San Antonio Breast Cancer Symposium® - December 10-13, 2024
P5-03-04

# The effectiveness of post–T-DXd treatments in patients with HER2-positive metastatic breast cancer: A nationwide Japanese cohort study (EN-SEMBLE)

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## Objective

- The aim of the EN-SEMBLE study was to examine the distribution of post-T-DXd regimens, including their effectiveness and the incidence of ILD, in real-world clinical practice in Japan.

## Conclusions

- In the current study, 73% of patients received anti-HER2 therapy and 54% received anti-HER2 antibody regimens as 1st post–T-DXd treatments.
- The rwPFS and OS results were numerically similar for anti-HER2 antibody and HER2-TKI-based therapies received as 1st post–T-DXd treatments.
- Patients who discontinued T-DXd due to AEs, including ILD, had numerically better outcomes than those who discontinued due to PD.
- The 1st post–T-DXd treatments were generally safe for patients with a history of ILD incidence caused by T-DXd treatment, with a recurrence rate of 3.2%.

## Limitations

- Inherent risks for bias may have occurred due to:
  - the study being non-blinded, non-randomized, and with no control arm
  - the fact that among the patients who were enrolled in the all-patient PMS, only those who were able to start the post-T-DXd treatment were enrolled in the present study.
- The all-patient PMS for T-DXd was conducted when prior T-DM1 treatment was required. Since T-DXd was administered as different lines of treatment, subsequent therapies were also different lines of treatment and may not be directly comparable.

## Plain language summary (PLS)

**Why did we perform this research?**
Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate (ADC) that is approved for the treatment of patients with advanced breast cancer that expresses high levels of a protein called human epidermal growth factor receptor 2 (HER2).[4–6] Some patients have to stop using T-DXd because their disease gets worse, or they experience side effects like interstitial lung disease (ILD). Since we don't know the best course of treatment for those who stop using T-DXd, this study addresses the important question of how different HER2-directed breast cancer therapies work post T-DXd use.

**How did we perform this research?**
The EN-SEMBLE study was carried out in real-world clinical settings and included those who were enrolled in the all-patient surveillance study of patients with unresectable and/or recurrent breast cancer treated with T-DXd (jRCT1080225197) who had stopped T-DXd and had started a new medication. The study investigated the distribution of medications and assessed their effectiveness in the post–T-DXd treatment period. Additionally, we investigated outcomes in patients who stopped T-DXd due to ILD.

**What were the findings of this research?**
This study enrolled 664 patients from 222 sites in Japan. After stopping T-DXd, patients received the following medications: anti-HER2 antibodies (trastuzumab with or without pertuzumab; 54%), HER2-tyrosine kinase inhibitors (TKIs [including lapatinib]; 17%), ADCs (T-DM1; 2%), and other (27%). The median length of time that patients lived with their cancer before the disease got worse or caused death (progression-free survival) in the real-world setting was 4.1 months for anti-HER2 antibodies, 4.3 months for HER2-TKIs, and 2.6 months for ADCs. The median length of time that patients survived post-T-DXd treatment (overall survival) was 17.2 months for anti-HER2 antibodies, 16.3 months for HER2-TKIs, and 9.3 months for ADCs. Out of the 155 patients who had a history of ILD related to T-DXd treatment, only a small proportion (3.2%) had their lung disease come back or get worse after stopping T-DXd and starting the first next treatment.

**What are the implications of this research?**
The effectiveness of anti-HER2 antibodies and HER2-TKI therapies was similar when used as the first treatment after T-DXd. Moreover, patients who had to stop taking T-DXd due to adverse events, including ILD, had better outcomes than those who had to stop due to worsening disease. Findings also showed that the first next treatment after T-DXd was generally safe.

**Where can I access more information?**
https://jrct.niph.go.jp/en-latest-detail/jRCT1030220506

**Poster**

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This study was sponsored by Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201). Poster presented at SABCS2024 by Kazuki Nozawa.

## Introduction

- In the DESTINY-Breast01, 02, and 03 clinical trials, T-DXd has shown significant clinical benefits in patients with HER2-positive mBC.[1–3]
- Patients discontinue T-DXd treatment mainly due to PD or AEs, such as ILD, in real-world clinical practice.
- However, limited information is available about the efficacy of HER2-directed therapies post T-DXd; more is needed in order to define the optimal treatment strategy for HER2+ mBC previously treated with T-DXd.

## Methods

### Study design

**EN-SEMBLE Study: A nationwide cohort study in real-world settings in Japan**

**All-patient PMS** (jRCT1080225197)
- Started T-DXd treatment between May 2020 (launch date of T-DXd) and May 2021.
- With HER2-positive metastatic or recurrent BC.

