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

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Conflict of Interest disclosure slide for representative speakers or investigators

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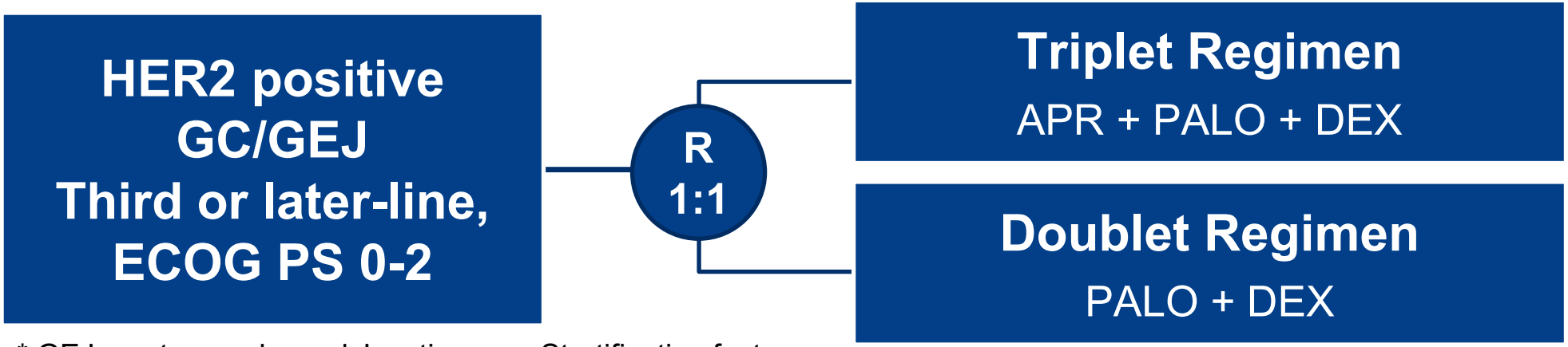
Background and Objectives

- Trastuzumab deruxtecan (T-DXd) is considered moderately or high risk emetogenicity.[1,2]
- However, the risk of emesis has not been fully evaluated in the DESTINY-Gastric01, and the effectiveness of conventional prophylaxis remains unknown.
- This study's objective was to evaluate the complete response (CR) rate of the Triplet or Doublet antiemetic regimens as a primary endpoint for 3rd or later line for gastric cancer in Japan.

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

Study Design

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



APR: aprepitant
PALO: palonosetron
DEX: dexamethasone

* GEJ: gastroesophageal Junction

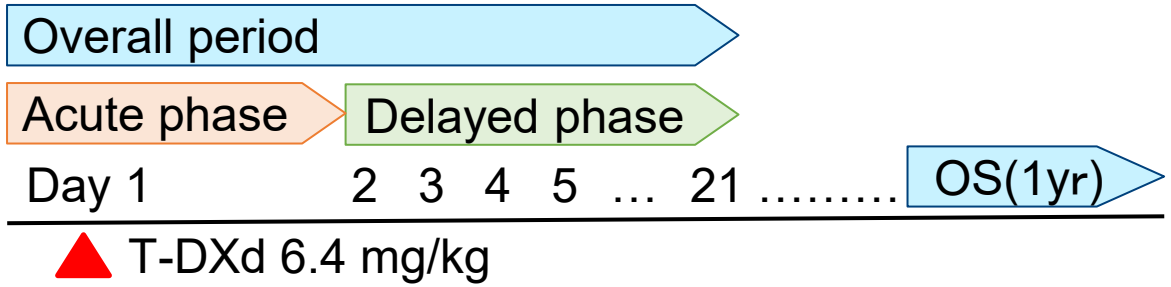
Stratification factor:
Study site, gastrectomy(Y/N), and gender

Protocol Treatment

Regimen Group	Day1	Day2	Day3	Day4	Day5
Triplet Regimen	**T-DXd** 6.4□ /kg **APR** 125 mg **PALO** 0.75 mg **DEX** 9.9 mg	**APR** 80 mg **DEX** 8.0 mg	**APR** 80 mg **DEX** 8.0 mg	**DEX** 8.0 mg	※
Doublet Regimen	**T-DXd** 6.4□ /kg **PALO** 0.75 mg **DEX** 9.9 mg	**DEX** 8.0 mg	**DEX** 8.0 mg	※	

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

Schedule



The emetic events and nausea were evaluated based on patient reported outcome for 21 days.

