A health-related quality-of-life analysis from ERICA study (WJOG14320B)

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Conflict of Interest disclosure slide for representative speakers or investigators

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Name of lead presenter	Hitomi Sakai	Institution or company/position	Showa Medical University

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Name of principal investigator	Hitomi Sakai	Institution or company/position	

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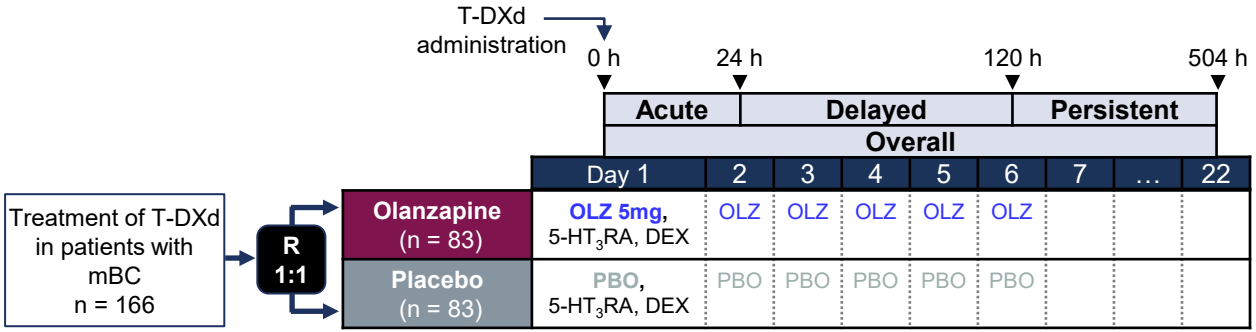
Background: Study design and Primary results

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



- **Stratification factors:** Type of 5-HT_3RA (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
- QOL

Primary results

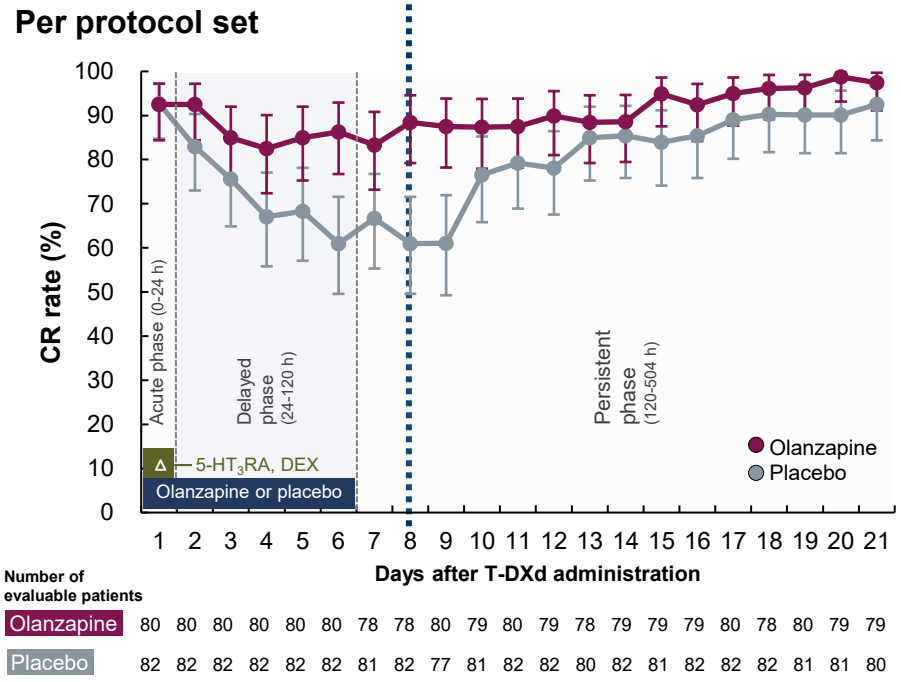
	Olanzapine (n = 80)	Placebo (n = 82)	Fisher's exact test
CR rate in the delayed phase (24–120h) , %	70.0	56.1	p = 0.047[a]
Risk difference, % (60%CI)	13.9 (6.9–20.7)		

