Olanzapine-based triplet antiemetic therapy for patients undergoing trastuzumab deruxtecan: ERICA (WJOG14320B)

トラスツズマブデルクステカン治療を受ける患者に対するオランザピン込みの3剤併用制吐療法:ERICA試験(WJOG14320B)

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On behalf of the ERICA investigators

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発表者・研究責任者の利益相反開示事項

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Background

- Nausea and vomiting are among the most common adverse events reported with T-DXd[1-3]
  - *The incidence of nausea and vomiting is often highest in the first cycle and decreases in subsequent cycles; persistent symptoms may occur throughout the 21-day cycle*[4,5]
  - *The DESTINY clinical trial program did not define specific antiemetic therapy in the protocol and have not evaluated the use, type or efficacy of antiemetic therapy;*[1-3] *therefore, the emetogenic risk of T-DXd has not been fully described, even in recent guidelines*
  - *The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) classify trastuzumab deruxtecan as a high emetogenic risk anticancer agent and the MASCC/ESMO guidelines classify T-DXd's emetogenicity at the high end of the moderate category , which means a triplet or even quadruplet is recommended as prophylactic anti-emetic treatment* [6,7]
- Olanzapine, a multiple neurotransmitter receptor blocker, has been shown to be effective in relieving refractory nausea and vomiting, and when used in combination with 5-HT_3RA and dexamethasone, it is more effective than NK1RA in preventing delayed nausea[8-13]

The ERICA study evaluated the antiemetic efficacy of "*prophylactic olanzapine + 5-HT_3RA + dexamethasone combination therapy*" compared with '*placebo + 5-HT_3RA + dexamethasone combination therapy*' for T-DXd therapy-induced nausea and vomiting in patients with HER2 positive or HER2 low mBC

5-HT_3RA, 5-hydroxytryptamine 3 receptor antagonist; HER2, human epidermal growth factor receptor 2; MASCC, Multinational Association of Supportive Care on Cancer; mBC, metastatic breast cancer; NCCN, National Comprehensive Cancer Network; NK1RA, neurokinin-1 receptor antagonist; T-DXd, trastuzumab deruxtecan.

1. Modi S et al. *N Eng J Med* 2019;382(7): 610-621. 2. Cortés J et al. *N Engl J Med* 2022;386(12):1143-1154. 3. Modi S et al. *N Engl J Med* 2022;387(1):9-20. 4. Park YH et al. *J Clin Oncol* 2024; 42 (16_suppl):12118-12118. 5. Sakai H et al. *BMJ Open* 2023;13(4):e070304. 6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V. 1.2024.© National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed [August 23, 2024]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 7. Jordan, K et al. *Support Care Cancer* 2024;32(53). 8. Bymaster FP et al. *Neuropsychopharmacol* 1996;14(2):87-96. 9. Navari RM. *Eur J Pharmacol* 2014;722:180-186. 10. Navari RM et al. *N Engl J Med* 2016;375(2):134-142. 11. Hashimoto H et al. *Lancet Oncol* 2020;21(2):242-249. 12. Navari RM et al. *J Support Oncol* 2011;9(5):188-195. 13. Zhang Z et al. *Oncologist* 2018;23(5):603-616.

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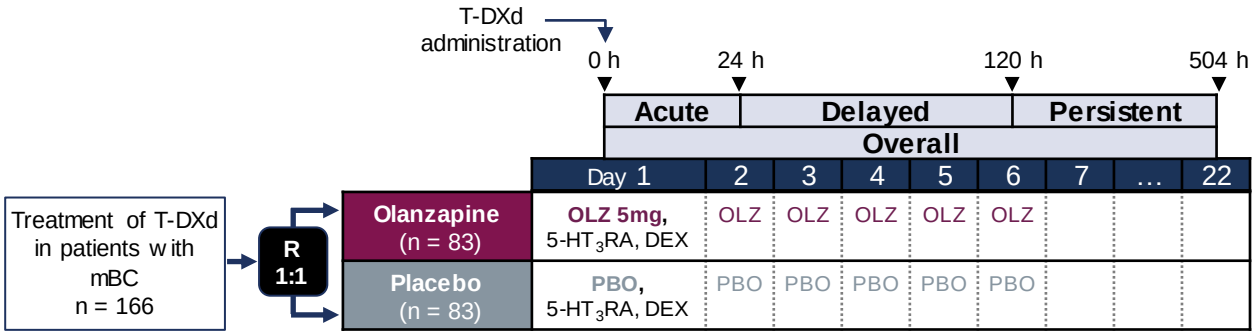
Study design

A multicenter, placebo-controlled, double-blind, randomized phase II study (jRCTs031210410)



- **Stratification factors:** Type of 5-HT$_3$RA (palonosetron/others) and motion sickness (presence/absence)
- Observational period was one cycle (day1–22) following the first cycle of T-DXd administration
- Patients were assessed daily from day 1 to day 22 for symptoms of nausea and vomiting and confirmation of additional anti-nausea medications using an electronic symptom diary