Endpoints

Primary Endpoint

- **CR rate (Overall period)**

Secondary Endpoints

- **CR rate (Acute phase, Delayed phase)**
- **CC rate**
- **TC rate**
- **TTF**
- **Safety (Day 1-21)**
- **OS (1 year)**

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

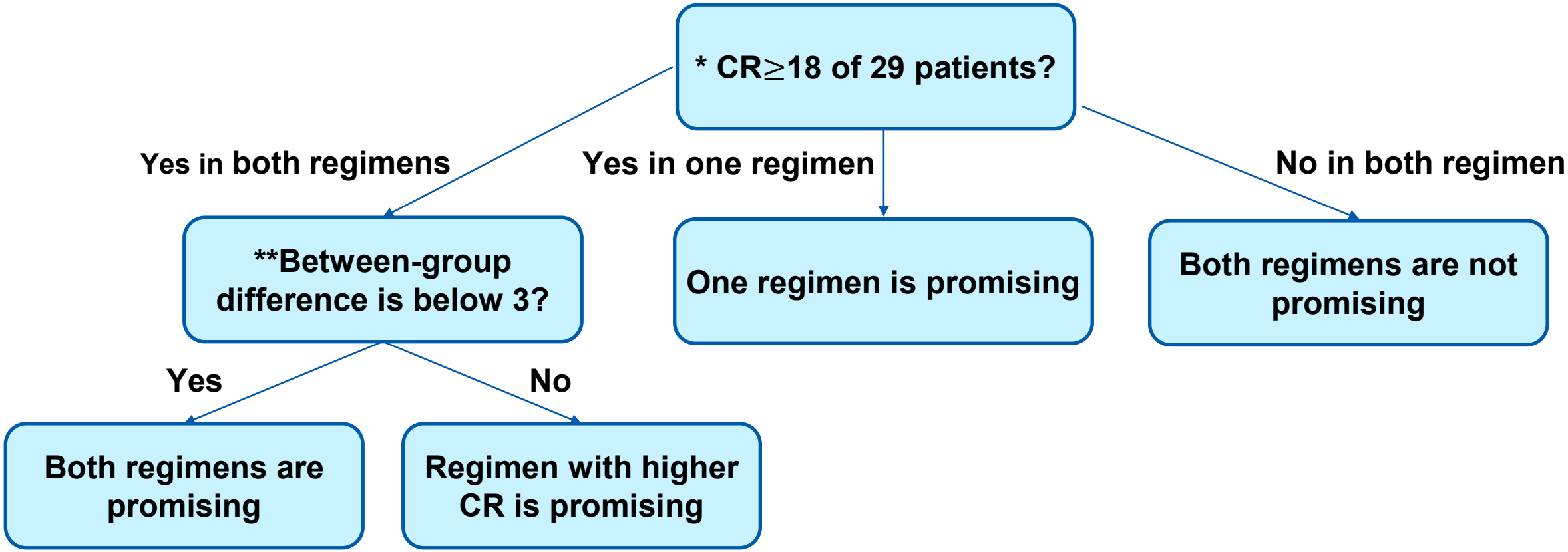
- Age ≧ 20 years
- HER2 positive GC or GEJ adenocarcinoma
- 3rd or later-line treatment
- ECOG PS 0 to 2
- Maintaining adequate organ functions and met the criteria
- Written informed consent