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

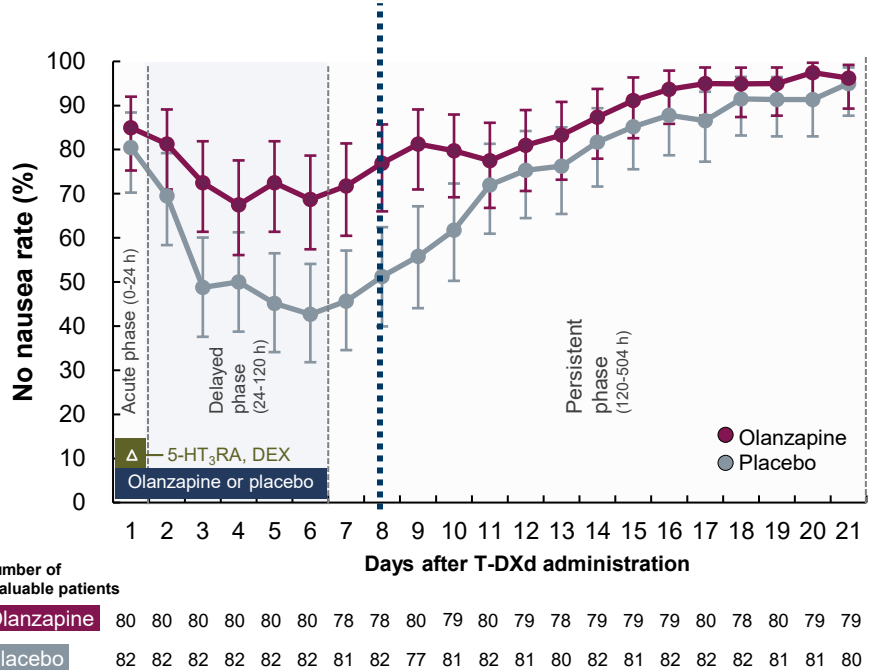
5-HT_3RA, 5-hydroxytryptamine 3 receptor antagonist; CC, complete control; CR, complete response; DEX, dexamethasone; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; OLZ, olanzapine; PBO, placebo; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; R, randomization; TC, total control; T-DXd, 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.

Primary results (continued)

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

CR rate was worse on Day 8,
No nausea rate worsened from Day 3 to Day 6, but began to recover on Day 8

QOL-endpoints

	From registration to first administration of T-DXd	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Questions about yourself	✓																						
Symptom assessment (nausea, vomiting)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Confirmation of use of rescue medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Confirmation of taking olanzapine or placebo[1)]			✓	✓	✓	✓	✓	✓															
Symptom assessment (decreased appetite, etc)[2)]	✓								✓							✓							✓
Quality of life assessment[3)]		✓							✓														

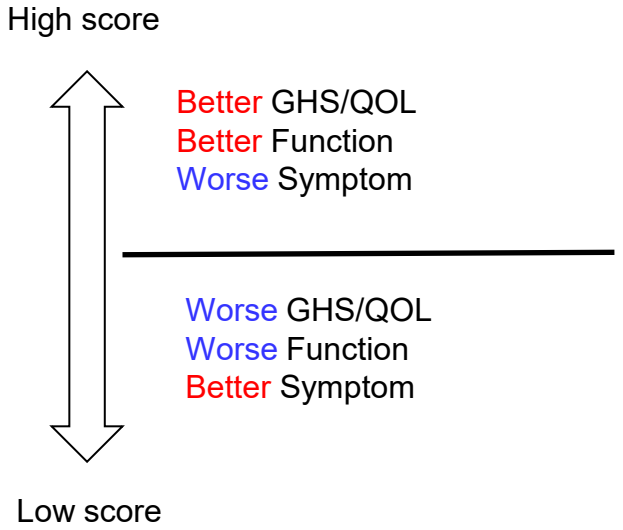
	Measures	Analyses
EORTC QLQ C-30	Global health status Functioning scales: physical, emotional, role, social and cognitive. Symptom scales: fatigue, pain, nausea/vomiting, dyspnea, appetite loss, Insomnia, constipation, diarrhea, financial difficulties	Change from baseline(Day1) The proportion of patients experiencing a moderate or greater change (defined as a decrease of 10 points or more in GHS or functioning scales and increase of 10 points or more in symptom scales)

1) Record the day after taking it
2) PRO-CTCAE assessment of the following symptoms; Diarrhea, constipation, bloating, abdominal pain, decreased appetite, fatigue, insomnia.

