813P

Efficacy and safety of trastuzumab deruxtecan in HER2-expressing uterine carcinosarcoma (STATICE TRIAL, NCCH1615): A MULTICENTER, PHASE 2 CLINICAL TRIAL

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Introduction

- Uterine carcinosarcoma (UCS) is an uncommon and highly aggressive tumor. Ifosfamide + Paclitaxel, Paclitaxel + Carboplatin therapies are considered as the current standard treatment[1) 2)], however, their prognosis remains poor. The development of novel therapeutics for UCS is needed.
- Human epidermal growth factor receptor 2 (HER2) is a promising therapeutic target for UCS.
- The amplification of *HER2* has been reported in 14–20% of UCS cases[3) 4)] , and the reported overexpression of HER2 (immunohistochemistry (IHC) score 3+) ranges from 20 to 50% [5) 6)].
- Trastuzumab deruxtecan (T-DXd) is a HER2-targeted antibody-drug conjugate with potent topoisomerase I inhibitor payload. We conducted pre-clinical PDX study (1767P) and clinical trial for UCS with T-DXd (813P).

Methods

Key Inclusion Criteria

- Unresectable uterine carcinosarcoma histologically confirmed by the pathologist of each trial site
- Progression after one or more lines of chemotherapy (Ifosfamide + Paclitaxel, Ifosfamide + Cisplatin, Paclitaxel + Carboplatin, Docetaxel + Carboplatin, etc)
- HER2-positive (IHC score 1+ or more lines) by central pathological review
- Age ≥ 20 • Performance status (ECOG) 0 or 1 • ≥ 1 measurable disease (RECIST version 1.1)

Key Exclusion Criteria

- Active concurrent malignancy (except for carcinoma in situ) • History of interstitial lung disease
- Symptomatic congestive heart failure (New York Heart Association Classification II - IV)
- Cancerous meningitis / Symptomatic brain metastasis / Spinal metastasis requiring surgery

HER2 Evaluation

- IHC score was evaluated according to the latest ASCO/CAP criteria for gastric cancer (2016) [7) 8)]
- IHC was performed using a standard FDA-approved IVD kit, the Pathway HER-2 (Clone 4B5), on the BenchMark XT automated system (Ventana Medical Systems Inc., Tucson, AZ, USA) according to the manufacturer's recommended protocol
- Fluorescence in situ hybridization (FISH) was conducted using the PathVysion HER2 DNA probe kit (Abbott Molecular, Des Plaines, IL, USA) according to the manufacturer's recommendations by SRL Co. Ltd., Japan
- HER2 IHC 1+ is defined as HER2-low and HER2 IHC 2+ or 3+ are defined as HER2-high in the trial

Study Design

- STATICE TRIAL (NCCH1615) is a phase 2, multicenter, single arm study (UMIN000029506)
- Primary endpoint
  - ✓ Overall Response Rate (ORR) in HER2-high (HER2 IHC 2+ or 3+) (Central review)
- Secondary endpoints
  - ✓ ORR in HER2-high (Site review)
  - ✓ ORR in HER2-low (HER2 IHC 1+) (Central/Site)
  - ✓ Progression free survival (PFS), Overall survival (OS), Incidence of adverse events
- Thall & Simon (Bayesian) design
- Planned registration number of patients 15 - 35 pts / 2.5 years
  - ✓ HER2-high 15 - 25 pts / 2.5 years
  - ✓ HER2-low 0 - 10 pts / 2.5 years
- Prior distribution (threshold 5%) β (10, 190)
- Posterior distribution (expected 30%) β (0.6, 1.4)
- Required number of response cases 3 - 4 pts

(The posterior probability of ORR exceeds threshold (5%) is over 95%)

Number of patients	15	16	17	18	19	20	21	22	23	24	25
Required response cases	3	3	3	3	3	3	3	4	4	4	4

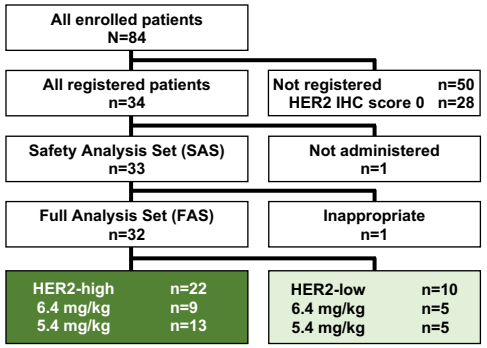
Treatment

- T-DXd was administered every 3 weeks until progressive disease (PD) or intolerable toxicity appeared. Initially 6.4 mg/kg was administered (n=14), following safety evaluation, the dosage was reduced to 5.4 mg/kg (n=18)

