454P

A Multicenter Randomized Open-Label Phase 2 Study Investigating Optimal Antiemetic Therapy for Patients with Advanced/Recurrent Gastric Cancer Treated with Trastuzumab Deruxtecan (T-DXd) : EN-hance Study

Akira Ooki[1], Toru Aoyama[2], Koji Oba[3], Kazuhiro Nishikawa[4], Ryohei Kawabata[5], Michitaka Honda[6], Hiromichi Maeda[7], Mitsuro Kanda[8], Keiji Sugiyama[9], Akitaka Makiyama[10], Kenki Segami[11], Masazumi Takahashi[12], Yoshiaki Shindo[13], Tsutomu Namikawa[7], Takashi Oshima[14], Aya Katayama[15], Kazuhito Shiosakai[15], Junichi Sakamoto[16]

1 The Cancer Institute Hospital of Japanese Foundation for Cancer Research, 2 Yokohama City University Hospital, 3 The University of Tokyo Graduate School of Medicine, 4 Osaka Police Hospital, 5 Sakai City Medical Center, 6 Fukushima Medical University, 7 Kochi Medical University Hospital, 8 Nagoya University Graduate School of Medicine, 9 Nagoya Medical Center, 10 Gifu University Hospital, 11 Saiseikai Yokohama-shi Nanbu Hospital, 12 Yokohama Municipal Citizen's Hospital, 13 Nakadori general Hospital, 14 Kanagawa Cancer Center Hospital, 15 Daiichi Sankyo Co., Ltd, 16 Tokai Central Hospital

BACKGROUND

- Trastuzumab deruxtecan (T-DXd) is approved as treatment for HER2-positive gastric cancer, HER2-positive and HER2-low breast cancer, and for HER2 mutated NSCLC in several countries and is considered moderately or high risk emetogenicity. [1,2]
- The emesis associated with T-DXd treatment has not been fully evaluated, and the effectiveness of conventional prophylaxis is unknown.
- Nausea and vomiting can significantly affect a patient's quality of life, leading to poor compliance with further treatment. Therefore, we sought to identify the optimal combination of antiemetic agents with T-DXd.

OBJECTIVES

- This study's objective was to compare the complete response rate of the Triplet or Doublet antiemetic regimens as a primary endpoint for 3rd or later line for gastric cancer in Japan.
- Considering the importance of objective patient assessment in the evaluation of antiemetics, the emetic events and nausea were evaluated using Likert scale and NRS based on voluntary patient reported outcome for 21 days after T-DXd administration
- The onset time and duration of emetic events/nausea were also evaluated.
- The data from this study might contribute to improving the continuity of T-DXd treatment, reducing the physical and mental burden on patients associated with T-DXd treatment, and improving their QOL.

CONCLUSION

- Both antiemetic prophylaxis regimens did not meet the prespecified antiemetic CR rate（≥18 of 29 patients）.
- This study, which used patient reported outcome to assess emetic events, has resulted in a higher rate of emetic events compare to monitoring by physicians reported in previous studies.
- The long half-life of T-DXd might be a contributory factor to delayed N&V. Further research may help to fully characterize nausea and vomiting with T-DXd in GC patients.

METHODS

Study Design

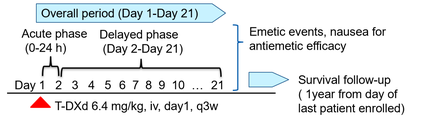
- This study was an exploratory, parallel-group, open-label, active-controlled, randomized, Phase 2 controlled study.

*GEJ: gastroesophageal Junction

(allocation ratio 1.0 as FAS patients)

Stratification factor:
Study site, gastrectomy (Y/N), and gender

Evaluation Schedule



Scheduled Prophylactic Antiemetic Regimen

Regimen Group	Antiemetic treatment	Day 1	Day 2	Day 3	Day 4	Day 5
Triplet Regimen	aprepitant (fosaprepitant) palonosetron dexamethasone	125 mg, po (150 mg, iv) 0.75 mg, iv 9.9 mg, iv	80 mg, po 8.0 mg, po	80 mg, po 8.0 mg, po	8.0 mg, po	※
Doublet Regimen	palonosetron dexamethasone	0.75 mg, iv 9.9 mg, iv	8.0 mg, po	8.0 mg, po	※	

※ Can extend DEX administration according to doctor's decision.