Abbreviations: PRO-CTCAE, patient-reported outcomes version of the common terminology criteria for adverse events; T-DXd, trastuzumab deruxtecan.

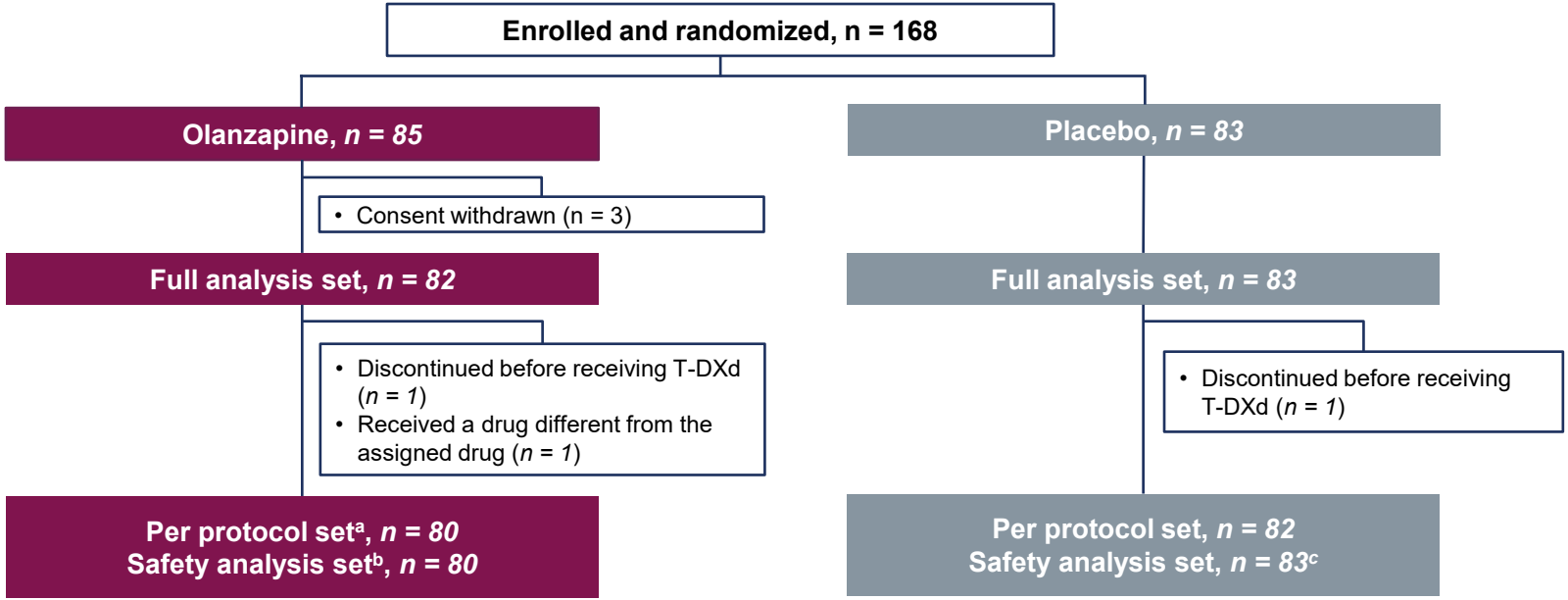
QOL-Analysis

- The raw scores for the scales and single items were linearly transformed to values between 0 and 100 as described in the EORTC QLQ scoring manual.[1)]
- With a change in the 0-100−point converted QOL score being defined as “(a score at the end of the observation period) − (a score at baseline),” the mean change in the QOL score and its 95% confidence interval (CI) was calculated for each treatment arm.
- The difference of the change between the two groups was calculated with adjustment for the baseline converted QOL score, using mixed-effects model. The results are displayed as “adjusted change difference.”
- For each treatment arm, the proportion of patients with a reduction of 10 converted points or more in the GHS/QOL or functional scale score, or an increase of 10 converted points or more in the symptom scale score (moderate or greater deterioration), and its 95% CI were calculated. The “adjusted odds ratio” was calculated with adjustment for the baseline converted QOL score, using mixed-effects model.