Statistical analysis

- CR rate in the delayed phase under placebo was set at 35% based on our preliminary survey, in which CR rate within 120 h was 32%; CR rate under olanzapine was set at 50% based on previous studies[1-5]
- Under the significance level of 20% (one-sided) and the power of 80%, sample size based on Fisher's exact test was calculated as 78 in each group; the planned number for enrollment was set at 83 per group (166 in total), with consideration of ineligible and untreated patients

Primary endpoint[a]

- **CR (no emetic events and no rescue drugs)** rate during the delayed phase

Secondary endpoints[b]

- CR rate during the acute, persistent phase
- **CC (no emetic events, no rescue drugs, and no/mild nausea[c])** rate during the acute, delayed, persistent phase
- **TC (no emetic events, no rescue drugs, and no nausea[c])** rate during the acute, delayed, persistent phase
- No nausea rate during the acute, delayed, persistent phase
- CR per day
- No nausea per day
- Other symptoms assessed by PRO-CTCAE
- Safety

5-HT$_3$RA, 5-hydroxytryptamine 3 receptor antagonist; CC, complete control; CR, complete response; DEX, dexamethasone; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; OLZ, olanzapine; PBO, placebo; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; R, randomization; TC, total control; TDXd, trastuzumab deruxtecan. [a]The one-sided p-value for comparing CR rate in the delayed phase between olanzapine and placebo was calculated using Fisher's exact test. As an efficacy measure, risk difference was derived with the 60% CI. [b]The risk differences were derived with 95% CIs and the subgroup analyses were performed. Time to first onset of nausea was evaluated using the Kaplan-Meier method. Median number of nauseous days in patients who experienced nausea, where days without the symptoms were excluded from the time, under the understanding that this was a post-randomization subgroup analysis. [c]The severity of nausea was evaluated using the following Likert scale: 0, no nausea; 1, mild nausea; 2, moderate nausea; 3, severe nausea.
1. Navari RM et al. *J Support Oncol* 2011; 9(5):188-195. 2. Hashimoto H et al. *Lancet Oncol* 2020;21(2):242-249. 3. Kawaguchi T et al. *J Patient Rep Outcomes* 2017; 2(1):2. 4. Mukhopadhyay S et al. *Support Care Cancer* 2017;25(1):145-154. 5. Tienchaiananda P, et al. *Ann Palliat Med* 2019;8(4):372-380.

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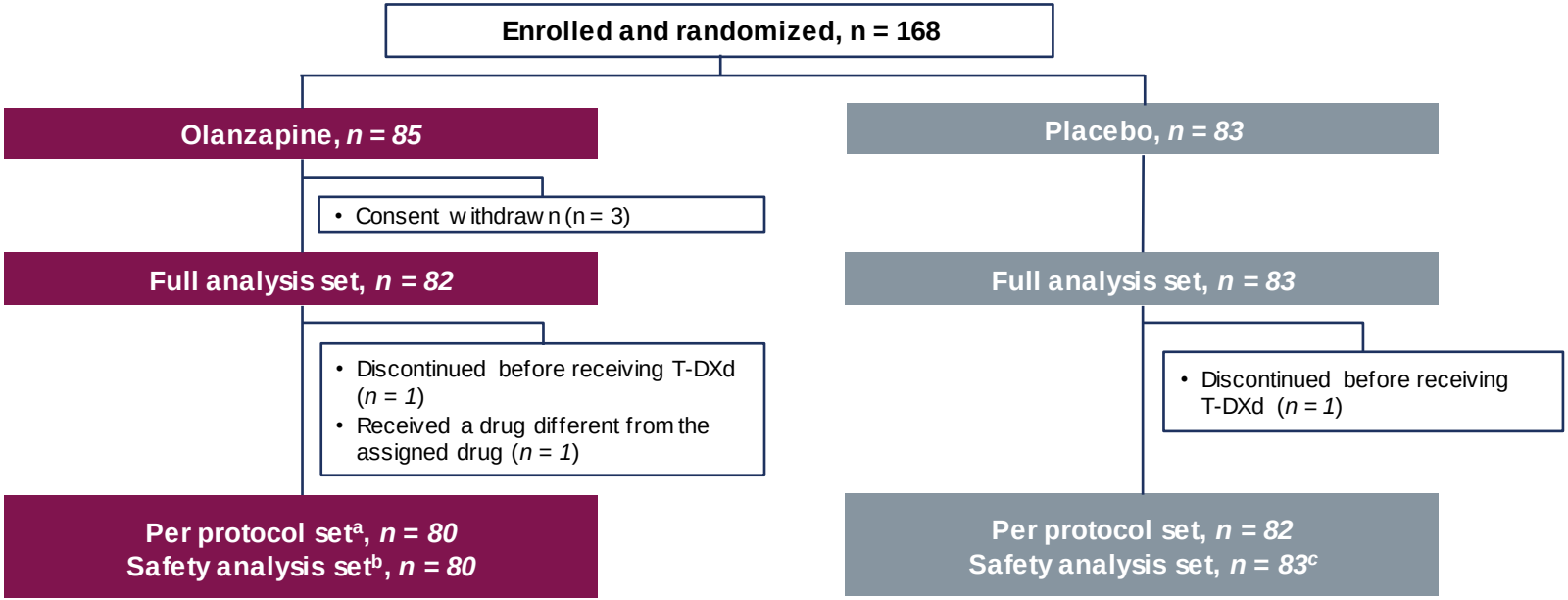
Patient disposition



Registration period: November 4, 2021 to September 1, 2023
Database lock date: December 13, 2023

T-DXd, trastuzumab deruxtecan.
[a]Patients who received the assigned treatment. [b]Based on treatment groups regardless of the assigned treatment.
Efficacy and safety analyses were performed in the per protocol set and safety analysis set, respectively
[c]One patient who was assigned olanzapine but received placebo treatment was included in the placebo group in the safety analysis set but was excluded from the per protocol set.

