JBCRG-M06/EMERALD post-hoc analysis by physician's choice of docetaxel or paclitaxel: Efficacy and safety of eribulin mesylate vs taxanes combined with trastuzumab and pertuzumab as first-line for HER2-positive locally advanced or metastatic breast cancer

Norikazu Masuda, MD, PhD[1], Shigehira Saji, MD, PhD[2], Yasuyuki Kojima, MD, PhD[3], Masahiro Kitada, MD, PhD[4], Hiroshi Tada, MD, PhD[5], Tsutomu Iwasa, MD, PhD[6], Kei Koizumi, MD, PhD[7], Hideo Shigematsu, MD, PhD[8], Yasuaki Sagara, MD, MPH[9], Toshitaka Okuno, MD[10], Yoshie Hasegawa, MD, PhD[11], Eriko Tokunaga, MD, PhD[12], Tadahiko Shien, MD, PhD[13], Uhi Toh, MD, PhD[14], Takashi Kuwayama, MD, PhD[15], Masafumi Shimoda, MD, PhD[16], Hiroki Hasegawa, MBA[17], Satoshi Morita, PhD[18], Toshinari Yamashita, MD, PhD[19]

[1]Department of Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Department of Medical Oncology, Fukushima Medical University, Fukushima, Japan, [3]Division of Breast Surgical Oncology, Department of Surgery, Showa Medical University Hospital, Tokyo, Japan, [4]Department of Breast Disease Center, Asahikawa Medical University Hospital, Hokkaido, Japan, [5]Division of Breast and Endocrine Surgery, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, Miyagi, Japan, [6]Department of Medical Oncology, Kindai University Hospital, Osaka, Japan, [7]Department of Breast Surgery, Hamamatsu University Hospital, Shizuoka, Japan, [8]Department of Breast Surgery, Hiroshima University Hospital, Hiroshima, Japan, [9]Department of Breast and Thyroid Surgical Oncology, Social Medical Corporation Hakuaikai, Sagara Hospital, Kagoshima, Japan, [10]Department of Breast Surgery, Kobe City Nishi-Kobe Medical Center, Hyogo, Japan, [11]Department of Breast Surgery, Hachinohe City Hospital, Aomori, Japan, [12]Department of Breast Oncology, NHO Kyushu Cancer Center, Fukuoka, Japan, [13]Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan, [14]Department of Breast Surgery, Kurume University Hospital, Fukuoka, Japan, [15]Department of Breast Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [16]Department of Breast and Endocrine Surgery, Hyogo Medical University Hospital, Hyogo, Japan, [17]Medical HQs, Eisai Co., Ltd., Tokyo, Japan, [18]Department of Biomedical Statistics and Bioinformatics, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [19]Department of Breast Surgery and Oncology, Kanagawa Cancer Center, Kanagawa, Japan

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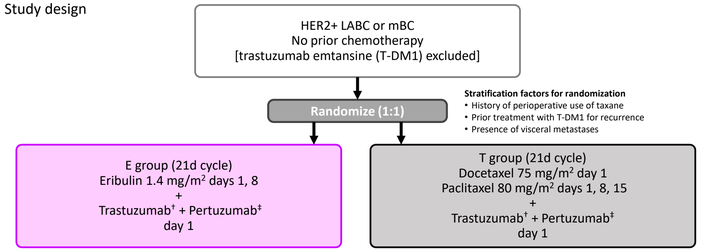
Introduction

