Antitumor efficacy and safety of sacibertinib (Hemay022) in combination with endocrine therapy in patients with ER+/ HER2+ metastatic breast cancer: A phase Ib study

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Introduction

Patients with hormone receptors -positive (HR+)/human epidermal growth factor receptor 2-positive (HER2+) breast cancer comprise 10%–15% of total breast cancer population[1,2]. The main guidelines recommend HER2-targeted therapy in combination with chemotherapy as the basis of treatment for HR+/HER2+ breast cancer irrespective of HR status[3,4]. However, resistance to anti-HER2 treatment remains challenging, highlighting the clinical need for new therapeutic approaches.

Preclinical studies have shown that the complex molecular signaling crosstalk between the HER2 and estrogen receptor (ER)signaling pathways may contribute to treatment resistance and will promote tumor progression[5]. Given that patients with HR+/HER2+ breast cancer are less likely to respond to standard combination of anti-HER2 and chemotherapy, blocking ER and HER2 signaling pathways simultaneously may solve this problem.

Sacibertinib (hemay022) is an oral, novel EGFR/HER2 tyrosine kinase irreversible inhibitor, which showed promising antitumor activity and acceptable tolerability when used alone in pre-clinical and phase Ia trials (Clinical Trials.gov identifier: NCT02476539). This study aimed to explore the safety and efficacy of sacibertinib plus endocrine therapy in patients with ER+ and HER2+ metastatic breast cancer (MBC).

Methods

Patient Population

Patients enrolled in all of the combination cohorts were required to have ER+ (immunochemistry >1%) / HER2+ (immunochemistry 3+, or immunochemistry 2+ confirmed by fluorescent in situ hybridization) disease and be postmenopausal. Eligible participants with relapsed or cannot be cured by standard therapy.

Study Design

Using a phase 1b 3+3 dose escalation and expansion study design, patients with ER+/ HER2+ MBC were treated with sacibertinib (200mg-500mg daily) plus endocrine therapy including exemestane, letrozole, fulvestrant. The safety and clinical efficacy, including objective response rate (ORR), clinical benefit rate (CBR), disease control rate (DCR) and progression-free survival (PFS) were assessed.

Results

Table 1. Demographics and baseline disease characteristics.

	Sacibertinib (200mg/d) +exemestane N=3	Sacibertinib (300mg/d) +exemestane N=8	Sacibertinib (400mg/d) N=31			Sacibertinib (500mg/d) +exemestane N=13	Total N=55
			+exemestane N=19	+letrozole N=6	+fulvestrant N=6		
Median age (range)	55 (39-55)	52 (46-61)	57 (44-69)	58 (52-67)	53 (34-58)	54 (36-67)	55(34-69)
ECOG performance status 0 1	 2(66.7) 1(33.3)	 7(87.5) 1(12.5)	 17(89.5) 2(10.5)	 6(100.0) 0(0)	 6(100.0) 0(0)	 12(92.3) 1(7.7)	 50(90.9) 5(9.1)
Tumor site Visceral Nonvisceral	 0(0) 3(100.0)	 3(37.5) 5(62.5)	 3(15.8) 16(84.2)	 2(33.3) 4(66.7)	 0(0) 6(100.0)	 2(15.4) 11(84.6)	 10(18.2) 45(81.8)
Receptor status ER-positive HER2-positive	 3 (100.0) 3 (100.0)	 8(100.0) 8(100.0)	 19(100.0) 19(100.0)	 6(100.0) 6(100.0)	 6(100.0) 6(100.0)	 13(100.0) 13(100.0)	 55(100.0) 55(100.0)
Previous endocrine therapy	3(100.0)	7(87.5)	13(68.4)	2(33.3)	6(100.0)	11(84.6)	42(76.4)
Previous chemotherapy	3(100.0)	8(100.0)	19(100.0)	6 (100.0)	5(83.3)	13(100.0)	54 (98.2)
Previous anti-HER2 therapy	3(100.0)	8(100.0)	19(100.0)	6(100.0)	6(100.0)	13(100.0)	55(100.0)

Table 2. Summary of efficacy data(EAS)

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	Sacibertinib (200mg/d) +exemestane N=3	Sacibertinib (300mg/d) +exemestane N=7	Sacibertinib (400mg/d) N=31			Sacibertinib (500mg/d) +exemestane N=12	Total N=51
			+exemestane N=18	+letrozole N=6	+fulvestrant N=5		
Best overall response, n (%)							
Complete (CR)	0（0）	1（14.3）	0（0）	0（0）	0（0）	0（0）	1（2.0）
Partial response (PR)	0（0）	1（14.3）	7（38.9）	3（50.0）	1（20.0）	3（25.0）	15（29.4）
Stable disease (SD)	2（66.7）	3（42.9）	6(33.3)	2（33.3）	4(80.0)	9(75.0)	26（51.0）
Progressive disease (PD)	1（33.3）	2(28.6)	5(27.8)	1（16.7）	0（0）	0（0）	9（17.6）
Disease control rate(DCR)	2(66.7)	5(71.4)	13(72.2)	5(83.3)	5(100.0)	12(100.0)	42(82.4)
Overall response rate (ORR)	0（0）	2(28.6)	7(38.9)	3（50.0）	1(20.0)	3(25.0)	16(31.4)
Clinical benefit rate (CBR)	1（33.3）	3(42.9)	12(66.7)	5（83.3）	4(80.0)	6(50.0)	31（60.8）
Median PFS (months)	3.6(1.8~NA)	5.4(1.7~9.5)	8.9(2.7~16.4)	12.7(1.7~NA)	13.3(5.7~NA)	9.0(2.1~NA)	9.0(5.5~11.0)

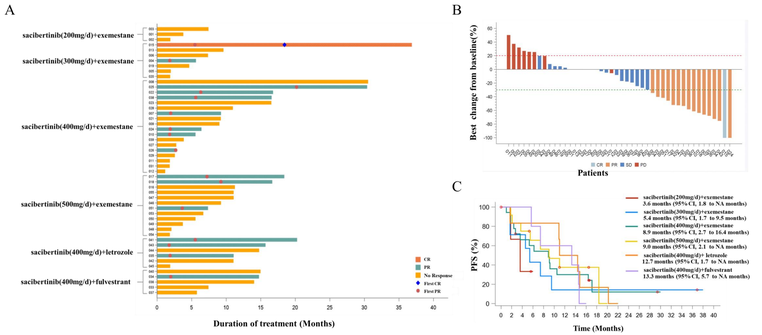

Figure 1. Clinical outcomes of patients. (A) Swimmer plot indicating Response of patients. (B) Waterfall plot of best change rate in target-lesion size from baseline. (C) Kaplan–Meier curve representing PFS (FAS).

Safety

Among the 55 subjects, TEAEs were mostly within grades 1–2. The most frequent grade 3 TEAE was diarrhoea (9.1%). One (1.8%) had grade 4 abnormal liver function.

Conclusions

In conclusion, sacibertinib plus endocrine therapy in this chemotherapy-free strategy had a favorable safety profile and antitumor activity in patients with ER+/ HER2+ MBC, 400-500mg daily showed more efficacy, supporting further assessment in randomized studies. A phase III clinical study of sacibertinib (500 mg daily) in combination with endocrine therapy for ER+/ HER2+ MBC is ongoing. (Clinical Trials.gov identifier: NCT05122494).

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