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Baseline demographics and clinical characteristics

Per protocol set

		Olanzapine (n = 80)	Placebo (n = 82)
Age, median (range), years		60 (28–77)	57 (38–75)
Sex, n (%)	Men	2 (2.5)	1 (1.2)
	Women	78 (97.5)	81 (98.8)
ECOG PS, n (%)	0	61 (76.3)	61 (74.4)
	1	19 (23.8)	19 (23.2)
	2	0 (0.0)	2 (2.4)
Motion sickness,[a] n (%)	Absent	56 (70.0)	58 (70.7)
	Present	24 (30.0)	24 (29.3)
Types of 5-HT$_3$ receptor antagonists,[a] n (%)	Palonosetron	64 (80.0)	67 (81.7)
	Granisetron	16 (20.0)	15 (18.3)
HER2 status, n (%)	HER2 low	29 (36.3)	34 (41.5)
	HER2 positive	51 (63.8)	48 (58.5)
Number of prior treatment regimens,[b] n (%)	1≥	24 (30.0)	30 (36.6)
	≥2	56 (70.0)	52 (63.4)
Metastatic site before T-DXd administration, n (%)	Brain	14 (17.5)	14 (17.1)
	Liver	39 (48.8)	37 (45.1)

The two groups were well balanced in baseline demographics and clinical characteristics

5-HT$_3$, 5-hydroxytryptamine 3; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.
[a]On the case report form. [b]For metastatic setting, excluding endocrine treatment.

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Primary endpoint: CR rate in the delayed phase (24–120h)

Per protocol set

	Olanzapine (n = 80)	Placebo (n = 82)	Fisher's exact test
CR rate in the delayed phase (24–120h), %	70.0	56.1	p = 0.047[a]
Risk difference, % (60% CI)	13.9 (6.9–20.7)		

CR rate in the delayed phase was significantly higher in the olanzapine group than in the placebo group, and the primary endpoint was met

CR, complete response.

[a] Using a significance level of 0.20 (one-sided)

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Secondary endpoints

Per protocol set

		Olanzapine	Placebo	Risk difference, % (95%CI)
Patients who achieved CR, n (%)	Acute phase (0–24h)	74/80 (92.5)	76/82 (92.7)	-0.2 (-9.3 – 8.7)
	Persistent phase (120–504h)	46/72 (63.9)	32/72 (44.4)	19.4 (2.4 – 35.3)
	Overall phase (0–504h)	35/72 (48.6)	29/72 (40.3)	8.3 (-8.2 – 24.6)
Patients who achieved CC, n (%)	Acute phase (0–24h)	73/80 (91.3)	76/82 (92.7)	-1.4 (-11.1 – 7.6)
	Delayed phase (24–120h)	54/80 (67.5)	44/82 (53.7)	13.8 (-1.4 – 28.7)
	Persistent phase (120–504h)	44/72 (61.1)	32/72 (44.4)	16.7 (-0.0 – 32.7)
	Overall phase (0–504h)	33/72 (45.8)	29/72 (40.3)	5.6 (-10.9 – 21.8)
Patients who achieved TC, n (%)	Acute phase (0–24h)	66/80 (82.5)	65/82 (79.3)	3.2 (-9.3 – 15.9)
	Delayed phase (24–120h)	44/80 (55.0)	29/82 (35.4)	19.6 (3.1 – 34.6)
	Persistent phase (120–504h)	36/72 (50.0)	20/72 (27.8)	22.2 (5.6 – 37.5)
	Overall phase (0–504h)	24/72 (33.3)	18/72 (25.0)	8.3 (-6.9 – 23.6)
Patients who achieved no nausea, n (%)	Acute phase (0–24h)	68/80 (85.0)	66/82 (80.5)	4.5 (-7.5 – 16.6)
	Delayed phase (24–120h)	46/80 (57.5)	31/82 (37.8)	19.7 (3.1 – 34.6)
	Persistent phase (120–504h)	37/72 (51.4)	23/72 (31.9)	19.4 (2.9 – 35.1)
	Overall phase (0–504h)	27/72 (37.5)	19/72 (26.4)	11.1 (-4.5 – 26.3)

Across all endpoints, the Olanzapine group was consistently higher in the delayed phase and the persistent phase.

CC, complete control; CR, complete response; TC, total control.