- Aprepitant, palonosetron, dexamethasone were prohibited from 24 h prior to T-DXd administration until the end of the efficacy evaluation period, except prespecified antiemetic treatment.
- Other antiemetics agents were allowed for use only as rescue agents.
- NK1 receptor antagonists were also prohibited as rescue agents.

Endpoints

Primary Endpoint

- Complete Response (CR) rate (Overall period; Day 1-21)

$$\text{CR rate (\%)} = \frac{\text{No. of patients with no emetic events, no antiemetic rescue treatment after starting T-DXd}}{\text{No. of patients for analysis}} \times 100$$

Secondary Endpoints

- **CR rate (Acute phase; Day 1, Delayed phase; Day 2-21)**
- **Complete Control (CC) rate (Overall period; Day 1-21, Acute phase; Day 1, Delayed phase; Day 2-21)**

$$\text{CC rate (\%)} = \frac{\text{No. of patients with no emetic events, no antiemetic rescue treatment, and no or mild nausea after starting T-DXd}}{\text{No. of patients for analysis}} \times 100$$

- **Total Control (TC) rate (Overall period; Day 1-21, Acute phase; Day 1, Delayed phase; Day 2-21)**

$$\text{TC rate (\%)} = \frac{\text{No. of patients with no emetic events, no antiemetic rescue treatment, and no nausea after starting T-DXd}}{\text{No. of patients for analysis}} \times 100$$

- **Time to Treatment Failure**
  Time to the first emetic event or the first antiemetic treatment
- **Safety Assessment (Day 1-21)**
  CTCAE ver.5.0
- **Overall Survival (1 year follow-up)**
  * Not yet reported

Definitions for Emetic Events' Endpoints	Emetic Events	Antiemetic Rescue Treatment	Nausea
Complete Response (CR)	No	No	Any allowed
Complete Control (CC)	No	No	No / mild allowed
Total Control (TC)	No	No	No

Criteria

Key Inclusion Criteria

- Age ≧ 20 years (at informed consent)
- HER2 positive (IHC 3+ or IHC 2+ and, ISH +) GC or GEJ adenocarcinoma
- Scheduled to receive T-DXd as 3rd or later-line treatment
- ECOG PS 0 to 2
- Maintaining adequate organ functions and met the criteria
  - ALT: ≤126U/L (liver met: ≤210 U/L), AST: ≤126 U/L (liver met: <150 U/L), T-Bil: ≤2.5 mg/dl (liver met: ≤4.5 mg/dl), Ccr: ≥30 mL/min
- Written informed consent

Key Exclusion Criteria

- Complication or history of interstitial lung disease
- History of hypersensitivity to NK1 receptor antagonist, 5-HT_3 receptor antagonist, DEX, Trastuzumab, excipients of T-DXd
- Vomiting or nausea ≧ CTCAE Grade 2
- History of T-DXd therapy

Rationale for the Target Sample Size

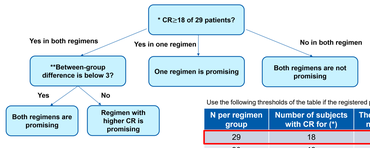
- Previously reported incidence of emetic events are as follows.

	T-DXd Phase 1 study, 6.4 mg/kg Multiple cancer type[3]	DESTINY-Gastric01 study, 6.4 mg/kg 3rd or later-line, gastric cancer[4]
Vomiting (%, n)	52.5% (31/59)	26.4% (33/125)
Any antiemetic treatment predefined in the protocol?	No prophylactic antiemetic treatment	Used prophylactic antiemetic treatments (5-HT only, DEX only, Dex+5-HT, DEX+5-HT+NK1, other)