1) Fayers P, et al. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer, 2001.

Patient disposition



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

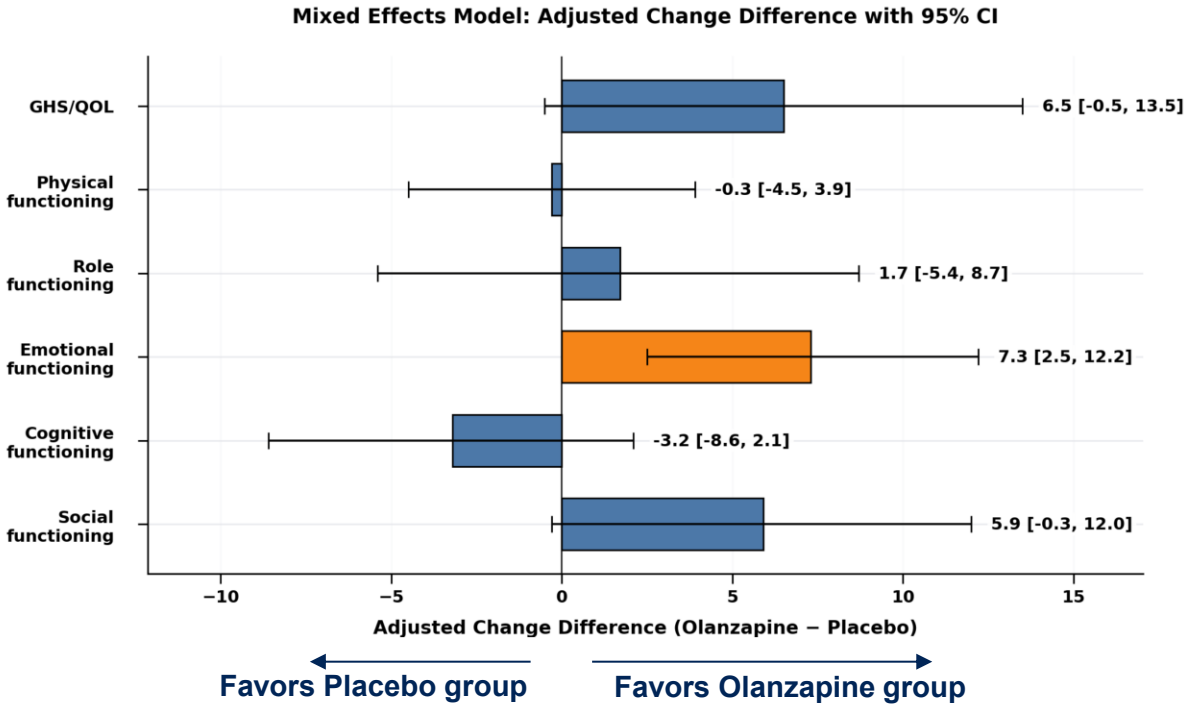
T-DXd, trastuzumab deruxtecan.
[a]Patients who received the assigned treatment. [b]Based on treatment groups regardless of the assigned treatment.
Efficacy and safety analyses were performed in the per protocol set and safety analysis set, respectively
[c]One patient who was assigned olanzapine but received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

Results; Changes in GHS/QOL and Functioning scales

Per protocol set

	mean	Olanzapine	Placebo
GHS/QOL	Baseline	65.8	61.8
	Day8	58.0	48.1
	Change*	-7.5	-14.0
Physical functioning	Baseline	82.8	79.8
	Day8	79.6	76.9
	Change*	-3.1	-2.8
Role functioning	Baseline	84.2	80.7
	Day8	70.7	65.4
	Change*	-13.0	-14.6
Emotional functioning	Baseline	79.8	81.9
	Day8	82.9	77.7
	Change*	3.5	-3.8
Cognitive functioning	Baseline	83.5	84.8
	Day8	77.4	82.1
	Change*	-6.0	-2.7
Social functioning	Baseline	84.6	85.0
	Day8	80.6	74.9
	Change*	-3.6	-9.5