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Patients who achieved TC, n (%)	Acute phase (0–24h)	66/80 (82.5)	65/82 (79.3)	3.2 (-9.3 – 15.9)
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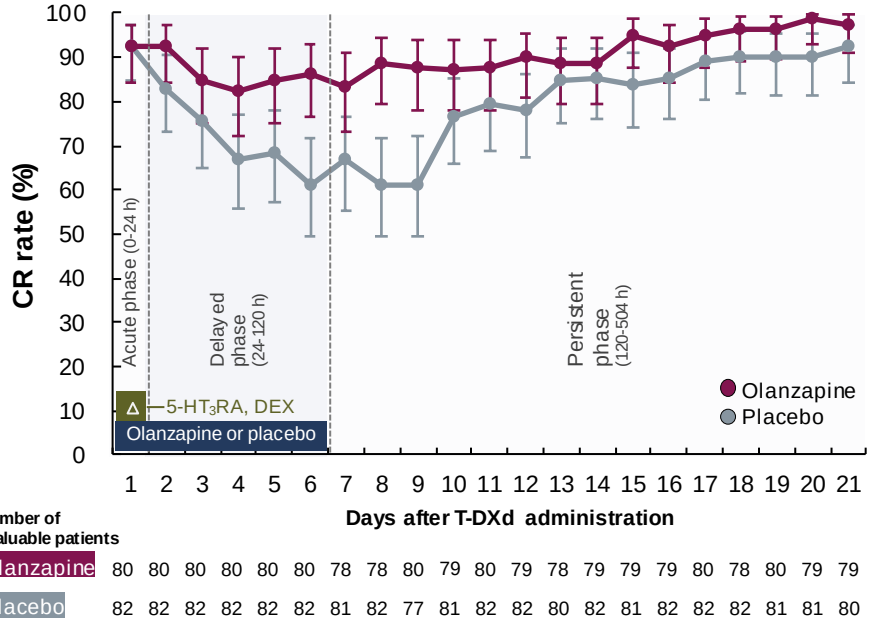
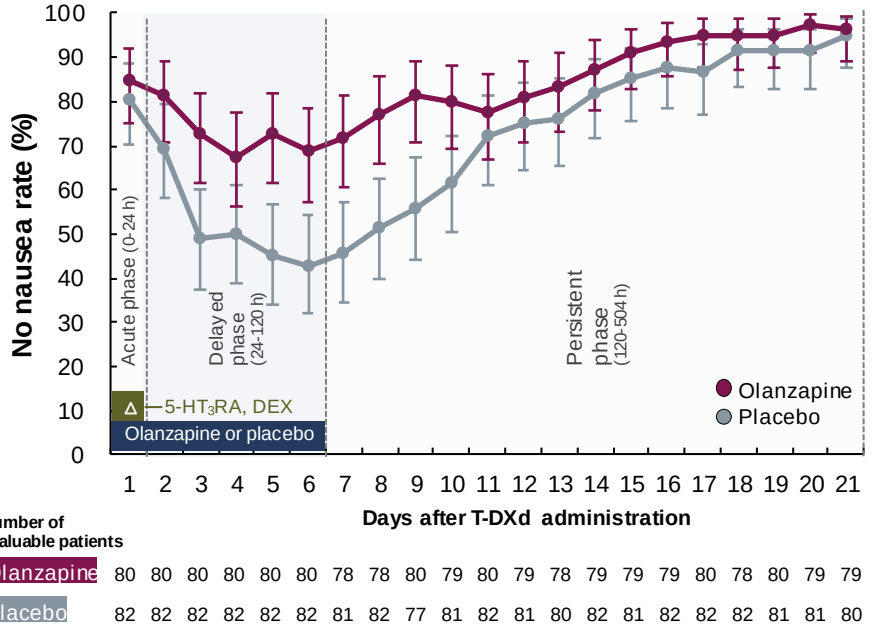
Daily CR rates and no nausea rates by study groups

Per protocol set



Number of evaluable patients

Olanzapine	80	80	80	80	80	80	78	78	80	79	80	79	78	79	79	79	80	78	80	79	79
Placebo	82	82	82	82	82	82	81	82	77	81	82	82	80	82	81	82	82	82	81	81	80



Number of evaluable patients

Olanzapine	80	80	80	80	80	80	78	78	80	79	80	79	78	79	79	79	80	78	80	79	79
Placebo	82	82	82	82	82	82	81	82	77	81	82	81	80	82	81	82	82	82	81	81	80

Higher CR rates and no nausea rates in the olanzapine arm were observed throughout the 21-day observation period.

CR, complete response; T-DXd, trastuzumab deruxtecan.
Error bars in the graph indicate 95% confidence intervals.