- In T-DXd phase 1 study, emetic events occurred 52.5% (31 of 59 pts). Since the phase 1 study did not use systemic antiemetic administration, it is referred to as the standard in the case of not adequately using antiemetic agents.
- Given the use of antiemetics in the DESTINY-Gastric01 study and the possibility of a relatively better PS, the expected CR rate for EN-hance study was set at 70% (equivalent to a 30% incidence of emetic events).
- With the threshold CR rate of 45% and the expected CR rate of 70%, and alpha 1 = 0.05, beta 1 = 0.2, alpha 2 = 0.05, and beta 2 = 0.3, as proposed in Hou et al.,5 the target sample size is calculated to be 29 subjects per group, for a total of 58 subjects.
- Assuming 10% dropout/withdrawal during the study period, the target sample size for each of the triplet and doublet antiemetic regimen groups in this study is calculated to be 32 subjects.

Primary Analysis

- Estimated the CR rate in each regimen during the total study period and its 90% confidence interval based on the Agresti-Coull method.
- The following algorithm was applied for comparing two regimens.



Use the following thresholds of the table if the registered patients per group exceed 29.

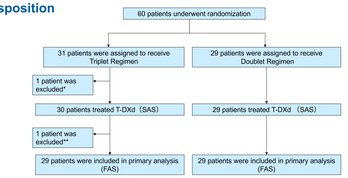
N per regimen group	Number of subjects with CR for (*)	The difference in subject number of CR for (**)
29	18	3
30	19	3
31	20	2
32	21	2
33	22	2

Patient Reported Outcome

- **Patient symptom diary (for Primary endpoint)**
  - Emetic events (defined as vomiting and retching) were recorded number of events and onset time of the first event every day up to Day 21.
  - Emetic events were recorded occurring with an interval of less than 1 minute were counted as one episode.
  - Nausea was recorded a four-item scale, as no nausea, mild, moderate, and severe, according to Likert scale every day up to Day 21.

RESULTS

Patient Disposition



*One patient was excluded due to inability to receive treatment with T-DXd for disease progression
** One patient was excluded due to Informed consent violation

Patients' Characteristics

Patients Characteristics	Triplet Regimen (N = 29)	Doublet Regimen (N = 29)	Total (N=58)
Age			
Median (range)	72.0 (53, 83)	72.0 (41, 82)	72.0 (41, 83)
Gender, n (%)			
Male	22 (75.9)	23 (79.3)	45 (77.6)
Female	7 (24.1)	6 (20.7)	13 (22.4)
Body mass index			
Median (range)	19.50 (13.5, 27.3)	21.00 (16.7, 27.8)	20.75 (13.5, 27.8)
ECOG performance status, n (%)			
0	14 (48.3)	17 (58.6)	31 (53.4)
1	14 (48.3)	11 (37.9)	25 (43.1)
2	1 (3.4)	1 (3.4)	2 (3.4)
HER2 status, n (%)			
IHC3+	21 (72.4)	20 (69.0)	41 (70.7)
IHC2+ and ISH positive	8 (27.6)	9 (31.0)	17 (29.3)
Histological type, n (%)			
Intestinal	24 (82.8)	26 (89.7)	50 (86.2)
Diffuse	4 (13.8)	2 (6.9)	6 (10.3)
Other	1 (3.4)	1 (3.4)	2 (3.4)
Previous systemic therapy, n (%)			
1/2 line	21 (72.4)	19 (65.5)	40 (69.0)
≧ 3 line	8 (27.6)	10 (34.5)	18 (31.0)
Gastrectomy, n (%)			
No	17 (58.6)	15 (51.7)	32 (55.2)
Yes	12 (41.4)	14 (48.3)	26 (44.8)
Previous platinum regimen, n (%)			
No	7 (24.1)	7 (24.1)	14 (24.1)
Yes	22 (75.9)	22 (75.9)	44 (75.9)
Previous immune check point inhibitor, n (%)			
No	19 (65.5)	21 (72.4)	40 (69.0)
Yes	10 (34.5)	8 (27.6)	18 (31.0)
Alcohol intake before 30 days			
No	25 (86.2)	19 (65.5)	44 (75.9)
Yes	4 (13.8)	10 (34.5)	14 (24.1)
Albumin			
Median (range)	3.40 (2.6, 4.3)	3.50 (2.0, 4.6)*	3.40(2.0, 4.6)**
Albumin-Bilirubin (ALBI)			
Median (range)	-2.280 (-3.10, -1.60)	-2.385 (-3.20, -0.82)*	-2.340 (-3.20, -0.82)**
CRP/Albumin ratio (CAR)			
Median (range)	0.060 (0.00, 2.71)	0.065 (0.00, 3.80)*	0.060 (0.00, 3.80)**