Key Exclusion Criteria

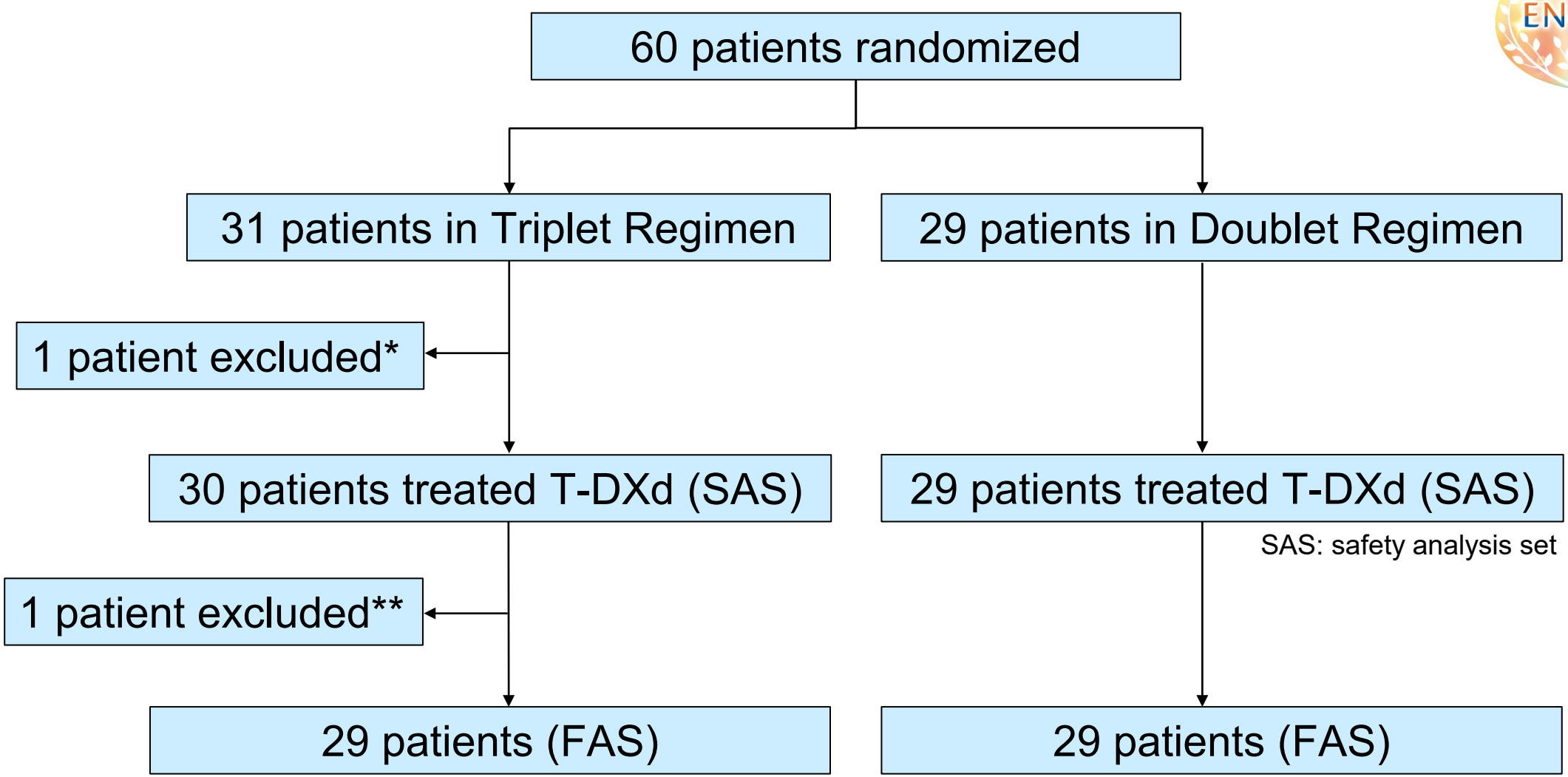
- Complication or history of ILD
- Vomiting or nausea CTCAE Grade 2 or higher
- History of T-DXd therapy

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.



