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Trastuzumab deruxtecan combined with pyrotinib in first-line HER2-positive unresectable or metastatic breast cancer: an exploratory, multi-center, single-arm, phase Ib/II study (TROPHY)

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Background

- Trastuzumab deruxtecan (T-DXd), a human epidermal growth factor receptor 2 (HER2)-directed antibody-drug conjugate (ADC), has demonstrated remarkable efficacy in the second-line or later treatment of HER2-positive (HER2+) metastatic breast cancer (mBC) in DESTINY-Breast03 [1-2], and its exploration as the first-line (1L) treatment (DESTINY-Breast09) is ongoing[3].
- Pyrotinib, an irreversible, pan-HER receptor tyrosine kinase inhibitor (TKI)[4], has also been approved in combination with trastuzumab and docetaxel for the 1L treatment of HER2+ mBC and is widely used in China[5].
- As preclinical and clinical studies have shown the synergistic effects of HER2 ADCs combined with TKIs[6-7], this phase Ib/II study evaluates the efficacy and safety of the promising combination of T-DXd and pyrotinib for the 1L treatment of HER2+ mBC in China (TROPHY, NCT06245824).

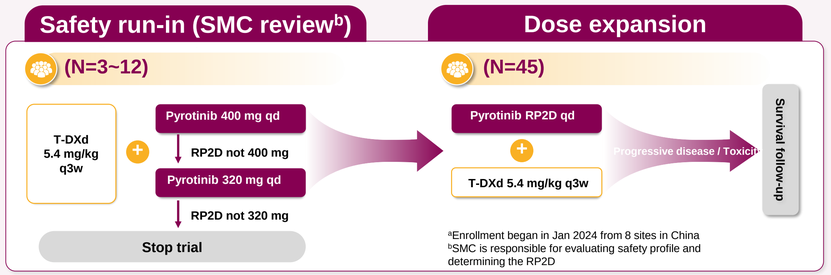
Methods

- This multi-center, single-arm, phase Ib/II study was conducted in 8 sites in China and is comprised of a dose finding stage (phase Ib) followed by a dose expansion stage (phase II).
- Patients with no prior chemotherapy or HER2-targeted therapy in the metastatic setting who have experienced relapse with a disease-free interval (DFI) > 6 months from the completion of neoadjuvant or adjuvant treatment to advanced or metastatic diagnosis are eligible for enrollment. Asymptomatic or treated brain metastases is allowed.
- The primary objective of phase Ib was to assess safety and tolerability and determine the recommended phase 2 dose (RP2D). Patients were followed up beyond the 21-day dose-limiting toxicity (DLT) period for safety events.
- The primary objective of phase II was to evaluate the efficacy of T-DXd plus pyrotinib as the 1L treatment of HER2+ mBC.

Study Design

Patients[a]

- Advanced and/or metastatic HER2+ breast cancer
- Treatment naïve in the metastatic setting (DFI > 6 months after the last chemotherapy or HER2-targeted therapy in neoadjuvant / adjuvant therapy permitted)
- Asymptomatic or treated brain metastases are allowed



[a]Enrollment began in Jan 2024 from 8 sites in China
[b]SMC is responsible for evaluating safety profile and determining the RP2D

Results

- As of 28 Jun 2024, 5 HER2+ mBC patients were treated with T-DXd 5.4 mg/kg every 21 days (Q3W) plus pyrotinib 400 mg (n=2) or 320 mg (n=3) once daily as starting dose, with a median duration of follow up of 3.5 months (range, 0.7-5.4). The median age of enrolled patients was 47 years (range, 33-68), and all of them had an ECOG performance status (PS) of 1, 60% (3 of 5) with visceral metastases (Table 1).
- The only DLT was grade 3 anorexia, which occurred during the first cycle in 1 patient who received 400 mg of pyrotinib. This was followed by a de-escalation to the pyrotinib 320 mg cohort, where no DLT occurred.
- The most common treatment-emergent adverse events (TEAEs) included diarrhea (100%, 5 of 5), nausea (100%, 5 of 5), vomiting (100%, 5 of 5), anorexia (60%, 3 of 5), alanine aminotransferase (ALT) increased (60%, 3 of 5), aspartate aminotransferase (AST) increased (60%, 3 of 5), and weight loss (60%, 3 of 5), etc. Grade 3 TEAEs included anorexia and ALT increased (in 1 patient in the pyrotinib 400 mg cohort), and diarrhea (in 1 patient in the pyrotinib 320 mg cohort). There was no grade 4 or 5 TEAEs (Table 2).
- All 4 patients whose tumors were evaluable had achieved partial responses.

