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ORIGINAL ARTICLE

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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Available online XXX

Background: Nausea and vomiting are common adverse events associated with trastuzumab deruxtecan (T-DXd). We evaluated the efficacy of an olanzapine-based triplet regimen for preventing nausea and vomiting in patients receiving their first cycle T-DXd.

Patients and methods: This multi-institutional, randomized, double-blind, placebo-controlled (ERICA) phase II study enrolled patients with human epidermal growth factor receptor 2-positive/human epidermal growth factor receptor 2-low metastatic breast cancer receiving their first cycle of T-DXd. Patients were randomized to olanzapine 5 mg or placebo once daily (1 : 1 ratio) from day 1 to day 6, plus a 5-hydroxytryptamine type 3 receptor antagonist and dexamethasone 6.6 mg intravenously or 8 mg orally on day 1. The total observation period was 504 h (21 days) from the first T-DXd administration. The primary endpoint was complete response (CR), defined as no emetic events and no rescue medications, in the delayed phase (24-120 h after T-DXd), with the type I error rate of 0.2 (one-sided) for the comparison. Secondary endpoints included no nausea rate in the delayed and persistent phases (120-504 h), adverse event by Common Terminology Criteria for Adverse Events (CTCAE) and patient-reported outcomes version of the CTCAE (PRO-CTCAE).

Results: In total, 168 patients were enrolled at 43 sites in Japan (November 2021-September 2023) with 162 patients (olanzapine, $n = 80$; placebo, $n = 82$) included in the per protocol set. The primary endpoint was met as the delayed phase CR rate was significantly greater with olanzapine than placebo (70.0% versus 56.1%, $P = 0.047$). Efficacy was maintained in the persistent phase (63.9% versus 44.4%). No nausea rate was also greater with olanzapine (delayed phase: 57.5% versus 37.8%; persistent phase: 51.4% versus 31.9%). CR rates in the delayed phase favored olanzapine across subgroups. Appetite loss was also decreased with olanzapine. Hyperglycemia and somnolence were mostly of low-grade severity.

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☆Note: Previous presentation: Abstract accepted for presentation at ESMO 2024

Conclusion: Olanzapine 5 mg for 6 days with 5-hydroxytryptamine type 3 receptor antagonist and dexamethasone appears effective for T-DXd-treated patients to prevent delayed and persistent nausea and vomiting.
Key words: trastuzumab deruxtecan, nausea, olanzapine, vomiting, persistent phase

INTRODUCTION

Trastuzumab deruxtecan (T-DXd) is an antibody—drug conjugate composed of a human epidermal growth factor receptor 2 (HER2)-targeting antibody, a cleavable tetrapeptide-based linker, and a DNA topoisomerase I inhibitor payload.[1] T-DXd is currently a standard therapy for patients with HER2-positive and HER2-low unresectable or metastatic breast cancer, which comprise 15% and 45%-55%, respectively, of all patients with metastatic breast cancer.[2] Gastrointestinal toxicities are common adverse events for T-DXd, with nausea the most frequently reported symptom. The DESTINY clinical trial program did not define specific antiemetic therapy in the protocol and has not evaluated the use, type or efficacy of antiemetic therapy. Further, this program recommended using anti-emetic treatments but did not mandate the use of prophylactic anti-emetics.[3,4] Across the clinical trials, any grade of nausea and vomiting were reported in 65.9%-77.7% and 27.2%-45.7% of patients, respectively.[3-6] Nausea and vomiting were observed most often in the first cycle and decreased in subsequent cycles.[7] Although only a very low percentage of treatment discontinuations due to nausea and vomiting was observed in the trials, quality of life was impaired by these symptoms. Furthermore, in DESTINY-Breast04, the median duration of the first episode of nausea and vomiting with T-DXd was 10 days and 3 days,[8] respectively, indicating those symptoms were 'persistent', but a daily evaluation of symptoms was not carried out over the course of a 21-day cycle. In recent guidelines, the emetic risk of T-DXd has not been fully described; the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology classify it as a high emetic-risk anticancer agent, while the Multinational Association of Supportive Care in Cancer and Japan Society of Clinical Oncology (JSCO) guidelines indicate that the emetic potential appears to be at the high end of the moderate category, most closely resembling that of carboplatin.[9-11] Taken together, antiemetic therapy tailored to the 'persistent' symptoms caused by T-DXd is needed.

Olanzapine effectively relieves chemotherapy-induced nausea and vomiting refractory to standard antiemetic therapy.[12-15] Daytime somnolence and increased appetite associated with olanzapine have been reported, however, in randomized trials.[15] The beneficial effect of olanzapine on refractory nausea and vomiting is achieved by blockade of multiple neurotransmitter receptors, including dopaminergic D_{1-4} receptors, serotonergic 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and 5-HT_6 receptors, the adrenergic α1 receptor, the histamine H_1 receptor, and several muscarinic receptor subtypes.[12-15] A randomized controlled trial[16] and network meta-analysis[17] have both demonstrated that olanzapine is more effective than a neurokinin-1 receptor antagonist (NK1RA) in preventing delayed nausea in combination with 5-hydroxytryptamine type 3 receptor antagonist (5-HT_3RA) and dexamethasone. In previous studies, olanzapine was found to be equally effective at 5 mg and 10 mg doses for the prophylaxis of chemotherapy-induced nausea and vomiting, but the 5 mg dose was associated with a lower incidence of adverse events than the 10 mg dose.[18,19] Furthermore, the lower dose has been shown to reduce the risk of delayed nausea and vomiting in Japanese patients undergoing highly emetogenic chemotherapy.[13] Taking into consideration the half-lives of T-DXd (6.03 days) and olanzapine (33 h), we administered olanzapine 5 mg once daily for 6 days in this study.[20,21]

The primary objective of this study was to examine the superiority of olanzapine over placebo, both in combination with 5-HT_3RA and dexamethasone, for the prevention of nausea and vomiting in patients with breast cancer receiving their first cycle of T-DXd in the delayed phase (24-120 h after T-DXd administration). In addition, we also evaluated the efficacy of olanzapine in persistent phases beyond 120 h as a secondary endpoint.