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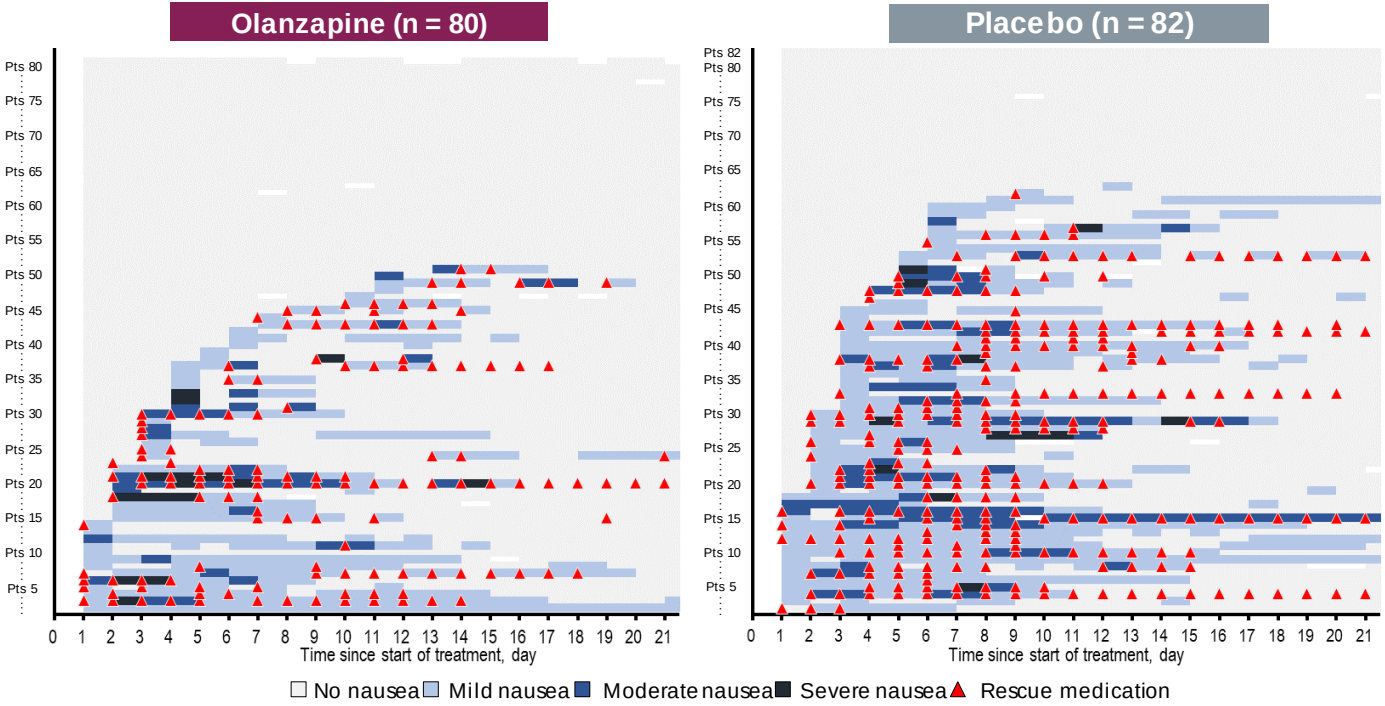
Treatment course of patients who experienced nausea



- Median time to first onset of nausea:
  - **Olanzapine: 6.5 days**
  - **Placebo: 3.0 days**
- Median number of total days of nausea in patients who experienced nausea:[a]
  - **Olanzapine** (n = 49)**: 4.0 days**
  - **Placebo** (n = 62): **8.0 days**
- Percentage of patients using rescue medications:
  - **Olanzapine : 38.8 %**
  - **Placebo** : **56.6 %**

Rescue medication and length of nausea episodes were reduced in olanzapine group
There were patients with refractory nausea in both groups, even with the use of rescue medication, indicating individual differences

[a]Post-randomization subgroup analysis.

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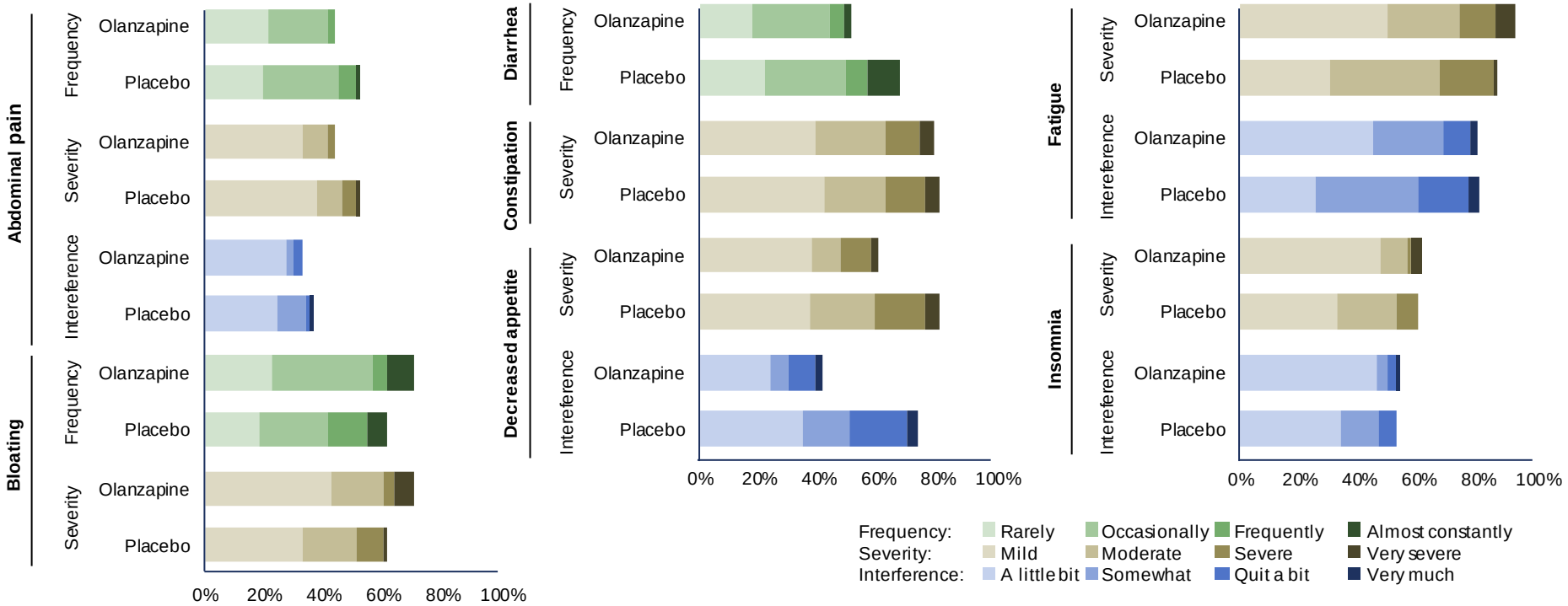
Patient self symptom assessment based on PRO-CTCAE