Results

Patient Flow Diagram

- Patients were enrolled from February 2018 to June 2020 at 7 institutions in Japan
- Data cut-off was done in December 2020
- Twenty-eight patients (33.3%) were excluded from registration due to HER2 IHC score 0
- One patient did not receive T-DXd due to progression of UCS
- One patient was excluded from FAS due to central review with no measurable target lesion

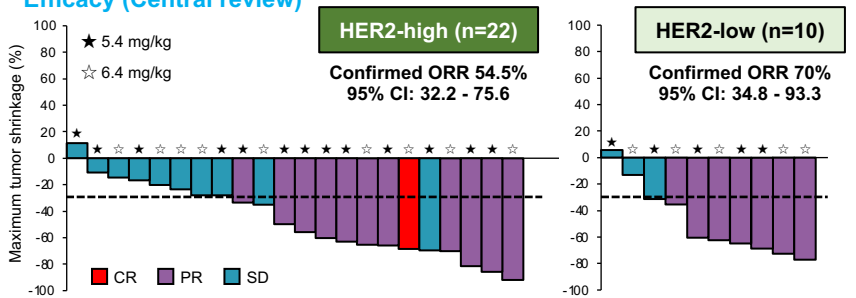


Patient Characteristics

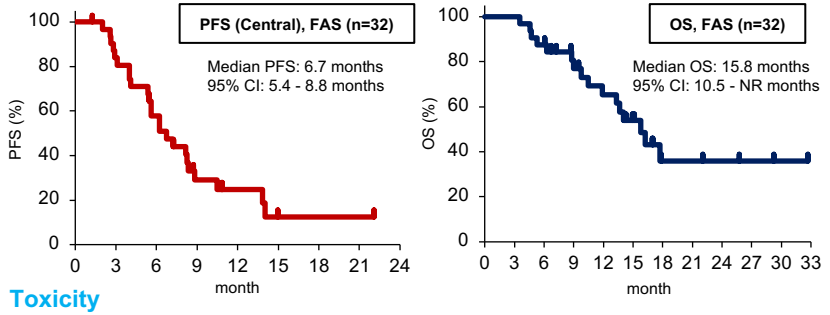
HER2 IHC score (N=84)
0: 28 (33%), 1: 24 (29%)
2: 22 (26%), 3: 10 (12%)

		All (n=34)	(%)	FAS (n=32)	(%)
Age (years)		45- 81	65.5 (median)	45-81	64.5 (median)
PS (ECOG)	0	25	(73.5)	24	(75)
	1	9	(26.5)	8	(25)
HER2 (IHC)	1	11	(32.4)	10	(31.3)
	2	16	(47.1)	15	(46.9)
	3	7	(20.6)	7	(21.9)
HER2 (FISH)	Negative	26	(76.5)	24	(75)
	Positive	8	(23.5)	8	(25)
Prior regimens	1			17	(53.1)
	2			9	(28.1)
	≥ 3			6	(18.8)

Efficacy (Central review)



Confirmed Response Rate	CR (n, %)		PR (n, %)		SD (n, %)		PD (n, %)		ORR (%)
HER2-high (n=22)	1	(4.5)	11	(50)	10	(45.5)	0	(0)	54.5
HER2-low (n=10)	0	(0)	7	(70)	3	(30)	0	(0)	70



Toxicity

Adverse Event	Grade	SAS (n=33)	(%)
Any	3 - 4	20	(60.6)
Anemia	3 - 4	8	(24.2)
Neutropenia	3 - 4	9	(27.3)
Fatigue	3 - 4	2	(6.1)
Pneumonitis	1	4	(12.1)
	2	4	(12.1)
	3	1	(3.0)
Leading to drug withdrawal (permanent)		11	(33.3)

Discussion

- T-DXd showed potent anti-tumor activity for UCS which has resistance to standard chemotherapy.
- Pneumonitis related to T-DXd was observed in 27% of patients, however all pneumonitis were clinically manageable and no death was reported from drug related AEs. It is necessary to investigate what causes T-DXd related pneumonitis of UCS patients.

Conclusion

- The primary endpoint of ORR in HER2 2+/3+ of unresectable UCS was met in STATICE TRIAL.
- T-DXd showed promising efficacy not only in HER2 2+/3+ but also in HER2 1+ of unresectable UCS.
- Pneumonitis must be monitored carefully.
- T-DXd has possibility to become a novel treatment option for UCS.

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