PATIENTS AND METHODS

Study design and patients

The ERICA study was a placebo-controlled, double-blind, randomized phase II trial, and the study design has been previously published.[22] This study was conducted in accordance with ethical standards in the Declaration of Helsinki (1964), Clinical Trial Act (2017), and their later amendment. The study protocol was approved by the West Japan Oncology Group (WJOG) protocol review committee (approved on 27 June 2021, trial number WJOG14320B) and Showa University Clinical Research Review Board (approved on 13 October 2021, trial number S8). All patients provided written informed consent before treatment initiation. The trial was registered at the Japan Registry of Clinical Trials (Clinical Trial Registration number: jRCTs031210410): https://jrct.niph.go.jp/en-latest-detail/jRCTs031210410.

This study was conducted in 43 hospitals in Japan between November 2021 and September 2023. Patients $\geq$20 years of age with histologically confirmed HER2-positive or HER2-low metastatic breast cancer were eligible if they were scheduled to receive their first cycle of T-DXd treatment and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Additional key eligibility criteria can be found in the previously published protocol.[22] Eligible patients had to be able to access the electronic symptom diary (ePRO) and accurately record their experience. Patients were excluded if they had nausea and vomiting requiring treatment with antiemetic agents at

the time of enrollment. Exclusion criteria are detailed in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2024.09.001.

Based on recent data of olanzapine use as antiemetic therapy including in elderly patients,[23,24] the study protocol was amended in November 2022, expanding the age-related inclusion criterion from up to 75 years of age to include patients 76 years and older. Based on the data of the DESTINY-Breast04 study, the second study protocol was amended in April 2023 to include patients with HER2-positive metastatic breast cancer as well as HER2-low metastatic breast cancer after T-DXd was approved for use in patients with HER2-low metastatic breast cancer.

Randomization and masking

Randomization was centrally carried out at a 1 : 1 ratio by random allocation modules of electronic data capture. The minimization method with a random component was applied for randomization. Patients were stratified according to the type of 5-HT_3RA (palonosetron or others) and motion sickness (present or absent).[25,26] We provided olanzapine and a matching placebo with no printed identification code. More details can be found in our previous paper.[22]

Treatment regimen

The approved primary dose of T-DXd is 5.4 mg/kg every 3 weeks; however, the protocol for this study did not specify the dose for T-DXd. Patients received either olanzapine 5 mg (2 tablets of 2.5 mg olanzapine) per day orally or matching placebo from days 1 to 6. Based on a previous study, we recommended that patients take olanzapine or placebo after their evening meal.[13] All patients received a 5-HT_3RA of type and dose chosen by the site investigator, with dexamethasone administered i.v. at a dose of 6.6 mg or orally at a dose of 8 mg on day 1 (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.09.001). Patients were allowed to take rescue medication throughout the study period for nausea or vomiting, if necessary. The investigators were able to select rescue medications from antiemetic agents other than olanzapine, 5-HT_3RA, steroids, NK1RA, serotonin-dopamine antagonists, selective serotonin reuptake inhibitors, and serotonin noradrenaline reuptake inhibitors.

Efficacy and safety assessment

The observation period of this study was 504 h (21 days) after T-DXd administration. In addition to an 'acute phase' (0-24 h after T-DXd administration) and 'delayed phase' (24-120 h after T-DXd administration), we defined 120-504 h as the 'persistent phase' and 0-504 h as the 'overall phase.' Efficacy was classified by the following definition of information as reported in the electronic symptom diary. Complete response (CR) was defined as no emetic episodes and no use of rescue medication. Complete control (CC) was defined as no emetic episodes, no use of rescue medication, and no or mild nausea (0 or 1 on a 4-point scale). Total control (TC) was defined as no emetic episodes, no use of rescue medication, and no nausea.

The primary endpoint was the CR rate during the delayed phase. Secondary endpoints included: (i) CR rate during the acute, persistent, and overall phases, (ii) CC rate during the acute, delayed, persistent, and overall phases, (iii) TC rate during the acute, delayed, persistent, and overall phases, (iv) no nausea rate during the acute, delayed, persistent, and overall phases, (v) daily CR rate, (vi) daily no nausea rate, (vii) other symptoms, including diarrhea, constipation, abdominal pain, bloating, decreased appetite, fatigue, and insomnia assessed by the Japanese version of the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria For Adverse Events (PRO-CTCAE),[27] and (viii) safety. Concerning safety, investigators evaluated and graded adverse events according to the Japanese version (JCOG/JSCO) of the Common Terminology Criteria for Adverse Events v5.0 (CTCAE v5.0).[28]

Study visits and assessment procedures

We defined the date of first T-DXd administration as day 1. Patients documented their symptoms in an electronic symptom diary every day during observation periods from day 1 to day 22 (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.09.001). Vomiting frequency was rated on a four-point categorical scale of none, once, twice, or three times or more, and nausea severity was rated on a four-point categorical scale of none, mild, moderate, or severe according to the Likert scale. Patients recorded daily whether or not olanzapine or placebo was taken from day 1 to day 6 as well as any use of rescue medication. The frequency, severity, and interference of diarrhea, constipation, abdominal pain, bloating, decreased appetite, fatigue, and insomnia were reported using PRO-CTCAE before T-DXd administration and on days 8, 15, and 22. Other assessment details can be found in our previous paper.[22]