Conclusions

Pyrotinib 320 mg was identified as RP2D. The combination regimen of T-DXd plus pyrotinib showed a manageable safety profile with preliminary antitumor activity as the 1L treatment in patients with HER2+ mBC and will be explored in phase II stage.

Table 1. Baseline characteristics

	Pyrotinib 400 mg (n=2)	Pyrotinib 320 mg (n=3)	Total (n=5)
Age, years - mean (range)	56 (47-65)	48 (33-68)	51 (33-68)
Female sex - no.(%)	2 (100)	3 (100)	5 (100)
ECOG PS - no.(%)			
0	0	0	0
1	2 (100)	3 (100)	5 (100)
HR Status - no.(%)			
Positive	0	2 (66.7)	2 (40)
Negative	2 (100)	1 (33.3)	3 (60)
HER2 Status - no.(%)			
IHC 3+	2 (100)	2 (66.7)	4 (80)
IHC 2+, ISH+	0	1 (33.3)	1 (20)
Sum of diametersof target lesions, mm - mean (range)	20 (18-22)	93 (36-138)	63.8 (18-138)
Metastasis - no.(%)			
Liver	2 (100)	1 (33.3)	3 (60)
Lung	0	1 (33.3)	1 (20)
Brain	0	0	0
Bone	2 (100)	1 (33.3)	3 (60)
Others	0	3 (100)	3 (60)
Previous therapy in the context of (neo)adjuvant setting - no.(%)			
Chemotherapy	1 (50)	2 (66.7)	3 (60)
Anti-HER2 therapy	1 (50)	1 (33.3)	2 (40)

Table 2. TEAEs of all grades that occurred in all patients and of grade ≥3 that occurred in one or more patients from screening visit until data cut-off date

TEAEs	Pyrotinib 400mg (n=2)		Pyrotinib 320mg (n=3)		Total (n=5)	
	No.	%	No.	%	No.	%
Diarrhea	2	100	3	100	5	100
Grade ≥3	0		1	33.3	1	33.3
Nausea	2	100	3	100	5	100
Vomiting	2	100	3	100	5	100
Anorexia	1	50	2	66.7	3	60
Grade ≥3	1	50	0		1	20
ALT increased	2	100	1	33.3	3	60
Grade ≥3	1	50	0		1	20
AST increased	2	100	1	33.3	3	60
Weight loss	2	100	1	33.3	3	60
Creatinine increased	2	100	0		2	40
Dental ulcer	2	100	0		2	40
Anemia	1	50	1	33.3	2	40
WBC decreased	1	50	1	33.3	2	40
Hypokalemia	1	50	1	33.3	2	40
Constipation	1	50	1	33.3	2	40
Dizziness	0		2	66.7	2	40
Asthenia	0		2	66.7	2	40
Pain of skin	0		2	66.7	2	40
Thrombocytopenia	1	50	0		1	20
Hypoalbuminemia	1	50	0		1	20
Urine output decreased	1	50	0		1	20
Dyspepsia	1	50	0		1	20
Neutrophil count decreased	0		1	33.3	1	20
GGT increased	0		1	33.3	1	20
ALP increased	0		1	33.3	1	20
Headache	0		1	33.3	1	20
Abdominal pain	0		1	33.3	1	20
Hyperhidrosis	0		1	33.3	1	20
Fever	0		1	33.3	1	20
Somnolence	0		1	33.3	1	20
Alopecia	0		1	33.3	1	20

Abbreviations

SMC, safety monitoring committee;; ECOG, Eastern Cooperative Oncology Group, ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; WBC, white blood cell

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Disclosures

Dr. Ying Fan declares no conflicts of interest.