Safety analysis set



Decreased appetite was less frequent in the olanzapine group and led to less interference with usual or daily activities

PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

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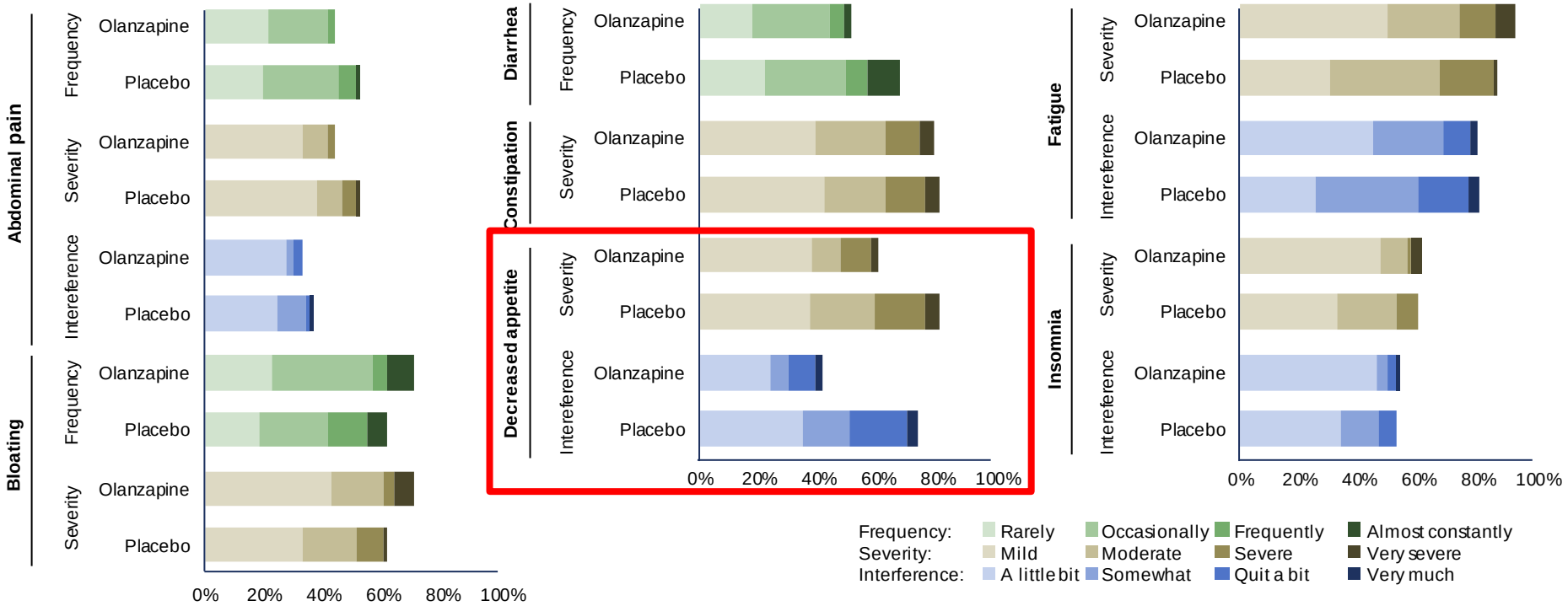

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Toxicities in ≥ 5 patients (either treatment group)

Safety analysis set

	Olanzapine (n = 80)		Placebo (n = 83)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutrophil count decreased	46 (57.5)	6 (7.5)	49 (59.0)	9 (10.8)
Nausea	32 (40.0)	3 (3.8)	54 (65.1)	0 (0)
Platelet count decreased	32 (40.0)	2 (2.5)	25 (30.1)	1 (1.2)
Alanine aminotransferase increased	31 (38.8)	2 (2.5)	26 (31.3)	0 (0)
White blood cell decreased	29 (36.3)	2 (2.5)	31 (37.3)	2 (2.4)
Constipation	27 (33.8)	0 (0)	25 (30.1)	0 (0)
Hypoalbuminemia	27 (33.8)	1 (1.3)	20 (24.1)	0 (0)
Aspartate aminotransferase increased	22 (27.5)	1 (1.3)	23 (27.7)	0 (0)
Decreased appetite	21 (26.3)	1 (1.3)	38 (45.8)	1 (1.2)
Malaise	20 (25.0)	0 (0)	26 (31.3)	0 (0)
Anemia	20 (25.0)	1 (1.3)	22 (26.5)	1 (1.2)
Somnolence	20 (25.0)	0 (0)	9 (10.8)	0 (0)
Vomiting	16 (20.0)	1 (1.3)	15 (18.1)	0 (0)
Fatigue	16 (20.0)	0 (0)	15 (18.1)	0 (0)