Statistical analysis

Sample size was determined as follows: the CR rate in the delayed phase under placebo was set at 35%, because an actual CR rate within 120 h was 32% (14 of 44 patients) in our preliminary survey. The CR rate under olanzapine was then set at 50%, because an additional CR rate of 15.0% would be clinically meaningful, as previous studies[13,16,27,29,30] had suggested. Using a type I error rate of 0.20 (one-sided) and type II error rate of 0.20, the sample size required was calculated as 78 patients in each group based on Fisher's exact test. The reason that such a large type I error rate was adopted is that, given the increasing number of patients currently being treated with T-DXd and the expanding practical use of olanzapine with only anecdotal evidence of efficacy, we considered it was imperative to evaluate the efficacy of olanzapine in a timely manner. The planned number of patients for enrollment was set at

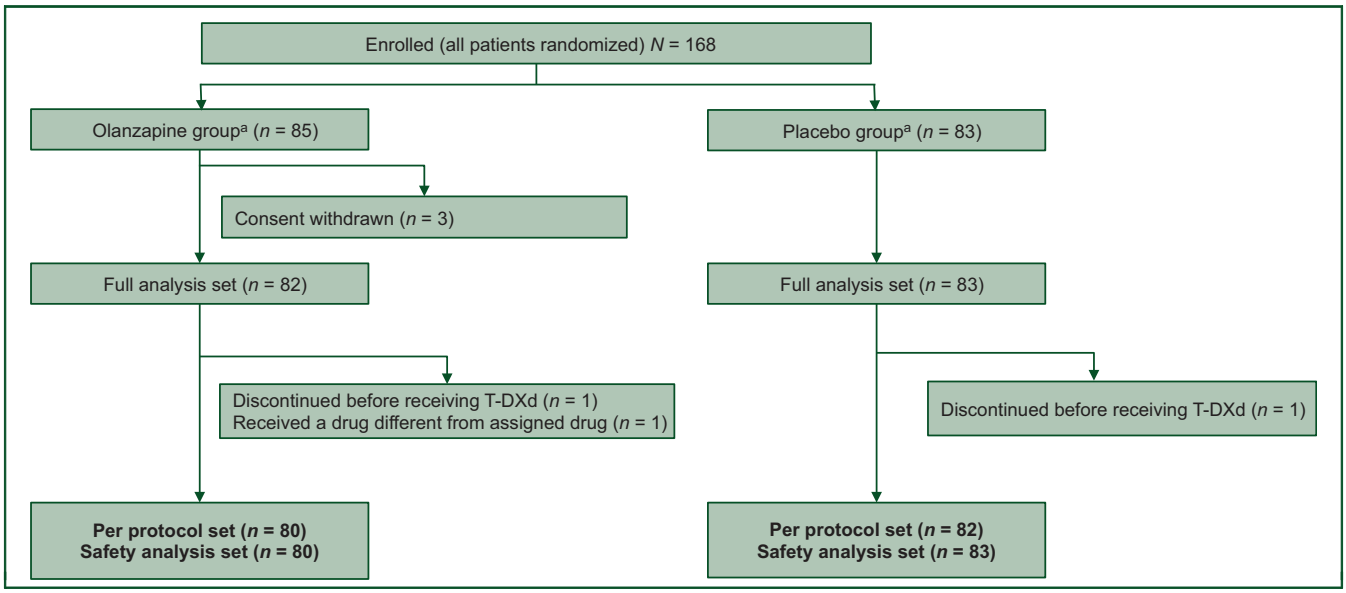

Figure 1. Patient disposition. CONSORT diagram according to randomization allocation for analysis set.
[a]There were 84 patients in each group who actually received placebo and olanzapine. Safety analysis set: the placebo group (actual) consisted of 83 patients, excluding 1 patient who discontinued before receiving T-DXd. The olanzapine group (actual) consisted of 80 patients, excluding 1 patient who discontinued before receiving T-DXd and 3 patients who withdrew consent from the 84 patients.
T-DXd, trastuzumab deruxtecan.

83 per group (166 in total), with consideration made for ineligible and untreated patients.

In this study, the efficacy analysis set was the per protocol set (PPS), which consisted of patients who received the assigned treatment. Safety analyses were carried out based on the groups by actual treatment received regardless of the assigned treatment.

For the primary endpoint, the one-sided *P* value for comparing CR rate in the delayed phase between olanzapine and placebo was calculated using Fisher's exact test. A promising signal for the improvement of CR by olanzapine was considered to be detected if the one-sided *P* value was <0.20. As an efficacy measure, risk difference was derived with the two-sided 60% confidence interval (CI). In addition, subgroup analyses were carried out on some significant factors, and whether the factors could be prognostic and/or predictive was further examined in an exploratory manner through a logistical regression model with treatment group, the factor, and their interaction term as explanatory variables. For secondary endpoints, the risk differences were derived with 95% CIs, and subgroup analyses were carried out. The CIs of risk differences were calculated using Chan and Zhang's[31] exact method.

In addition to the above analyses, time to the first episode of nausea/vomiting was evaluated using the Kaplan—Meier method. Furthermore, the total number of days with nausea/vomiting was examined in a *post hoc* summary both in the PPS and in a subgroup of patients who experienced these symptoms.

Statistical analysis was carried out with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patients

From November 2021 to September 2023, a total of 168 patients were enrolled and randomly assigned to olanzapine ($n = 85$) or placebo ($n = 83$) (Figure 1). Three patients in the olanzapine group withdrew consent before treatment, such that 165 patients who received study treatment were included in the full analysis set (FAS) (olanzapine, $n = 82$; placebo, $n = 83$). The PPS consisted of 162 patients (olanzapine, $n = 80$; placebo, $n = 82$). Two patients were excluded from the FAS in the olanzapine group: one discontinued before receiving T-DXd and one patient who was assigned olanzapine received placebo treatment. One patient was excluded from the FAS in the placebo group due to discontinuing the study before receiving T-DXd. The safety analysis set consisted of 163 patients (olanzapine, $n = 80$; placebo, $n = 83$). 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 PPS.

