text{-}2^{WT}$ Amp (Gastric)	$Her\text{-}2^{WT}$ Amp (Lung)	$Her\text{-}2^{G776V,\ Cis}$ (Lung)
Erlotinib	>1,000	>1,000	>1,000	>1,000	377.5	3,246
BIBW-2992	2.8	7.5	15.3	2.8	7.3	60.0
HM781-36B	1.0	1.3	1.8	0.6	2.1	4.0

Objectives

- To identify the maximum tolerated dose (MTD) of HM781-36B
- To characterize the pharmacokinetics of HM781-36B following oral administration
- To evaluate anticancer activity of HM781-36B in patients with advanced solid malignancies

Methods

This is an open label, multicenter, phase I dose escalation study with cohorts of 3~6 patients to determine the MTD. After the MTD is identified, 12 patients would be enrolled in the expansion cohort.

Dose escalation part: we used a standard 3+3 dose escalation design with MTD being as the dose with DLTs in 1/6 or fewer pts in the first cycle using NCI-CTCAE(version 3.0). Dose levels were 0.5mg, 1mg, 2mg, 4mg, 8mg, 12mg, 16mg, 20mg, 24mg, and 32mg.

Eligible patients were ≥ 18 years of age with advanced malignancies refractory to standard therapies. HM781-36B was administered once daily on a 14-day on, 7-day off schedule. PK samples were collected up to 24 hr on day 1 and up to 48 hr day 14 in cycle 1.

Results

Demographic:

A total of 55 pts were enrolled; 43 pts in the dose escalation cohorts and 12 pts in the expansion cohort. All pts were included in safety analysis. 3 pts is ongoing. The 37 pts were heavily pretreated (≥ 4 regimen, 67.3%) and the majority of primary cancer diagnosis were NSCLC (38.2%). Additional pts characteristics are provided Table 4.

Safety:

52 pts experienced at least one drug-related AE. The most common drug-related TEAEs were diarrhea, rash, stomatitis, pruritus, anorexia. Table 5 summarizes drug related TEAEs observed in all treatment cycles by CTCAE grade. DLTs were G3 diarrheas in 5 pts, one at 12 mg, 16 mg, 24 mg, and two at 32 mg (Table 6). The MTD was determined as 24mg.

Anticancer Activity:

Among 51 evaluable pts, 7pts achieved PR (4 breast, 1 rectal, 1 gastric, 1 NSCLC, duration of response: 36.7 wks , 55.9 wks, 35.0 wks+, 15.7 wks+, 12.6 wks, 44.0 wks, 19 wks), and 25 pts had SD. The median PFS was 11.7 wks (Table 7).

Pharmacokinetics:

During dose escalation, pharmacokinetic blood sampling were obtained after treatment on day 1 in 40 pts and day 14 in 36 pts. In the dose range of 0.5 to 32 mg, peak concentration(C_{max}) were reached before 6 hr post-dose, and mean terminal half-lives ranged 5.0 to 7.8 hr. Dose-proportional pharmacokinetics profiles were observed in terms of C_{max} and area under plasma concentration-time curve (AUC) in dose range of 0.5 to 24mg. The accumulation index ranged from 0.9 to 1.2 (Figure 1).

■ Table 4. Patient demographics and characteristics: all patients (N=55)

Demographic		No.	%
Gender	Male	31	56.4
	Female	24	43.6
Median Age (years)			55
	Range		25-83
ECOG performance status	0	29	52.7
	1	23	41.8
	2	2	3.6
	3	1	1.8
Primary cancer diagnosis	Breast	9	16.4
	Coloretal	9	16.4
	Gastric	10	18.2
	NSCLC	21	38.2
	Other	6	10.9
Previous chemotherapy regimens	1-2 regimens	7	12.7
	3 regimens	11	20.0
	≥ 4 regimens	37	67.3

■ Table 5. TEAEs related study drug (≥10% pts)

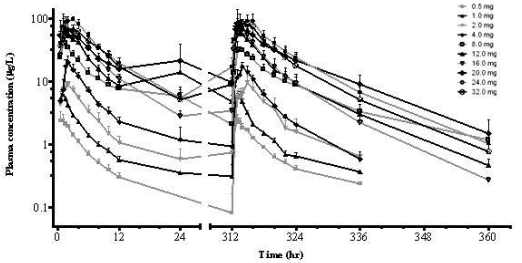
Preferred Terms	Total (N=55)	
	Grade 1 –Grade 4 N(%)	Grade 3 and above N(%)
Diarrhea	47 (85.5)	16 (29.1)
Rash	46 (83.6)	-
Stomatitis	41 (74.5)	-
Pruritus	32 (58.2)	-
Anorexia	20 (36.4)	-
Acne	17 (30.9)	-
Palmar-plantar erythrodysaesthesia syndrome	16 (29.1)	-
Rhinorrhoea	13 (23.6)	-
Paronychia	12 (21.8)	-
Mucosal inflammation	11 (20.0)	1 (1.8)
Nausea	9 (16.4)	1 (1.8)
Vomiting	9 (16.4)	1 (1.8)
Fatigue	8 (14.5)	-
Skin exfoliation	7 (12.7)	-
Weight decreased	6 (10.9)	-
Dry skin	6 (10.9)	-

■ Table 6. Dose Limiting Toxicities in dose escalation pts (DLTs)

Dose	# of patients	# of DLTs	Details
0.5 mg	3	-	-
1 mg	3	-	-
2 mg	3	-	-
4 mg	3	-	-
8 mg	3	-	-
12 mg	6	1	Diarrhea
16 mg	6	1	Diarrhea
20 mg	3	-	-
24mg	6	1	Diarrhea
32mg	7	2	Diarrhea

■ Table 7. Tumor response in evaluable patients

Response	n=51
Any PR	7 (13.7%)
Confirmed PR	5 (9.8%)
Any PR+SD	32 (62.7%)
Median PFS (wks)	11.7



■ Figure 1. Mean plasma concentraion-time of HM781-36 after once-daily oral administraion of HM781-36B.(log-linear scale)

Conclusion

- HM781-36B is a potent pan-HER inhibitor, and shows potent activities for EGFR related cancer models including mutant EGFR and HER-2.[4]
- Human PK of HM781-36B showed dose dependent oral absorption.
- HM781-36B was safe and well tolerable in advanced solid malignancies.
- Preliminary evidence of anticancer activity has been observed in patients with advanced malignancies.

References

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