*Day8- BL



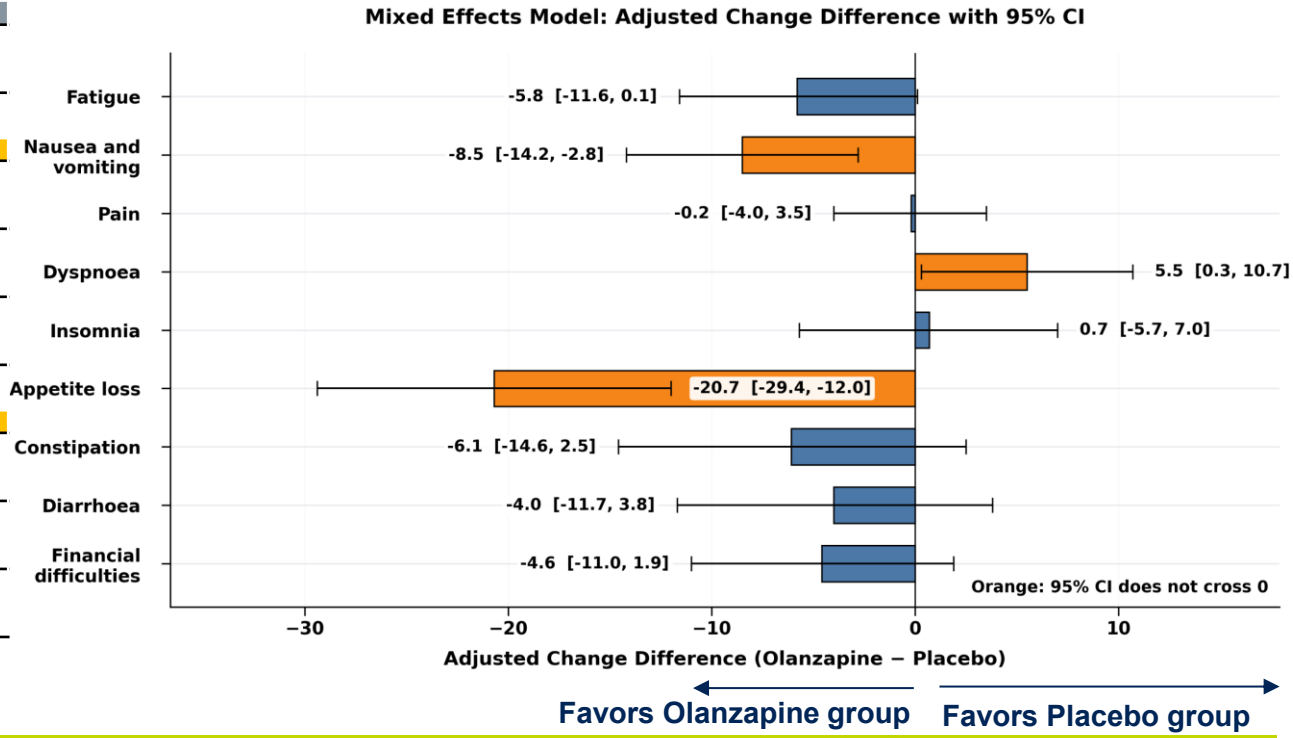
Emotional functioning: A significant difference was observed in QOL between the two groups

Results; Changes in Symptom scales

Per protocol set

	mean	Olanzapine	Placebo
Fatigue	Baseline	30.6	29.4
	Day8	37.2	43.2
	Change	6.4	13.1
Nausea and Vomiting	Baseline	1.3	2.4
	Day8	12.2	21.9
	Change	10.9	19.4
Pain	Baseline	20.2	24.6
	Day8	15.6	19.4
	Change	-4.7	-5.5
Dyspnoea	Baseline	20.4	19.5
	Day8	22.2	17.3
	Change	1.3	-3.0
Insomnia	Baseline	17.1	21.1
	Day8	18.8	20.3
	Change	1.7	-0.4
Appetite loss	Baseline	15.0	14.2
	Day8	25.6	45.1
	Change	10.3	31.2
Constipation	Baseline	17.5	11.4
	Day8	32.9	32.5
	Change	15.4	21.9
Diarrhoea	Baseline	30.8	30.1
	Day8	40.2	44.3
	Change	9.0	13.5
Financial difficulties	Baseline	15.8	17.1
	Day8	18.8	24.5
	Change	3.0	6.8