Patient characteristics of the PPS were well balanced between the olanzapine and placebo groups (Table 1 and Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.09.001). Median (range) age was 60 years (28-77 years) in the olanzapine group and 57 years (38-75 years) in the placebo group and almost all patients in each group were women. Among 162 patients, 61.1% ($n = 99$) had HER2-positive and 38.9% ($n = 63$) had HER2-low status. About 50% of patients received T-DXd as second- or third-line treatment of metastatic disease in both groups.

Table 1. Baseline demographics and clinical characteristics in per protocol set population

	Olanzapine group ($n = 80$)	Placebo group ($n = 82$)
Age, median (range), years	60 (28-77)	57 (38-75)
Age category, years		
<55	26 (32.5)	31 (37.8)
≥55	54 (67.5)	51 (62.2)
Sex		
Male	2 (2.5)	1 (1.2)
Female	78 (97.5)	81 (98.8)
ECOG PS		
0	61 (76.3)	61 (74.4)
1	19 (23.8)	19 (23.2)
2	0 (0.0)	2 (2.4)
Motion sickness		
Absent	56 (70.0)	58 (70.7)
Present	24 (30.0)	24 (29.3)
5-HT_3 receptor antagonists		
Palonosetron	64 (80.0)	67 (81.7)
Granisetron	16 (20.0)	15 (18.3)
Prior experience with olanzapine		
No	76 (95.0)	78 (95.1)
Yes	4 (5.0)	4 (4.9)
Prior experience with anthracycline treatment		
No	44 (55.0)	54 (65.9)
Yes	36 (45.0)	28 (34.1)
Insomnia before T-DXd administration		
No	35 (43.8)	33 (40.2)
Yes	45 (56.3)	49 (59.8)
HER2 status		
HER2-low (IHC1+ or 2+, ISH-negative)	29 (36.3)	34 (41.5)
HER2-positive (IHC3+, ISH-positive)	51 (63.8)	48 (58.5)
Hormone receptor expression		
ER-positive	49 (61.3)	59 (72.0)
PgR-positive	35 (43.8)	42 (51.2)
Objective of T-DXd administration		
Recurrent	51 (63.8)	54 (65.9)
de novo stage IV	28 (35.0)	27 (32.9)
Other	1 (1.3)	1 (1.2)
Number of prior treatment regimens[a]		
0	2 (2.5)	2 (2.4)
1	22 (27.5)	28 (34.1)
2	23 (28.8)	19 (23.2)
3	12 (15.0)	15 (18.3)
4	12 (15.0)	7 (8.5)
5	5 (6.3)	7 (8.5)
≥6	4 (5.0)	4 (4.9)
Median	2	2
Metastatic site before T-DXd administration		
No	0 (0.0)	0 (0.0)
Yes	80 (100.0)	82 (100.0)
Lung	34 (42.5)	44 (53.7)
Pleura/pleural effusion	11 (13.8)	13 (15.9)
Peritoneal/ascites	3 (3.8)	5 (6.1)
Brain	14 (17.5)	14 (17.1)
Liver	39 (48.8)	37 (45.1)
Bone	44 (55.0)	45 (54.9)
Other	44 (55.0)	46 (56.1)

Data are *n* (%) unless otherwise indicated.

5-HT_3, 5-hydroxytryptamine type 3; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; PgR, progesterone receptor; PS, performance status; T-DXd, trastuzumab deruxtecan.

[a]For metastatic setting, excluding endocrine treatment.

Efficacy

The CR rate in the delayed phase (primary endpoint) was higher in the olanzapine group than in the placebo group: 56 (70.0%) of 80 patients versus 46 (56.1%) of 82 patients achieved CR, with a difference of 13.9% and two-sided 60% CI 6.9-20.7 (one-sided $P = 0.047$) (Table 2). Likewise, the CR rate in the persistent phase was higher in the olanzapine group than in the placebo group: [46 (63.9%) of 72 patients versus 32 (44.4%) of 72 patients, with a difference of 19.4% and 95% CI 2.4-35.3]. The CR rates in the acute phase did not differ between the olanzapine groups and the placebo groups [74 (92.5%) of 80 patients versus 76 of 82 (92.7%) of 82 patients, with a difference of −0.2% and 95% CI −9.3% to 8.7%]. The no nausea rate was also greater with olanzapine than placebo [delayed phase: 46 (57.5%) of 80 patients versus 31 (37.8%) of 82 patients, with a difference of 19.7% and 95% CI 3.1% to 34.6%, persistent phase: 37 (51.4%) of 72 patients versus 23 (31.9%) of 72 patients with a difference of 19.4% and 95% CI 2.9% to 35.1%]. CR rates, no nausea rates, CC rates, and TC rates by phases are summarized in Table 2. The daily CR rates and daily no nausea rates by treatment group showed continuous greater efficacy of olanzapine versus placebo through 21 days of the observation period (Figure 2). In a pre-planned subgroup analysis, there was a consistent trend toward better outcomes in the olanzapine group during the delayed phase across major subgroups, but this should be considered with caution as the patient numbers of some subsets were small (Supplementary Figures S2 and S3, available at https://doi.org/10.1016/j.annonc.2024.09.001).