CONSORT Flow Diagram



*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)
Age, median (range)	72.0 (53, 83)	72.0 (41, 82)
Gender, n (%)		
Male	22 (75.9)	23 (79.3)
Female	7 (24.1)	6 (20.7)
BMI, median (range)	19.50 (13.5, 27.3)	21.00 (16.7, 27.8)
ECOG PS, n (%)		
0	14 (48.3)	17 (58.6)
1	14 (48.3)	11 (37.9)
2	1 (3.4)	1 (3.4)
HER2 status, n (%)		
IHC3+	21 (72.4)	20 (69.0)
IHC2+ and ISH positive	8 (27.6)	9 (31.0)
Histological type, n (%)		
Intestinal	24 (82.8)	26 (89.7)
Diffuse	4 (13.8)	2 (6.9)
Other	1 (3.4)	1 (3.4)
Previous systemic therapy, n (%)		
1/2 line	21 (72.4)	19 (65.5)
> 3 line	8 (27.6)	10 (34.5)

Patients Characteristics	Triplet Regimen (N = 29)	Doublet Regimen (N = 29)
Gastrectomy, n (%)		
No	17 (58.6)	15 (51.7)
Yes	12 (41.4)	14 (48.3)
Previous platinum regimen, n (%)		
No	7 (24.1)	7 (24.1)
Yes	22 (75.9)	22 (75.9)
Previous ICI, n (%)		
No	19 (65.5)	21 (72.4)
Yes	10 (34.5)	8 (27.6)
Alcohol intake before 30 days, n (%)		
No	25 (86.2)	19 (65.5)
Yes	4 (13.8)	10 (34.5)

Results

CR Rate in Overall Period as Primary Endpoint (FAS analysis)

	Triplet Regimen (N = 29)	Doublet Regimen (N = 29)
CR, n	11	12
CR Rate, % (90%CI)	37.9 (24.7, 53.2)	41.4 (27.7, 56.5)

Both regimens did not meet the prespecified CR（≥18 of 29 patients）.