*Day8- BL

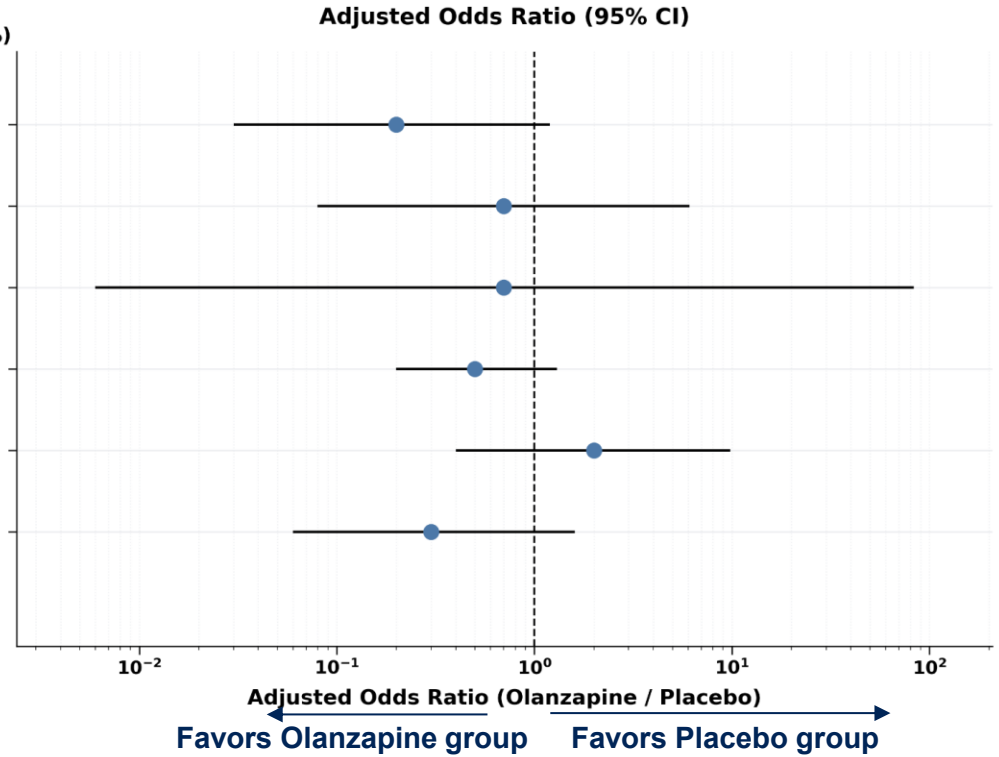


Nausea and vomiting, Appetite loss:

QoL scores increased compared to before T-DXd administration in both groups. When comparing the Olanzapine group and the Placebo group, the decrease in QOL was less in the Olanzapine group.

Results; The proportion of patients experiencing a moderate or greater change (GHS/QOL and Functioning scales)