To reveal changes in daily symptoms and the nature of response to rescue medication, we plotted the treatment course of patients in each treatment group (Figure 3 and Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2024.09.001). It was found that there were individual differences in the occurrence of nausea and vomiting during the delayed and persistent phases, as well as in the use of rescue medication. Rescue medication was taken by 31 of 80 patients (38.8%) in the olanzapine group and 47 of 83 patients (56.6%) in the placebo group. Dopamine receptor antagonist was the most commonly used rescue medication (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.09.001). The median time to first onset of nausea was longer in the olanzapine group than the placebo group (6.5 versus 3.0 days) while the median time to onset of vomiting was not reached in both groups (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2024.09.001). Among patients who experienced nausea (olanzapine, $n = 49$; placebo, $n = 62$), the median total number of nausea days during the observation period was 4 days for the olanzapine group and 8 days for the placebo group (Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2024.09.001). Among patients who experienced vomiting (olanzapine, $n = 28$; placebo, $n = 26$), the median total number of vomiting days during the observation period was 2 days for the olanzapine group and 4 days for the placebo

Table 2. Comparison of CR rates, no nausea rates, TC rates, and CC rates in per protocol set population

		Olanzapine group	Placebo group	Risk difference, % (% CI[a])	One-sided *P* value
Primary endpoint					
Patients who achieved CR	Delayed phase (24-120 h)	56/80 (70.0)	46/82 (56.1)	13.9 (6.9-20.7)	$P = 0.047$
Secondary endpoints					
Patients who achieved CR	Acute phase (0-24 h)	74/80 (92.5)	76/82 (92.7)	−0.2 (−9.3 to 8.7)	—
	Persistent phase (120-504 h)	46/72 (63.9)	32/72 (44.4)	19.4 (2.4-35.3)	—
	Overall phase (0-504 h)	35/72 (48.6)	29/72 (40.3)	8.3 (−8.2 to 24.6)	—
Patients who achieved CC	Acute phase (0-24 h)	73/80 (91.3)	76/82 (92.7)	−1.4 (−11.1 to 7.6)	—
	Delayed phase (24-120 h)	54/80 (67.5)	44/82 (53.7)	13.8 (−1.4 to 28.7)	—
	Persistent phase (120-504 h)	44/72 (61.1)	32/72 (44.4)	16.7 (−0.0 to 32.7)	—
	Overall phase (0-504 h)	33/72 (45.8)	29/72 (40.3)	5.6 (−10.9 to 21.8)	—
Patients who achieved TC	Acute phase (0-24 h)	66/80 (82.5)	65/82 (79.3)	3.2 (−9.3 to 15.9)	—
	Delayed phase (24-120 h)	44/80 (55.0)	29/82 (35.4)	19.6 (3.1-34.6)	—
	Persistent phase (120-504 h)	36/72 (50.0)	20/72 (27.8)	22.2 (5.6-37.5)	—
	Overall phase (0-504 h)	24/72 (33.3)	18/72 (25.0)	8.3 (−6.9 to 23.6)	—
Patients who achieved no nausea	Acute phase (0-24 h)	68/80 (85.0)	66/82 (80.5)	4.5 (−7.5 to 16.6)	—
	Delayed phase (24-120 h)	46/80 (57.5)	31/82 (37.8)	19.7 (3.1-34.6)	—
	Persistent phase (120-504 h)	37/72 (51.4)	23/72 (31.9)	19.4 (2.9-35.1)	—
	Overall phase (0-504 h)	27/72 (37.5)	19/72 (26.4)	11.1 (−4.5 to 26.3)	—

Data are *n* (%) unless otherwise indicated.
CC, complete control; CI, confidence interval; CR, complete response; TC, total control.
[a]60% CI for primary endpoint; 95% CI for secondary endpoints.

group (Supplementary Figure S7, available at https://doi.org/10.1016/j.annonc.2024.09.001). Patients with refractory nausea and vomiting remained in both groups, even with rescue medication (Figure 3 and Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2024.09.001).

Prognostic and predictive factors

Logistic regression analyses found no prognostic or predictive factors of CR in the delayed phase (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.09.001).

Patient-reported outcomes

Decreased appetite was less frequent in the olanzapine group (any grade severity: 60.0% versus 80.7%) and led to less interference with usual or daily activities (any grade: 41.3% versus 73.5%) according to PRO-CTCAE (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.09.001). Diarrhea was also less frequent in the olanzapine group (any grade: 51.3% versus 67.5%). PRO-CTCAE scores of diarrhea, constipation, abdominal pain, bloating, decreased appetite, fatigue, and insomnia are summarized in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.09.001.

Safety

Somnolence was observed in 20 of 80 olanzapine-treated patients (25.0%) and 9 of 83 (10.8%) placebo-treated patients with no grade $\geq$3 cases in both groups (Table 3). Hyperglycemia was observed in 6 of 80 (7.5%) olanzapine-treated patients and no placebo-treated patients. Decreased appetite and diarrhea were also less frequent in the olanzapine group compared with the placebo group (any grade: 26.3% versus 45.8%, 7.5% versus 19.3%, respectively) consistent with PRO-CTCAE. No grade 5 events were observed.

DISCUSSION

ERICA is the first study to explore the concept of the 'persistent phase' as the period from 120 to 504 h after T-DXd administration and evaluate the nausea and vomiting during this phase. The results of this study indicate that olanzapine, in combination with a 5-HT_3RA and dexamethasone, is promising in preventing nausea and vomiting during delayed and persistent phases in patients with HER2-positive and HER2-low metastatic breast cancer who were receiving their first cycle of T-DXd.