Results

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

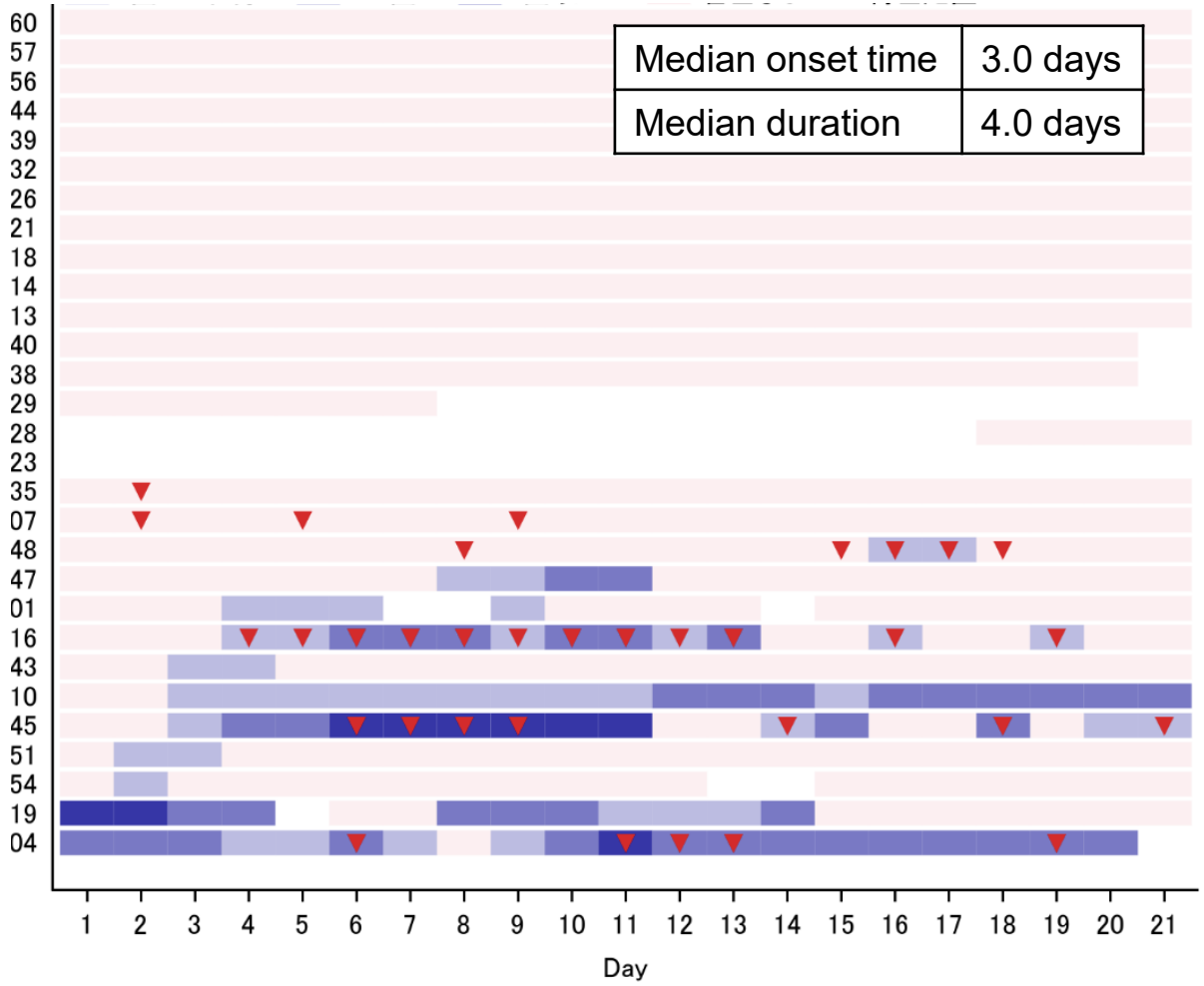
	Triplet Regimen (N = 29)		Doublet Regimen (N = 29)	
	n	% (90% CI)	n	% (90% CI)
CR				
Overall period	11	37.9 (24.7, 53.2)	12	41.4 (27.7, 56.5)
Acute phase*	25	86.2 (72.2, 94.1)	25	86.2 (72.2, 94.1)
Delayed phase**	11	37.9 (24.7, 53.2)	12	41.4 (27.7, 56.5)
CC				
Overall period	9	31.0 (19.0, 46.4)	11	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)
TC				
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)