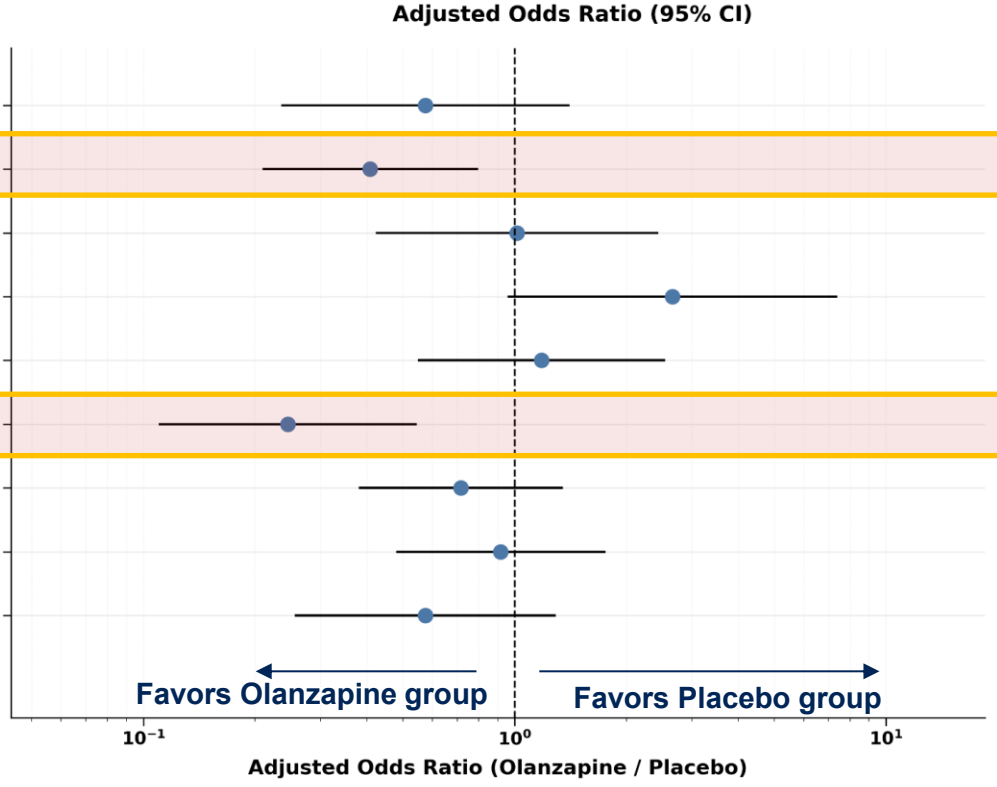
Scale	Olanzapine (%)	Placebo (%)	Adjusted OR [95% CI]
GHS/QOL	39.7%	55.1%	0.2 [0.03, 1.2]
Physical functioning	20.5%	22.8%	0.7 [0.08, 6.1]
Role functioning	43.6%	46.8%	0.7 [0.006, 83.2]
Emotional functioning	9.0%	17.7%	0.5 [0.2, 1.3]
Cognitive functioning	35.9%	30.4%	2 [0.4, 9.8]
Social functioning	28.2%	41.8%	0.3 [0.06, 1.6]



No significant difference was observed between the two groups in the proportion of patients with moderate or greater changes in QOL scores.

Results; The proportion of patients experiencing a moderate or greater change, (Symptom scales)

Item	Olanzapine (%)	Placebo (%)	Adjusted OR [95% CI]
Fatigue	48.7%	60.8%	0.574 [0.235, 1.41]
Nausea and vomiting	43.6%	64.6%	0.408 [0.209, 0.796]
Pain	15.4%	15.2%	1.01 [0.423, 2.44]
Dyspnoea	17.9%	7.6%	2.66 [0.958, 7.39]
Insomnia	23.1%	20.3%	1.18 [0.549, 2.54]
Appetite loss	34.6%	63.3%	0.245 [0.11, 0.545]
Constipation	43.6%	51.9%	0.716 [0.38, 1.35]
Diarrhoea	37.2%	39.2%	0.916 [0.479, 1.75]
Financial difficulties	15.4%	24.1%	0.574 [0.256, 1.29]



The rate of moderate or greater deterioration for Nausea and vomiting and appetite loss were lower in Olanzapine group

Conclusions

- **Change of GHS and Functioning scales**
  - **GHS/QOL:** Scores decreased compared to before T-DXd administration in both groups. The olanzapine group tended to show a smaller decrease in QoL compared to the placebo group（adjusted change difference; 6.5 [95% CI -0.5, 13.5], but this difference was not significant.
  - **Emotional functioning:** A difference favoring the olanzapine group was observed in QoL between the two groups (adjusted change difference; 7.3 [95% CI 2.5, 12.2].
- **Change of Symptom scales**
  - **Nausea and vomiting, Appetite loss:** Scores increased compared to before T-DXd administration in both groups. Nausea and vomiting：adjusted change difference; -8.5 [95% CI -14.2, -2.8])
  - **Appetite loss**：Adjusted change difference; -20.7 [95% CI -29.4, -12.0])

  ⇒QoL seems to be better maintained when olanzapine is given.
- **The proportion of patients experiencing a moderate or greater change**
  - The rate of moderate or greater deterioration for nausea and vomiting and appetite loss were lower in Olanzapine group.

QOL results assessed on Day 8 further support olanzapine as an antiemetic therapy option in patients with breast cancer receiving T-DXd in the first cycle.

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