Olanzapine demonstrated several benefits as an antiemetic therapy for T-DXd treatment. Firstly, higher CR rates and higher no nausea rates were observed in the olanzapine group through 21 days of the observation period, with the greatest extent in the first 10 days. Secondly, the benefit of olanzapine in controlling nausea appeared consistent with previous studies.[16,17] Nausea is a symptom that often precedes vomiting, and controlling nausea is more difficult than controlling vomiting.[32,33] The vomiting reflex is mediated in the brainstem, whereas the sensation of nausea is thought to originate from activation of cortical structures involved in conscious perception, although the mechanism is not completely understood.[34] Olanzapine, a multi-acting receptor-targeted antipsychotic, might effectively act on these neural pathways and reduce delayed and persistent nausea induced by T-DXd. Thirdly, in patients who experienced nausea or vomiting, we observed that the total number of nausea or vomiting days was shorter for the olanzapine group than the placebo group although it was a post-randomization subgroup analysis. A previous study showed that the prolonged duration of nausea and

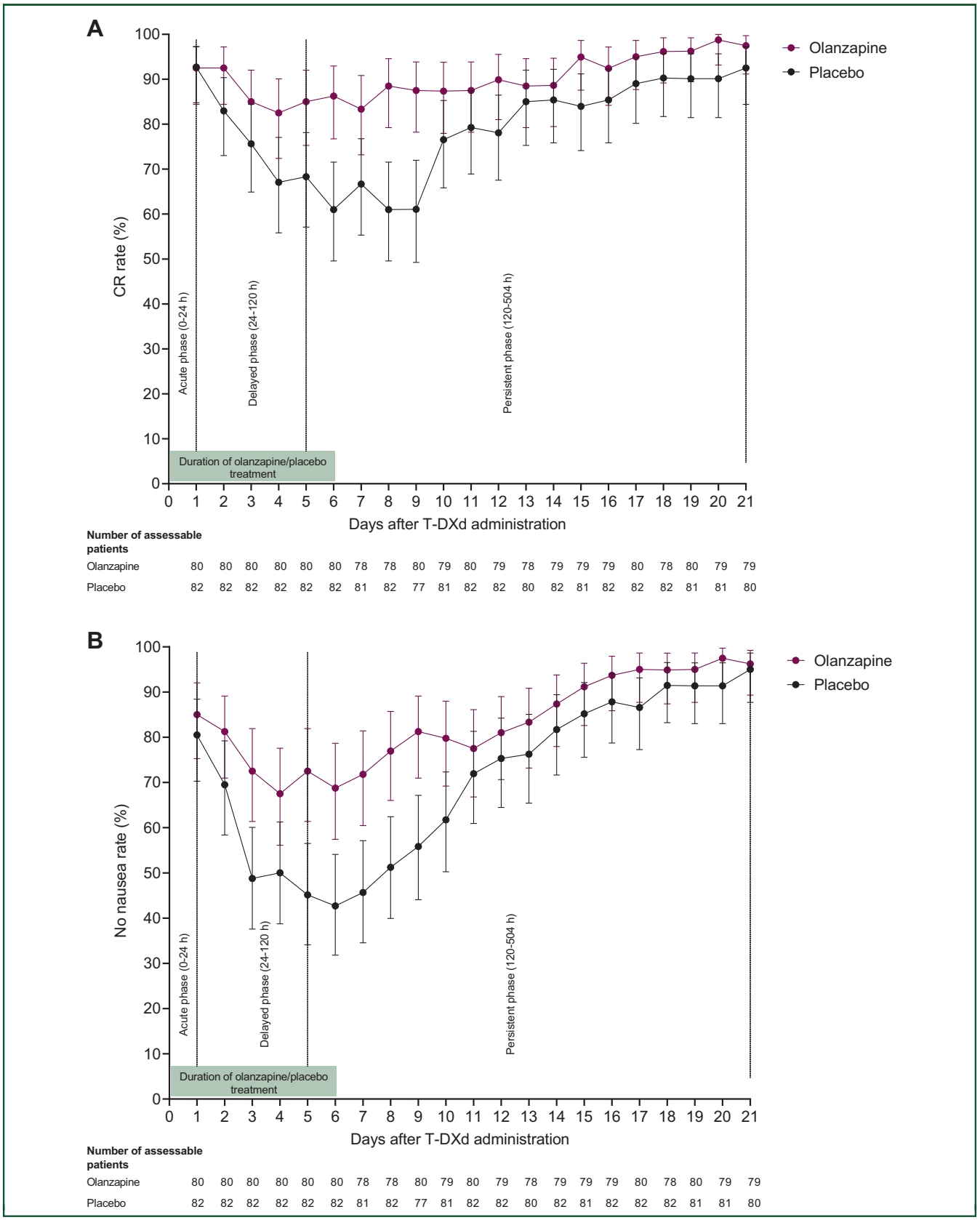

Figure 2. Daily CR rates and no nausea rates by study groups. (A) Daily CR rates and (B) daily no nausea rates by study groups per protocol set population. Cases with missing data were excluded from the analysis. Error bars in the graph indicate 95% confidence intervals.
CR, complete response; T-DXd, trastuzumab deruxtecan.