*Acute phase; 0h-24h, **Delayed phase; Day2-Day21

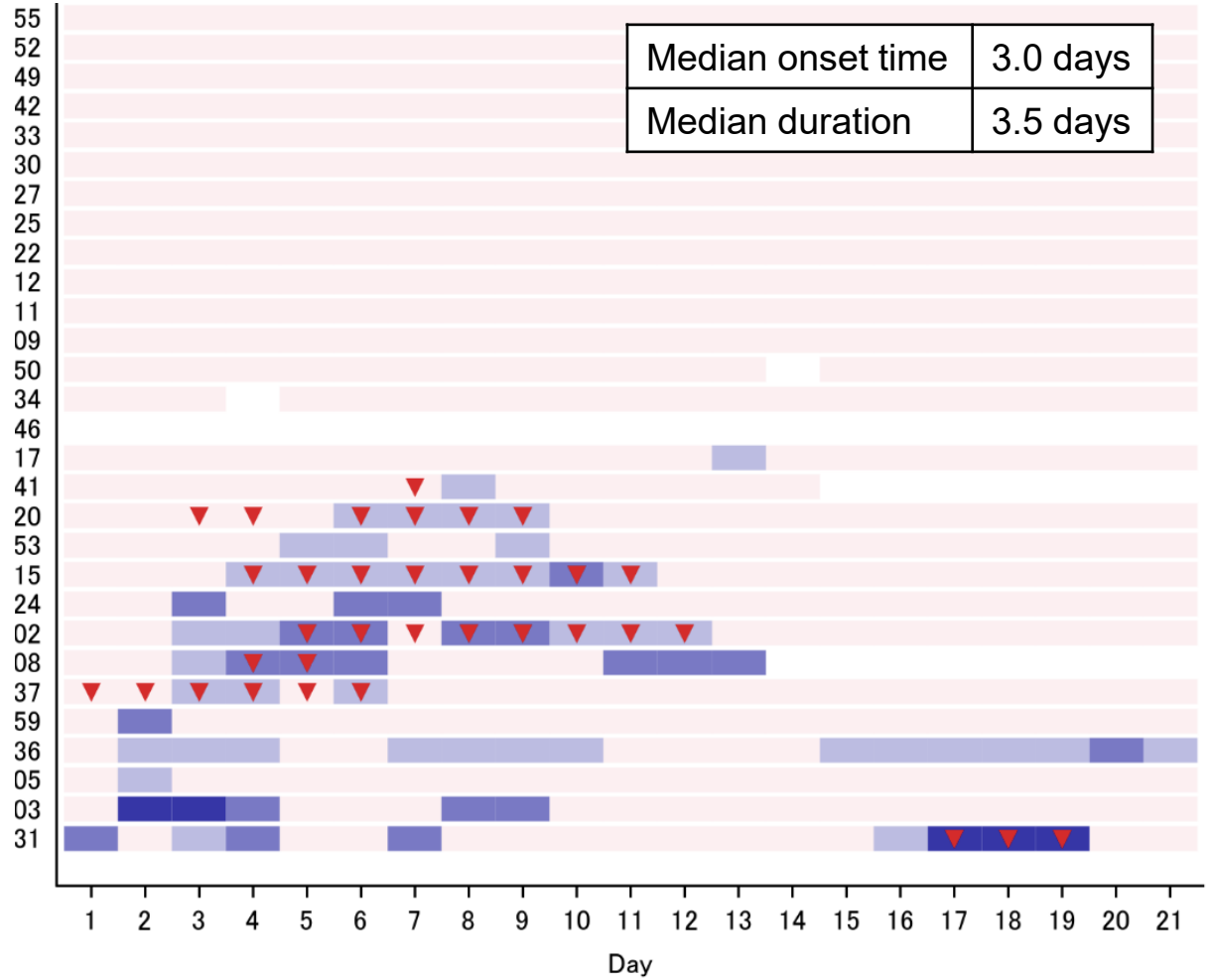
Emetic events and nausea were controlled 86% of patients in the acute phase, but less than 40% of patients in the delayed phase.