- A taxane with trastuzumab + pertuzumab is considered a preferred treatment regimen for HER2+ metastatic breast cancer (mBC) [1-3].
- The randomized open-label phase 3 JBCRG-M06/EMERALD study (NCT03264547) was the first to show the non-inferiority of eribulin (E) to taxane (T) (docetaxel [DTX] or paclitaxel [PTX]) when combined with dual HER2 blockade as first-line chemotherapy for HER2+ locally advanced breast cancer (LABC) or mBC [4].
  - In the primary analysis results, median progression-free survival (PFS) was 14.0 and 12.9 months in the E and T groups, respectively (hazard ratio, 0.95).
  - Although median treatment duration was longer with E (28.1 weeks) than with DTX or PTX (18.1 and 20.5 weeks, respectively), the incidences of adverse events (AEs) were similar between the E and T groups.
- While DTX and PTX have some pharmacological similarities, their distinct properties may result in differences in therapeutic outcomes and tolerability [5,6]. Therefore, we conducted post hoc analyses of the EMERALD study to compare the effectiveness and safety of E vs either DTX or PTX independently.

Patients and Methods

- Patients aged 20–70 years with HER2+ LABC/mBC who had not previously received cytotoxic chemotherapy (other than trastuzumab emtansine [T-DM1]) were eligible, and were randomized (1:1) to receive E (1.4 mg/m^2 on days 1 and 8) or T (DTX 75 mg/m^2 on day 1 or PTX 80 mg/m^2 on days 1, 8, and 15), intravenously in a 21-day cycle, each with trastuzumab + pertuzumab [4,7] (**Fig.1**).
- For patients in the T group, the attending physician selected either DTX or PTX, with the choice required to be declared prior to enrollment. Patients in the E group were then allocated in numbers corresponding to the DTX and PTX subgroups of the T group.
- This post hoc analysis focused on survival outcomes (cutoff date: Jun 30, 2023 for PFS and Dec 31, 2024 for OS), response rates, and safety (drug-related AEs).
- The Kaplan–Meier method was used to assess survival outcomes.
- Frequencies of drug-related AEs were assessed using the Japanese version of the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and tabulated by preferred term and grade as the number (%) of patients.

Fig. 1. Study design



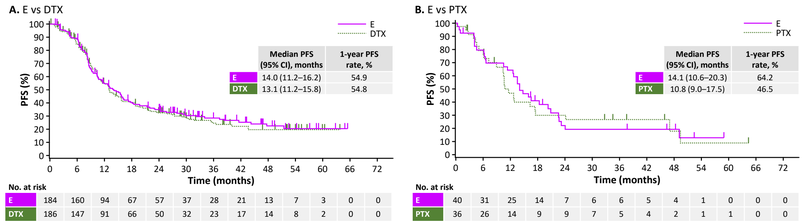
† Trastuzumab: 8 mg/kg loading dose, 6 mg/kg subsequent doses. ‡ Pertuzumab: 840 mg/body loading dose, 420 mg/body subsequent doses.

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Results

- Of the total 446 patients enrolled (August 2017 - June 2021), 224 received E and 222 received T (DTX, n = 186; PTX, n = 36) (intention-to-treat population, ITT); 224 in the E group and 218 in the T group (DTX, n = 184; PTX, n = 34) received at least one dose of the study drug (safety analysis population).
- Baseline characteristics were well balanced between the groups (**Table 1**). In the T group, there were no differences in age or ECOG performance status between the DTX and PTX subgroups.
- Survival outcomes were similar between patients who received DTX or PTX in terms of PFS and OS.
- Median PFS was 14.0 vs 13.1 months in the E vs DTX subgroups (**Fig. 2A**), and 14.1 vs 10.8 months in the E vs PTX subgroups (**Fig. 2B**).
- In the E vs DTX arm, the objective response rate (ORR) was 77.3% (140/181; CR, 11.0%; PR, 66.3%) with E and 75.4% (138/183; CR, 13.1%; PR, 62.3%) with DTX. In the E vs PTX arm, the ORR was 75.0% (30/40; CR, 15.0%; PR, 60.0%) with E and 72.7% (24/33; CR, 15.2%; PR, 57.6%) with PTX (**Fig. 3**).
- Median OS was not reached (NR) in both the E and DTX subgroups (**Fig. 4A**), and 75.5 months vs NR in the E vs PTX subgroups (**Fig. 4B**).
- The incidences of drug-related AEs were generally similar between the E and T groups, regardless of the type of T used (**Fig. 5A, B**).
  - However, the incidence of peripheral sensory neuropathy tended to be higher in the PTX subgroup (PTX vs E: 82.4% vs 52.5%) and lower in the DTX subgroup (DTX vs E: 47.3% vs 63.0%) compared with E.
  - Additionally, the incidence of neutropenia tended to be lower with DTX (DTX vs E: 28.8% vs 62.0%) than with PTX (PTX vs E: 41.2% vs 60.0%), but was numerically more frequent in the E subgroups.
  - The incidences of skin-related disorders, diarrhea, edema, and infusion reactions tended to be higher with DTX and PTX than with E.
- Time to deterioration of QoL tended to be longer with E than with DTX (**Fig. 6A**) and PTX (**Fig. 6B**), although the difference did not appear to be significant.