https://doi.org/10.1016/j.annonc.2024.09.001

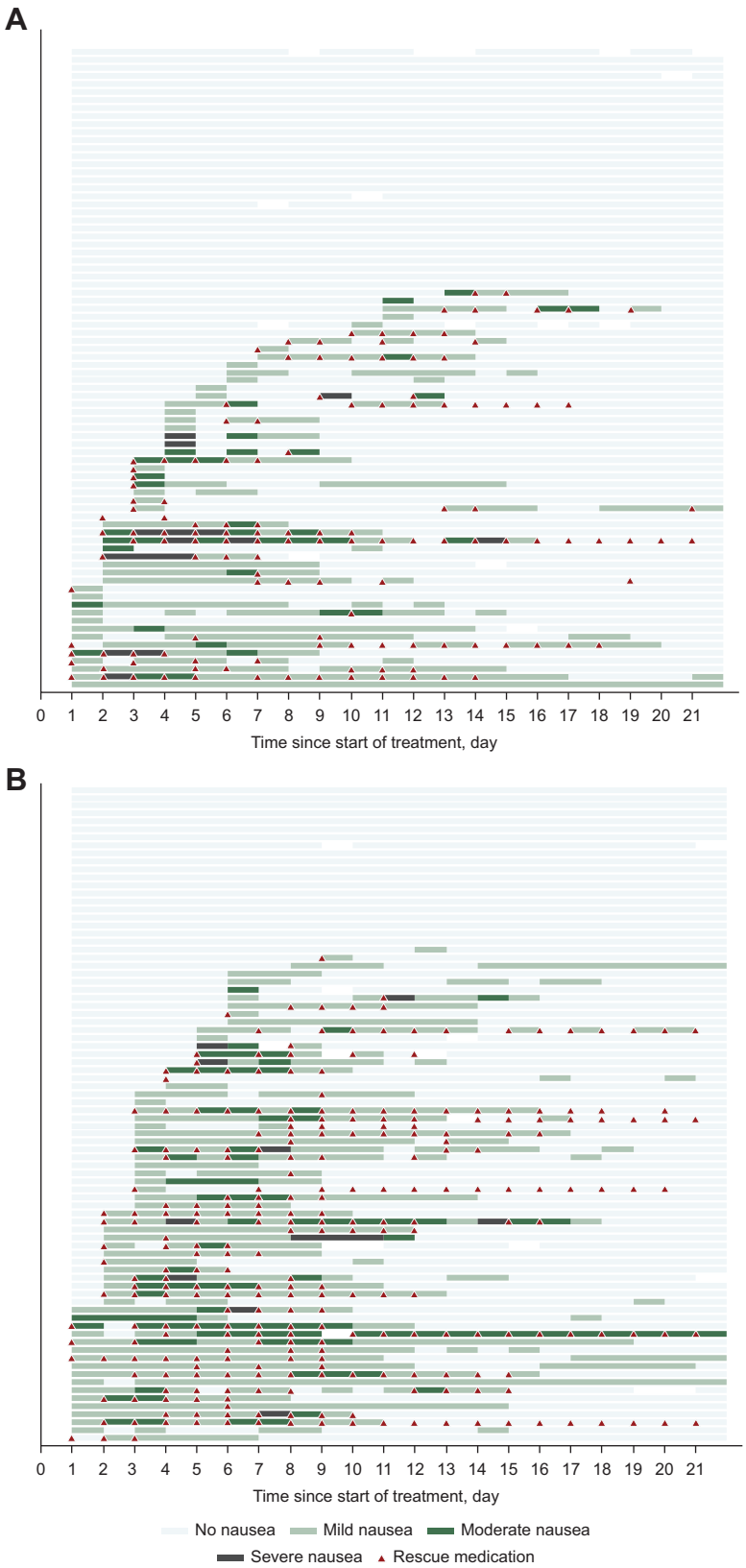

Figure 3. Treatment course of patients who experienced nausea. (A) olanzapine ($n = 80$) and (B) placebo ($n = 82$). Lanes illustrating 80 patients in olanzapine group and 82 patients in placebo group in per protocol set. X axis indicates the days since start of study treatment. Red triangle indicates taking rescue medication. Gray indicates no nausea, light green indicates mild nausea, green indicates moderate nausea, and dark green indicates severe nausea. No color indicates missing values.

Table 3. Any grade and grade ≥3 adverse events in the safety analysis set population

Patients with AE	Olanzapine group (n = 80)		Placebo group (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)
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)

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

vomiting symptoms in the first cycle contributes to the development of recurrent nausea and vomiting during doxorubicin and cyclophosphamide treatment.[35] Thus, we consider that close monitoring of symptom duration is important for the quality of life of patients and may predict recurrence of nausea and vomiting in later cycles. Finally, appetite loss was less frequent and milder in the olanzapine group, consistent with previous studies.[13,36] Olanzapine, therefore, appears to be a potentially effective option for preventing nausea, vomiting, and appetite loss caused by T-DXd treatment.

A recent open-label randomized phase II study showed that antiemetic therapy with aprepitant, granisetron, and dexamethasone had better CR late in the overall phase (0-120 h) than granisetron and dexamethasone in patients with breast cancer undergoing T-DXd treatment.[37] To date, there have been no trials that evaluate the efficacy of adding olanzapine in combination with 5-HT_3RA and dexamethasone in patients treated with T-DXd. Based on the frequency of vomiting in previous clinical trials,[3-5] we considered T-DXd as having moderate emetic risk and the combination therapy of 5-HT_3RA and dexamethasone was appropriate for the control arm in the current study.

There were patients with refractory nausea and vomiting in both groups, even with the use of rescue medication. For patients at high risk of emesis, a four-drug regimen consisting of olanzapine, NK1RA, 5-HT_3RA, and dexamethasone could be an option. Neither specific risk factors for nausea and vomiting during delayed phase nor predictive factors for olanzapine treatment were found through exploratory analysis in this study. In addition, we did not evaluate whether sex is a predictive or prognostic factor due to the small sample size of the male cohort. Further investigation with larger sample size is needed to consider this.