Duration of Emetic Events based on patient-reported outcome

Triplet Regimen



Doublet Regimen

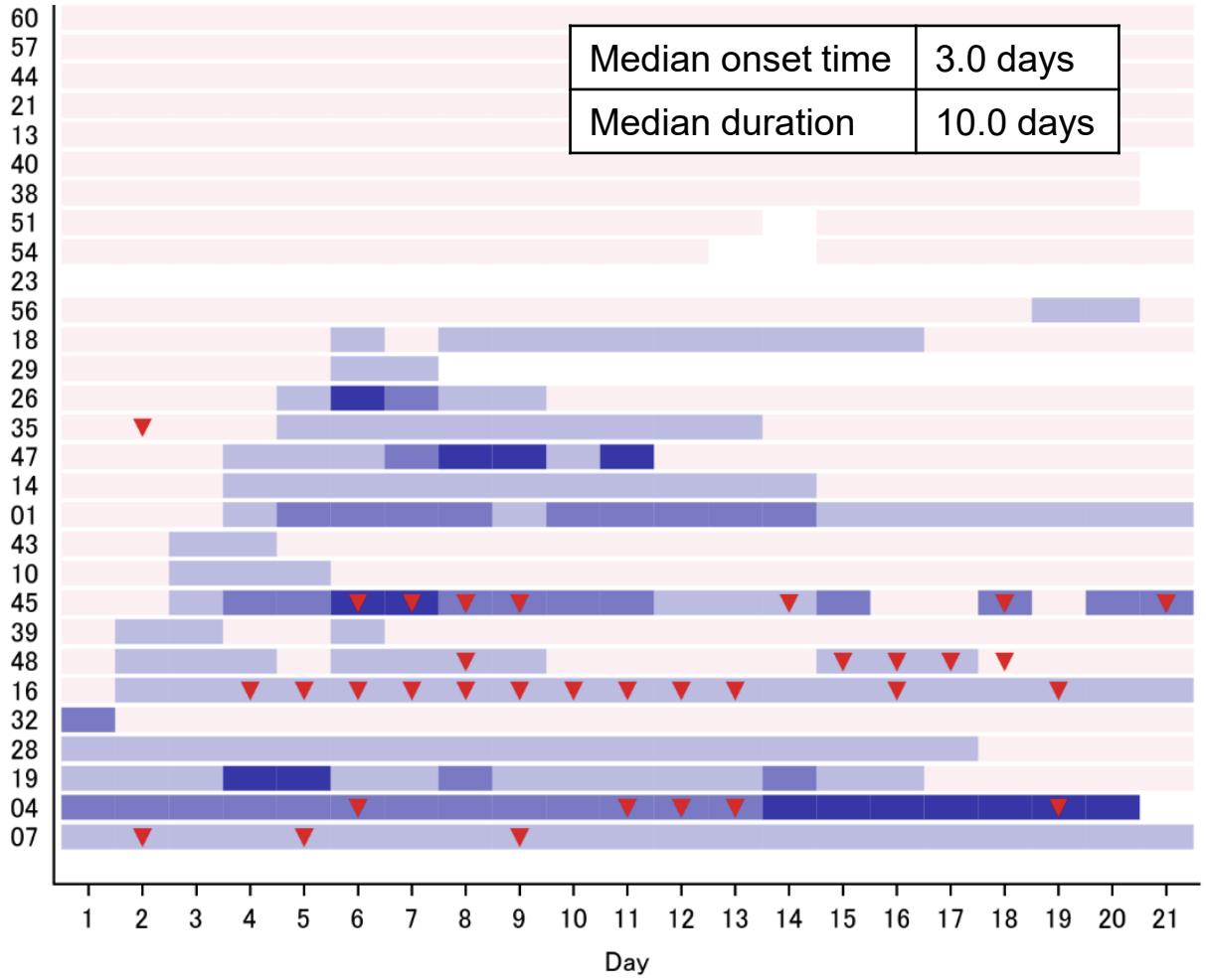


Once or unknown | 2-4 times | 5 times or more | No emetic events | Antiemetic treatment