	Olanzapine (n = 80)		Placebo (n = 83)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Creatinine increased	14 (17.5)	1 (1.3)	12 (14.5)	0 (0)
Hyponatremia	13 (16.3)	0 (0)	21 (25.3)	2 (2.4)
Hypokalemia	11 (13.8)	1 (1.3)	10 (12.0)	1 (1.2)
Bloating	9 (11.3)	0 (0)	9 (10.8)	0 (0)
Hypocalcemia	8 (10.0)	0 (0)	5 (6.0)	0 (0)
Alkaline phosphatase increased	7 (8.8)	0 (0)	4 (4.8)	0 (0)
Diarrhea	6 (7.5)	1 (1.3)	16 (19.3)	0 (0)
Dry mouth	6 (7.5)	0 (0)	4 (4.8)	0 (0)
Blood bilirubin increased	6 (7.5)	0 (0)	2 (2.4)	0 (0)
Hyperglycemia	6 (7.5)	0 (0)	0 (0)	0 (0)
Hyperkalemia	5 (6.3)	0 (0)	7 (8.4)	0 (0)
Hypercalcemia	5 (6.3)	0 (0)	3 (3.6)	0 (0)
Dizziness	5 (6.3)	0 (0)	3 (3.6)	0 (0)
Abdominal pain	3 (3.8)	0 (0)	5 (6.0)	0 (0)

Decreased appetite and diarrhea were also less frequent in the olanzapine group compared with the placebo group
Somnolence and hyperglycemia were frequent in the olanzapine group compared with the placebo group

Data are n (%) unless otherwise indicated. Adverse events that occurred in at least 5 cases in each group are described. No interstitial lung disease was reported during the observation period of this study. No grade 5 adverse events were observed.

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Toxicities in ≥ 5 patients (either treatment group)

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Decreased appetite	21 (26.3)	1 (1.3)	38 (45.8)	1 (1.2)
Malaise	20 (25.0)	0 (0)	26 (31.3)	0 (0)
Anemia	20 (25.0)	1 (1.3)	22 (26.5)	1 (1.2)
Somnolence	20 (25.0)	0 (0)	9 (10.8)	0 (0)
Vomiting	16 (20.0)	1 (1.3)	15 (18.1)	0 (0)
Fatigue	16 (20.0)	0 (0)	15 (18.1)	0 (0)

	Olanzapine (n = 80)		Placebo (n = 83)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Creatinine increased	14 (17.5)	1 (1.3)	12 (14.5)	0 (0)
Hyponatremia	13 (16.3)	0 (0)	21 (25.3)	2 (2.4)
Hypokalemia	11 (13.8)	1 (1.3)	10 (12.0)	1 (1.2)
Bloating	9 (11.3)	0 (0)	9 (10.8)	0 (0)
Hypocalcemia	8 (10.0)	0 (0)	5 (6.3)	0 (0)
Alkaline phosphatase increased	7 (8.8)	0 (0)	4 (4.8)	0 (0)
Diarrhea	6 (7.5)	1 (1.3)	16 (19.3)	0 (0)
Dry mouth	6 (7.5)	0 (0)	4 (4.8)	0 (0)
Blood bilirubin increased	6 (7.5)	0 (0)	2 (2.4)	0 (0)
Hyperglycemia	6 (7.5)	0 (0)	0 (0)	0 (0)
Hyperkalemia	5 (6.3)	0 (0)	7 (8.4)	0 (0)
Hypercalcemia	5 (6.3)	0 (0)	3 (3.6)	0 (0)
Dizziness	5 (6.3)	0 (0)	3 (3.6)	0 (0)
Abdominal pain	3 (3.8)	0 (0)	5 (6.0)	0 (0)

Decreased appetite and diarrhea were also less frequent in the olanzapine group compared with the placebo group
Somnolence and hyperglycemia were frequent in the olanzapine group compared with the placebo group

Data are n (%) unless otherwise indicated. Adverse events that occurred in at least 5 cases in each group are described. No interstitial lung disease was reported during the observation period of this study. No grade 5 adverse events were observed.