While a significant proportion of patients in the olanzapine group experienced somnolence, dry mouth, hyperglycemia, and dizziness, none of these included grade 3 or greater severity events. The aim to provide effective prophylaxis against nausea and vomiting while also minimizing adverse events, particularly somnolence, has led to several dose comparison studies of olanzapine 5 mg versus 10 mg in the oncology setting. These have concluded that olanzapine 5 mg appears to be equally efficacious to olanzapine 10 mg, and thereby a candidate for further phase III study partly based on lower somnolence rates.[18,19] The randomized, double-blind, placebo-controlled, phase III study (J-FORCE) investigated this concept of lowering the guideline-recommended olanzapine dose to 5 mg and concluded that it 'could be a new standard antiemetic therapy for patients undergoing cisplatin-based chemotherapy'.[13] On this basis, we chose 5 mg in this study as a trade-off between efficacy and tolerability, also with a view of further determining the potential of this lower dose in a subsequent phase III study. In a recent open-label,

randomized phase III study, olanzapine 2.5 mg daily was shown to be non-inferior to 10 mg in preventing nausea and vomiting in patients receiving highly emetic chemotherapy and triple antiemetic therapy with a lower incidence of somnolence.[38] It is unclear, however, whether olanzapine at a daily dose of 2.5 mg is sufficient in a triple therapy regimen that does not include NK1RA.

The present study has some limitations. Firstly, a prophylactic regimen including NK1RA was not used in this study. Secondly, we only evaluated 6 days of olanzapine treatment. Considering that 48.6% of patients experienced nausea during the persistent phase in the olanzapine group, taking olanzapine for longer than 6 days could be tested in future trials. Thirdly, this phase II study recruited a relatively small number of patients despite being powered to meet the statistical aims.

In conclusion, olanzapine-based triplet regimen appears to be a promising antiemetic therapy to prevent delayed and persistent nausea and vomiting induced by the first cycle of T-DXd treatment. Further studies are needed to confirm the efficacy and safety of olanzapine in patients with multiple types of cancer, including breast cancer, who receive T-DXd treatment.

ACKNOWLEDGEMENTS

We appreciate the patients, their families, caregivers, investigators, and study staff at participating sites. We thank Mark Snape, MB BS, of inScience Communications, Springer Healthcare, who edited the initial drafts of this manuscript. This medical writing assistance was funded by Daiichi Sankyo Co., Ltd. We also thank Kazuhito Shiosakai of Daiichi Sankyo Co., Ltd for his contribution in reviewing the statistical analysis plan for this study.

FUNDING

This work was supported by Daiichi Sankyo Co., Ltd (no grant number).

DISCLOSURE

HS has received support for the present manuscript (to institution) and medical writing support from Chugai Pharmaceutical Co, Ltd, lecture fees for Daiichi Sankyo, Chugai Pharmaceutical, and Eli Lilly, advisory role fee from Gilead Sciences. JT has received support for the present manuscript from Daiichi Sankyo (to institution), research grants from Eli Lilly, Daiichi Sankyo, and AstraZeneca (to institution), personal fees for consulting/honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events/advisory board from Daiichi Sankyo and AstraZeneca. YO has received honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Pfizer, Eli Lilly, Daiichi Sankyo, and Kyowa Kirin. HI has received research grants from Eisai, Daiichi Sankyo, Chugai Pharmaceutical, Takeda Pharmaceutical, AstraZeneca, Merck Sharp & Dohme (MSD), ONO Pharmaceutical, and Nipro (to institution), personal fee for consulting from Mitsubishi Tanabe, personal fees for honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Eisai, Chugai Pharmaceutical, Pfizer, Kyowa Kirin, Daiichi Sankyo, Taiho Pharmaceutical, AstraZeneca, and MSD. KN has received honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Daiichi Sankyo. TY has received personal fees for consulting from Daiichi Sankyo and Eli Lilly Japan, honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Daiichi Sankyo, AstraZeneca, Chugai, Pfizer, Eli Lilly Japan, Kyowa Kirin, and Taiho. KA has received honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Chugai Pharmaceutical, Eisai, AstraZeneca, Ono Pharmaceutical, Eli Lilly Japan, Astellas Pharma, Taiho Pharmaceutical, Daiichi Sankyo, Mochida Pharmaceutical, Pfizer Japan, Nestle Japan, and Gilead Sciences, advisory board fees from Taiho Pharmaceutical and Astellas Pharma. KM has received research grants from Daiichi Sankyo, MSD, Eli Lilly, and Gilead Sciences (to institution), honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from MSD, Kyowa Kirin, Eli Lilly, Daiichi Sankyo, Eisai, and Chugai, advisory board fees from Gilead Sciences, Daiichi Sankyo, Pfizer, Genmab, Takeda, Eisai, and Nippon Shinyaku. YM has received research grants from Daiichi Sankyo, Eisai, Chugai, MSD, Kyowa Kirin, Eli Lilly, and Taiho (to institution), personal fee for consulting from Daiichi Sankyo, honoraria for lectures from Daiichi Sankyo, Chugai, Eisai, Eli Lilly, AstraZeneca, Pfizer, Taiho, and Kyowa Kirin. CK has received honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Chugai Pharmaceutical, Daiichi Sankyo, Ono, and AstraZeneca (personal and to institution), from AbbVie, ALX Oncology, MSD, and Sanofi (to institution). YT has received honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Daiichi Sankyo. CI has received research grants from Eli Lilly Japan. DT and TE are employees of Daiichi Sankyo Co, Ltd. TT has received honoraria for lectures from Daiichi Sankyo, Eli Lilly, and Chugai. All other authors have declared no conflicts of interest.

DATA SHARING

Anonymized individual participant data and supporting clinical trial documents including protocol, informed consent form, and statistical analysis plan will be shared on reasonable request to the corresponding author (E-mail: sakai-h@med.showa-u.ac.jp).

ROLE OF THE FUNDER/SPONSOR

The funding provider was involved in the study design, planning of the data analysis, data interpretation, and development of the manuscript but was not involved in data management and statistical analysis. In March 2019, AstraZeneca entered into a global development and

commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

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