* n=28, ** n=57

Complete Response Rate in Overall Period as Primary Endpoint (FAS analysis)

	Triplet Regimen (N = 29)	Doublet Regimen (N = 29)
Complete Response, n	11	12
Complete Response Rate, % (90%CI)	37.9 (24.7, 53.2)	41.4 (27.7, 56.5)
Predefined CRs required to be considered effective, n	18	18

The designated threshold was not met in either group.

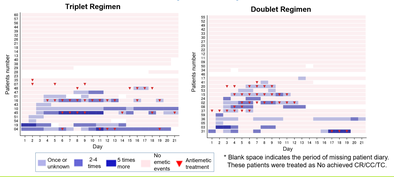
Proportion of Patients Achieving CR, CC and TC during Each Phase

	Triplet Regimen (N = 29)	Doublet Regimen (N = 29)
Complete Response (CR), n (%; 90%CI)		
Overall period	11 (37.9%; 24.7, 53.2)	12 (41.4%; 27.7, 56.5)
Acute phase*	25 (86.2%; 72.2, 94.1)	25 (86.2%; 72.2, 94.1)
Delayed phase**	11 (37.9%; 24.7, 53.2)	12 (41.4%; 27.7, 56.5)
First 5 days***	16 (55.2%; 40.2, 69.3)	15 (51.7%; 37.0, 66.2)
Complete Control (CC), n (%; 90%CI)		
Overall period	9 (31.0%; 19.0, 46.4)	11 (37.9%; 24.7, 53.2)
Acute phase*	24 (82.8%; 68.3, 91.7)	25 (86.2%; 72.2, 94.1)
Delayed phase**	10 (34.5%; 21.8, 49.8)	11 (37.9%; 24.7, 53.2)
First 5 days***	16 (55.2%; 40.2, 69.3)	15 (51.7%; 37.0, 66.2)
Total Control (TC), n (%; 90%CI)		
Overall period	5 (17.2%; 8.3, 31.7)	10 (34.5%; 21.8, 49.8)
Acute phase*	23 (79.3%; 64.5, 89.1)	23 (79.3%; 64.5, 89.1)
Delayed phase**	6 (20.7%; 10.9, 35.5)	10 (34.5%; 21.8, 49.8)
First 5 days***	11 (37.9%; 24.7, 53.2)	14 (48.3%; 33.8, 63.0)

*Acute phase; 0 h-24 h, **Delayed phase; Day 2-Day 21, ***First 5 days: Day 1-Day 5
† "First 5 days" is exploratory analysis

Emetic events and nausea were controlled in approx. 80% of patients in the acute phase, but less than 40% of patients in the delayed phase (over 24 h).

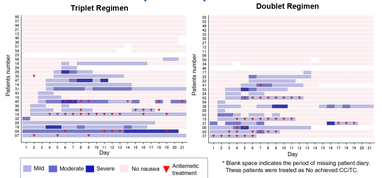
Duration of Emetic Events based on patient-reported outcome



* Blank space indicates the period of missing patient diary. These patients were treated as No achieved CR/CC/TC.

- Median onset time of the first emetic events was 3.0 days (range, 2-13 days) in Doublet regimen and 3.0 days (range, 1-16 days) in Triplet regimen.
- Median duration of emetic events was 3.5 days (range, 1-14 days) in Doublet regimen and 4.0 days (1-19 days) in Triplet regimen .

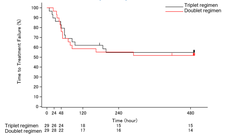
Duration of Nausea based on patient-reported outcome



* Blank space indicates the period of missing patient diary. These patients were treated as No achieved CC/TC.