Fig. 2. PFS according to treatment group (ITT population)

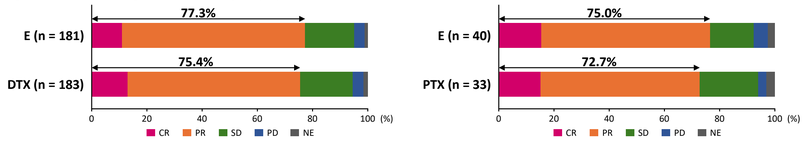


No. at risk

E	184	160	94	67	57	37	28	21	13	7	3	0	0
DTX	186	147	91	66	50	32	23	17	14	8	2	0	0

E	40	31	25	14	7	6	6	5	4	1	0	0	0
PTX	36	26	14	9	9	7	5	4	2	1	1	0	0

Fig. 3. ORR according to treatment group (patients with evaluable lesions)



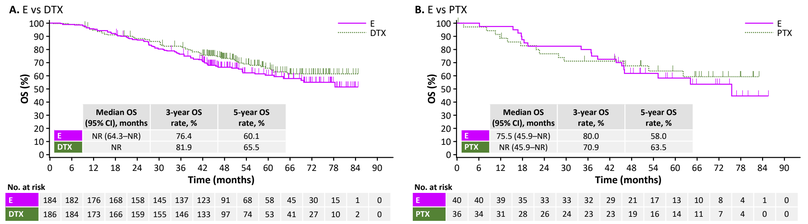
CR, complete response; FAS, full analysis set; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Table 1. Baseline characteristics (ITT population)

	E vs DTX		E vs PTX	
	E (n = 184)	DTX (n = 186)	E (n = 40)	PTX (n = 36)
Age, years, median (range)	56.0 (29–70)	57.0 (32–70)	55.5 (30–69)	57.0 (39–70)
ECOG PS				
0	151 (82.1)	158 (84.9)	33 (82.5)	29 (80.6)
1	32 (17.4) [a]	26 (14.0) [a]	7 (17.5)	7 (19.4)
ER status				
Positive	100 (54.3)	107 (57.5)	28 (70.0)	22 (61.1)
Negative	84 (45.7)	79 (42.5)	12 (30.0)	14 (38.9)
HER2 status				
IHC1+, 2+ / ISH+	30 (16.3)	37 (19.9)	6 (15.0)	11 (30.6)
IHC 3+	150 (81.5)	144 (77.4)	34 (85.0)	25 (69.4)
IHC not done/ISH+	4 (2.2)	5 (2.7)	0	0
Disease-free interval (time to recurrence)				
De novo stage 4	111 (60.3)	118 (63.4)	19 (47.5)	15 (41.7)
< 24 months[b]	19 (10.3)	12 (6.5)	3 (7.5)	6 (16.7)
≥ 24 months[b]	53 (28.8)	56 (30.1)	18 (45.0)	15 (41.7)
Taxanes as adjuvant or neoadjuvant therapy[c]				
Yes	55 (29.9)	48 (25.8)	16 (40.0)	19 (52.8)
No	18 (9.8)	20 (10.8)	5 (12.5)	2 (5.6)
Visceral metastasis[c]				
Yes	124 (67.4)	121 (65.1)	22 (55.0)	25 (69.4)
Brain metastasis				
Yes	8 (4.3)	6 (3.2)	0	1 (2.8)
No (confirmed by imaging test)	42 (22.8)	42 (22.6)	11 (27.5)	11 (30.6)
No (based on clinical assessment)	134 (72.8)	138 (74.2)	29 (72.5)	24 (66.7)