Duration of Nausea based on patient-reported outcome

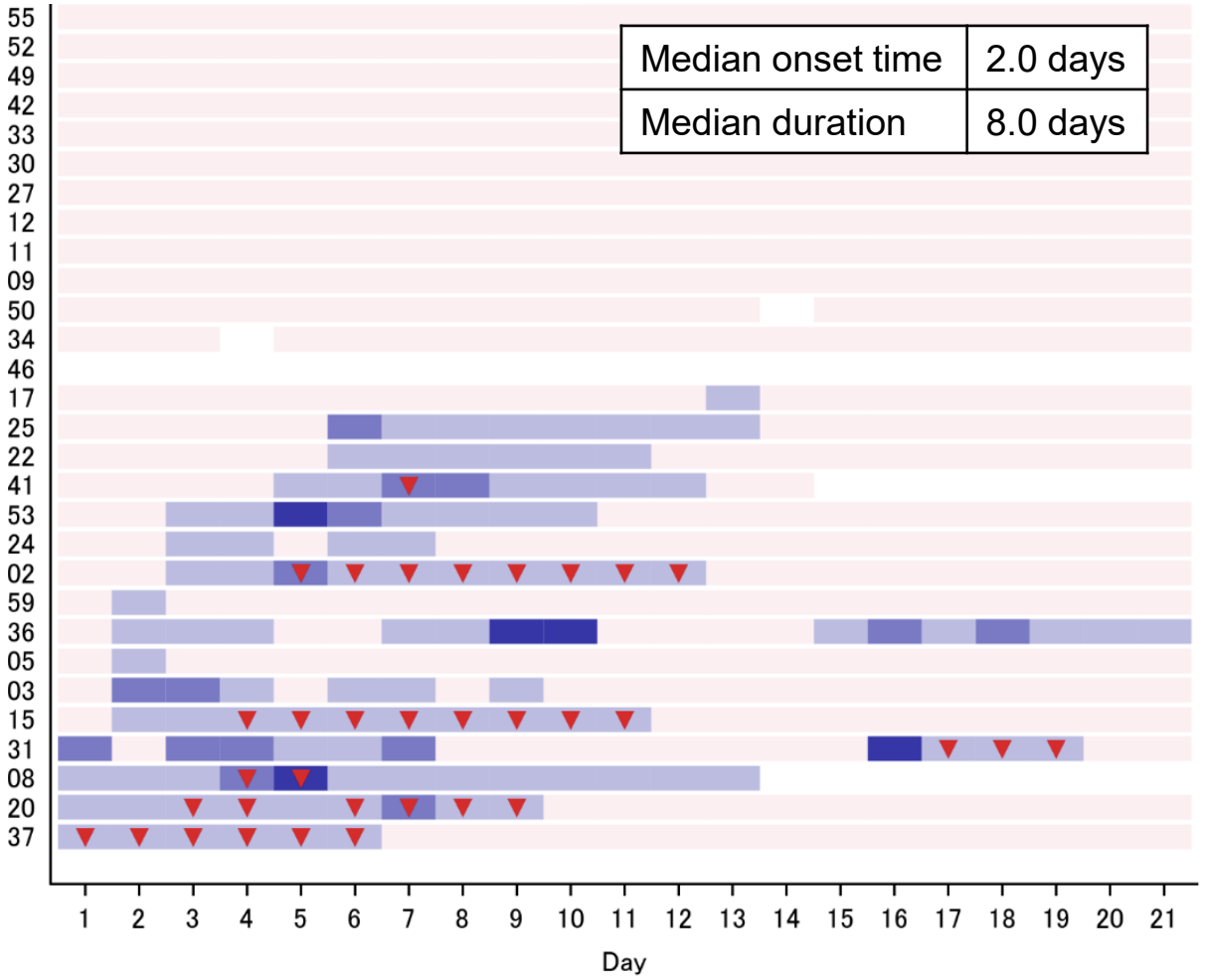
Triplet Regimen

Median onset time	3.0 days
Median duration	10.0 days



Doublet Regimen

Median onset time	2.0 days
Median duration	8.0 days



Mild Moderate Severe No nausea Antiemetic treatment

Adverse Events

Adverse Events Term*	Triplet Regimen (n = 30)		Doublet Regimen (n = 29)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Anorexia	8 (26.7)	4 (13.3)	5 (17.2)	0 (0.0)
Malaise	7 (23.3)	0 (0.0)	8 (27.6)	0 (0.0)
Neutrophil count decreased	7 (23.3)	6 (20.0)	3 (10.3)	1 (3.4)
Platelet count decreased	5 (16.7)	1 (3.3)	1 (3.4)	0 (0.0)
Fatigue	4 (13.3)	1 (3.3)	2 (6.9)	0 (0.0)
Anemia	4 (13.3)	2 (6.7)	3 (10.3)	1 (3.4)
Febrile neutropenia	3 (10.0)	3 (10.0)	2 (6.9)	1 (3.4)
Fever	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
White blood cell decreased	2 (6.7)	1 (3.3)	2 (6.9)	0 (0.0)
Aspartate aminotransferase increased	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	2 (6.7)	0 (0.0)	1 (3.4)	0 (0.0)

* At least 5% in either regimen or total
Common Terminology Criteria for Adverse Events (CTCAE) Version5.0

Conclusion

- Both antiemetic prophylaxis regimens did not meet the prespecified antiemetic CR（≥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 nausea and vomiting. Further research may help to fully characterize nausea and vomiting with T-DXd in GC patients.

Acknowledgements

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