- Median onset time of the first nausea was 2.0 days (1-13 days) in Doublet regimen and 3.0 days (range, 1-19 days) in Triplet regimen.
- Median duration of nausea was 8.0 days (1-14 days) in Doublet regimen and 10.0 days (range, 1-21 days) in Triplet regimen.

Time to Treatment Failure (TTF)



Regimen	n	Emetic events or antiemetic treatment	MST (90%CI)	log-rank test χ^2	log-rank test p
Triplet Regimen	29	13 (45.2)	- (84.0, -)	0.0621	0.8032
Doublet Regimen	29	14 (48.3)	- (71.0, -)		

TTF is the time from the start of T-DXd dosing to the onset of the first emetic event or the first antiemetic treatment, whichever occurs first.

No difference between Triplet regimen and Doublet regimen

Adverse Events Occurring >5%*

Adverse Events Term	Triplet Regimen (n = 30)		Doublet Regimen (n = 29)		Total (n = 59)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Anorexia	8 (26.7)	4 (13.3)	5 (17.2)	0 (0.0)	13 (22.0)	4 (6.8)
Malaise	7 (23.3)	0 (0.0)	8 (27.6)	0 (0.0)	15 (25.4)	0 (0.0)
Neutrophil count decreased	7 (23.3)	6 (20.0)	3 (10.3)	1 (3.4)	10 (16.9)	7 (11.9)
Platelet count decreased	5 (16.7)	1 (3.3)	1 (3.4)	0 (0.0)	6 (10.2)	1 (1.7)
Fatigue	4 (13.3)	1 (3.3)	2 (6.9)	0 (0.0)	6 (10.2)	1 (1.7)
Anemia	4 (13.3)	2 (6.7)	3 (10.3)	1 (3.4)	7 (11.9)	3 (5.1)
Febrile neutropenia	3 (10.0)	3 (10.0)	2 (6.9)	1 (3.4)	5 (8.5)	4 (6.8)
Fever	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)
White blood cell decreased	2 (6.7)	1 (3.3)	2 (6.9)	0 (0.0)	4 (6.8)	1 (1.7)
Aspartate aminotransferase increased	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)
Peripheral sensory neuropathy	2 (6.7)	0 (0.0)	1 (3.4)	0 (0.0)	3 (5.1)	0 (0.0)

* At least 5%* in either regimen or total
Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

Multivariable Analysis with CR, Emetic Events and Nausea

Variables	Multivariable analysis	
	Risk difference (95% CI)	*P* value
Achieved complete response (CR)		
BMI (≧ vs. < 20.75)	0.222 (-0.061, 0.505)	0.1211
Alcohol intake before 30 days (Yes vs. No)	-0.222 (-0.527, 0.083)	0.1493
Observed emetic events		
Age (≧ vs. < 65 years)	0.219 (-0.084, 0.523)	0.1521
BMI (≧ vs. < 20.75)	-0.362 (-0.647, -0.077)	**0.0139**
Gastrectomy (Yes vs. No)	0.255 (0.003, 0.507)	**0.0476**
Alcohol intake before 30 days (Yes vs. No)	0.288 (-0.029, 0.605)	0.0743
Albumin (≧ vs. < 3)	0.374 (0.046, 0.701)	**0.0263**
Albumin/ total protein (≧ vs. <0.55)	-0.222 (-0.500, 0.055)	0.1139
Observed nausea		
Age (≧ vs. < 65 years)	-0.229 (-0.525, 0.066)	0.1246
Gastrectomy (Yes vs. No)	0.202 (-0.102, 0.507)	0.1877
Previous ICI (Yes vs. No)	0.358 (0.036, 0.679)	**0.0299**
Previous systemic therapies (≧3 vs. 1/2)	-0.236 (-0.588, 0.116)	0.1834
ALBI (≧ vs. <-2.34)	0.350 (0.045, 0.654)	**0.0254**

The backward stepwise regression was used to test the robustness of the model.
Factors included in these analyses were regimen (doublet/triplet), age, gender, BMI, performance status, gastrectomy, previous ICI, previous platinum regimen, previous systemic therapies, smoking history, alcohol intake before 30 day at enrollment, albumin, albumin/total protein, ALBI and CAR(CRP/Albumin). Data was shown only selected variables (backward, p<0.2).