Values are expressed as n (%) unless otherwise stated.
[a] One patient in the E group (PS 3) and two patients in the DTX group (PS 2 and no data, each) were enrolled.
[b] One patient with unknown disease-free interval (but not de novo stage 4) was excluded from the count.
[c] Stratification factors for randomization – revised.

Fig. 4. OS according to treatment group (ITT population)



No. at risk

E	184	182	176	168	158	145	137	123	91	68	58	45	30	15	1	0
DTX	186	184	173	166	159	155	146	133	97	74	53	41	27	10	2	0

E	40	40	39	35	33	33	32	29	21	17	13	10	8	4	1	0
PTX	36	34	31	28	26	24	23	23	19	16	14	11	7	4	0	0

Fig. 5. Incidence of drug-related AEs according to treatment group (safety analysis population)

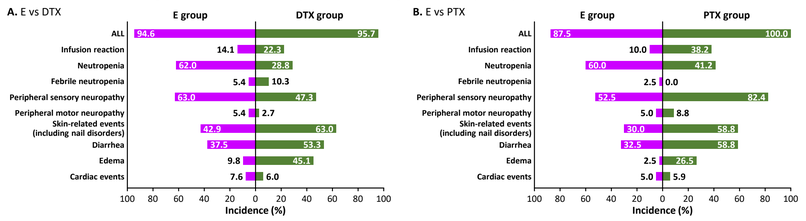
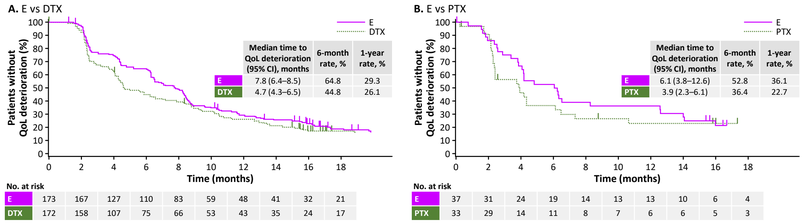


Fig. 6. Time to QoL deterioration* (QoL analysis set)



No. at risk

E	173	167	127	110	83	59	48	41	32	21
DTX	172	158	107	75	66	53	43	35	24	17

E	37	31	24	19	14	13	13	10	6	4
PTX	33	29	14	11	8	7	6	6	5	3

*Defined as ≥10-point decrease from baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Module C30.

Conclusions

- In the JBCRG-M06/EMERALD study, DTX and PTX were used to treat 84% and 16% of patients in the T group, respectively.
- No differences in PFS and OS were found in these post hoc analyses of E vs either DTX or PTX subgroups, underscoring the non-inferiority of E vs T in the intention-to-treat analysis [4].
- While drug-related AEs were generally similar between the E and T groups, regardless of the type of T used, a higher incidence of peripheral sensory neuropathy was noted with PTX compared with E or DTX.
- E is an effective and tolerable alternative to either DTX or PTX, combined with dual HER2 blockade, for patients with LABC/mBC.

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Disclosure

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Contact

Norikazu Masuda, MD, PhD
Department of Breast Surgery, Graduate School of Medicine, Kyoto University
54 Kawahara-cho, Shogoin Sakyo-ku, Kyoto City, Kyoto 606-8507, Japan
Email: nmasuda@alpha.ocn.ne.jp