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Toxicities in ≥ 5 patients (either treatment group)

Safety analysis set

	Olanzapine (n = 80)		Placebo (n = 83)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutrophil count decreased	46 (57.5)	6 (7.5)	49 (59.0)	9 (10.8)
Nausea	32 (40.0)	3 (3.8)	54 (65.1)	0 (0)
Platelet count decreased	32 (40.0)	2 (2.5)	25 (30.1)	1 (1.2)
Alanine aminotransferase increased	31 (33.8)	2 (2.5)	26 (31.3)	0 (0)
White blood cell decreased	29 (36.3)	2 (2.5)	31 (37.3)	2 (2.4)
Constipation	27 (33.8)	0 (0)	25 (30.1)	0 (0)
Hypoalbuminemia	27 (33.8)	1 (1.3)	20 (24.1)	0 (0)
Aspartate aminotransferase increased	22 (27.5)	1 (1.3)	23 (27.7)	0 (0)
Decreased appetite	21 (26.3)	1 (1.3)	38 (45.8)	1 (1.2)
Malaise	20 (25.0)	0 (0)	26 (31.3)	0 (0)
Anemia	20 (25.0)	1 (1.3)	22 (26.5)	1 (1.2)
Somnolence	20 (25.0)	0 (0)	9 (10.8)	0 (0)
Vomiting	16 (20.0)	1 (1.3)	15 (18.1)	0 (0)
Fatigue	16 (20.0)	0 (0)	15 (18.1)	0 (0)

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Hypokalemia	11 (13.8)	1 (1.3)	10 (12.0)	1 (1.2)
Bloating	9 (11.3)	0 (0)	9 (10.8)	0 (0)
Hypocalcemia	8 (10.0)	0 (0)	5 (6.3)	0 (0)
Alkaline phosphatase increased	7 (8.8)	0 (0)	4 (4.8)	0 (0)
Diarrhea	6 (7.5)	1 (1.3)	16 (19.3)	0 (0)
Dry mouth	6 (7.5)	0 (0)	4 (4.8)	0 (0)
Blood bilirubin increased	6 (7.5)	0 (0)	2 (2.4)	0 (0)
Hyperglycemia	6 (7.5)	0 (0)	0 (0)	0 (0)
Hyperkalemia	5 (6.3)	0 (0)	7 (8.4)	0 (0)
Hypercalcemia	5 (6.3)	0 (0)	3 (3.6)	0 (0)
Dizziness	5 (6.3)	0 (0)	3 (3.6)	0 (0)
Abdominal pain	3 (3.8)	0 (0)	5 (6.0)	0 (0)

Decreased appetite and diarrhea were also less frequent in the olanzapine group compared with the placebo group
Somnolence and hyperglycemia were frequent in the olanzapine group compared with the placebo group

Data are n (%) unless otherwise indicated. Adverse events that occurred in at least 5 cases in each group are described. No interstitial lung disease was reported during the observation period of this study. No grade 5 adverse events were observed.

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Conclusions

- CR rate in the delayed phase (24–120h) was significantly higher in the olanzapine group than in the placebo group (70.0% versus 56.1%, P = 0.047), indicating that the primary endpoint was met

- Continued efficacy of olanzapine was observed throughout the 21-day observation period

- The adverse events were similar to those previously reported for olanzapine and there were no new safety signals in both groups
  (somnolence: 25.0% in olanzapine, 10.8% in placebo; hyperglycemia: 7.5%, 0%)

Olanzapine-based triplet therapy appears to be an effective antiemetic therapy to prevent delayed and persistent nausea and vomiting induced by the first cycle of T-DXd treatment

CR, complete response; T-DXd, trastuzumab deruxtecan.

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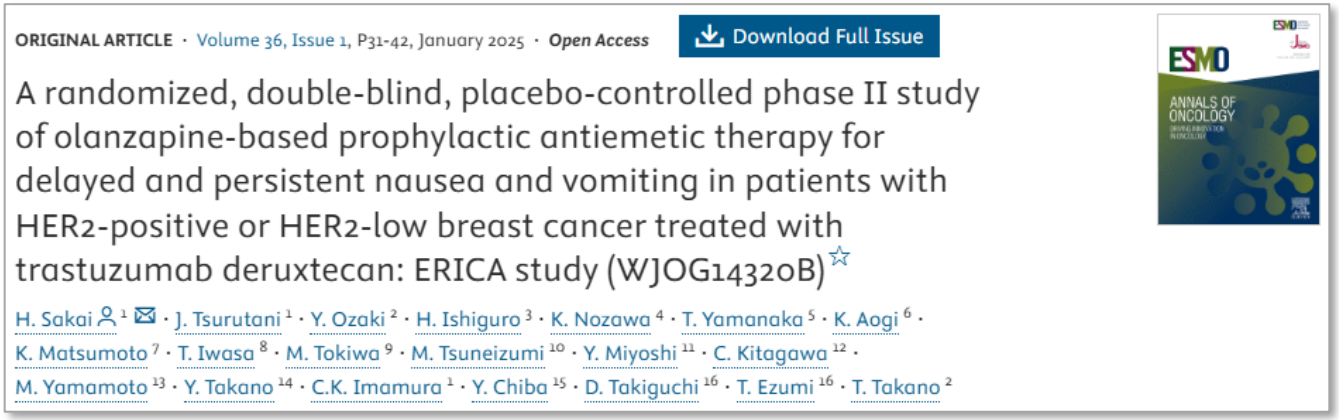

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A randomized, double-blind, placebo-controlled phase II study of olanzapine-based prophylactic antiemetic therapy for delayed and persistent nausea and vomiting in patients with HER2-positive or HER2-low breast cancer treated with trastuzumab deruxtecan: ERICA study (WJOG14320B) ☆

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