SUMMARY

- This EN-hance study's objective was to compare CR rate of Triplet or Doublet antiemetic regimens recommended by the Japanese guideline for 3rd or later line for GC in Japan. The emetic events and nausea were based on voluntary patient reported outcome.
- CR rate as primary endpoint was not met. Both regimens used during T-DXd treatment did not show enough of antiemetic efficacy. Although the CR rate was over 85% in the acute phase, emetic control was not achieved in the delayed phase.
- The median time for first emetic event or nausea was approximately 3 days, with no difference between the two regimens. In DESTINY-Gastric01 study, the median time for first vomiting and nausea were 6.0 days and 4.0 days, respectively. The EN-hance study's result showed that patient's symptoms appeared earlier than we expected.
- The median cumulative duration of the emetic event during the 21-day period in both regimens was approximately 4 days, with the median cumulative duration of the first nausea during the 21-day period was 8 days. These results suggested that emetic event or nausea due to T-DXd was longer duration than conventional cytotoxic agents. The EN-hance study's result suggested that the antiemetics evaluated in this study might not be enough for management of vomiting and nausea due to T-DXd.

DISCUSSION

- This EN-hance study's result suggests that current conventional antiemetic schedules are insufficient to adequately control, and improvements may be necessary.
- T-DXd is an antibody-drug conjugate with sustained compound generation and a long half-life, which may result in high drug efficacy but also a long duration of emetic events or nausea.
- At present, the mechanism of nausea and vomiting caused by T-DXd is not clear. Currently, clinical trials are being conducted to determine whether the antiemetic effects of T-DXd can be controlled by adding olanzapine to palonosetron + dexamethasone for breast cancer patients (jRCTs031210410/WJOG14320B). [6]
- Physicians reported the occurrence of vomiting in the previous T-DXd studies, while patients reported the occurrence of emetic events in the present study. The discrepancy of adverse events evaluation between physicians' decision and patients' decision was well known.[7]
- Thus, the incidence of vomiting in the EN-hance study's setting may had been underestimated. A future study aimed at preventing vomiting due to T-DXd need to consider incorporating a PRO assessment.
- Since EN-hance study evaluated in patients with late-stage GC, patient background may have influenced the results. Exploratory multivariate analysis suggested that low BMI or low albumin were associated with the risk of emetic events and nausea, but the small sample size made it difficult to draw conclusions. From the perspective of providing more appropriate supportive care, it will be important to consider identify emetic risks as well as more appropriate prophylactic treatment.

Acknowledgements

- We thank the patients who are participating in this EN-hance study as well as their families and caregivers.
- This EN-hance study was supported, in part, by the nonprofit organization Epidemiological & Clinical Research Information Network (ECRIN).
- We are grateful to Mr. Sadao Kikuta, Ms. Michiyo Yamakawa, Ms. Naomi Iwahori, Ms. Miho Sato and Ms.Wakako Fujiki for their excellent contributions as the clinical research coordinator of this study.

Disclosure

- This EN-hance study (jRCT s031200336) was funded by Daiichi Sankyo Co., Ltd.
- Akira Ooki, MD have no conflicts of interest directly relevant to the content of this study.
- For queries, please contact Akira Ooki, MD（akira.oki@jfcr.or.jp）and Toru Aoyama, MD (t-aoyama@lilac.plala.or.jp).

References

1. Japan Society of Clinical Oncology Clinical Practice Guidelines for the proper use of antiemetics, 2023.
2. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology "Antiemesis" Version 2. 2023.
3. Doi T, et al. Lancet Oncol. 2017;18(11):1512-22.
4. Shitara K, et al. N Engl J Med. 2020;382(25):2419-30.
5. Hou W, et al. Statist Med 2013;32(25):4367-79.
6. Sakai H, et al. BMJ Open 2023,13(4): e070304.
7. Basch E, et al. JAMA Oncol. 2017;3(8):1043-50.