**Registration period:** May 2020 to May 2023
**Observation period:** May 2020 to Nov 2023

**Eligibility Criteria**
- Enrolled in all-patient PMS
- Have discontinued T-DXd treatment
- Started a post–T-DXd treatment
- Informed consent/opt-out consent
- Age ≥ 18 years

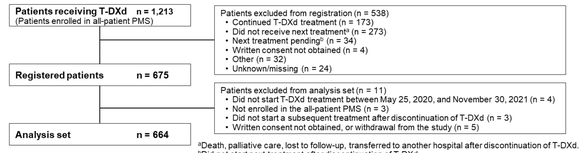
**EN-SEMBLE study** (jRCT1030220506)

**Endpoints**
- Distribution of post–T-DXd treatment regimens
- Effectiveness: rwPFS, rwTTF, rwTTNT, and OS from 1st post–T-DXd treatment
- Incidence of ILD in 1st post–T-DXd treatment

A pre-specified subgroup analysis was planned

Patients were registered at 222 sites nationwide in Japan; **median follow-up was 12.0 months** (range, 0.3–36.2 months)

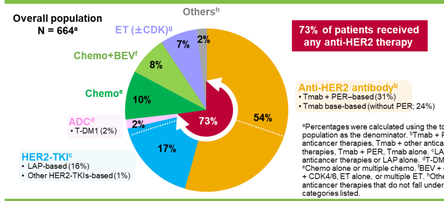
### Patient disposition




[a]Death, palliative care, lost to follow-up, transferred to another hospital after discontinuation of T-DXd. [b]Did not start next treatment after discontinuation of T-DXd.

## Results

### Figure 1. Distribution of 1st post–T-DXd treatments




[a]Percentages were calculated using the total patient population as the denominator. [b]Tmab + PER + other anticancer therapies, Tmab + other anticancer therapies, Tmab + PER, Tmab alone. [c]LAP + other anticancer therapies or LAP alone. [d]T-DM1 alone. [e]Chemo alone or multiple chemo. [f]BEV + chemo. [g]ET + CDK4/6, ET alone, or multiple ET. [h]Other anticancer therapies that do not fall under other categories listed.

### Table 1. Baseline characteristics

| | | All patients | 1st post–T-DXd treatment regimen: Anti-HER2 antibody | HER2-TKI | ADC |
|---|---|---|---|---|---|
| | | N = 664 | n = 361 | n = 113 | n = 12 |
| **At the start of 1st post–T-DXd treatment** | | | | | |
| **Age** | Median (range), years | 60.0 (30–89) | 61.0 (35–89) | 58.0 (35–83) | 61.5 (48–88) |
| | <65 years | 416 (62.7) | 219 (60.7) | 75 (66.4) | 7 (58.3) |
| | ≥65 years | 248 (37.3) | 142 (39.3) | 38 (33.6) | 5 (41.7) |
| **Sex** | Female | 661 (99.5) | 360 (99.7) | 112 (99.1) | 12 (100.0) |
| | Male | 3 (0.5) | 1 (0.3) | 1 (0.9) | 0 (0.0) |
| **HER2 status** | IHC 3+ | 407 (61.3) | 223 (61.8) | 78 (69.0) | 7 (58.3) |
| | IHC 2+/ISH+ | 173 (26.1) | 92 (25.5) | 31 (27.4) | 4 (33.3) |
| | ISH+ other than the above/ISH− | 33 (5.0) | 16 (4.4) | 1 (0.9) | 0 (0.0) |
| | Unknown/both missing | 51 (7.7) | 30 (8.3) | 3 (2.7) | 1 (8.3) |
| **ECOG PS** | 0 | 326 (49.1) | 185 (51.2) | 49 (43.4) | 3 (25.0) |
| | 1 | 251 (37.8) | 127 (35.2) | 50 (44.2) | 8 (66.7) |
| | >2 | 57 (8.6) | 26 (7.2) | 9 (8.0) | 1 (8.3) |
| | Unknown | 30 (4.5) | 23 (6.4) | 5 (4.4) | 0 (0.0) |
| **Visceral metastasis** | Yes | 529 (79.7) | 280 (77.6) | 91 (80.5) | 9 (75.0) |
| | No | 135 (20.3) | 81 (22.4) | 22 (19.5) | 3 (25.0) |
| **Brain metastasis** | Yes | 153 (23.0) | 79 (21.9) | 31 (27.4) | 4 (33.3) |
| | No | 500 (75.3) | 275 (76.2) | 80 (70.8) | 8 (66.7) |
| | Unknown | 11 (1.7) | 7 (1.9) | 2 (1.8) | 0 (0.0) |
| **Prior cancer therapy for unresectable or recurrent BC before T-DXd treatment** | | | | | |
| **Number of prior regimens** | Median (range), line | 3 (1–42) | 4 (1–25) | 3 (1–15) | 3 (1–13) |
| | ≤2 lines | 190 (28.6) | 87 (24.1) | 46 (40.7) | 5 (41.7) |
| | ≥3 lines | 459 (69.1) | 265 (73.4) | 64 (56.6) | 7 (58.3) |
| **Prior regimens** | Anti-HER2 therapy | 654 (98.5) | 355 (98.3) | 110 (97.3) | 12 (100.0) |
| | Trastuzumab | 620 (93.4) | 342 (94.7) | 103 (91.2) | 11 (91.7) |
| | Pertuzumab | 601 (90.5) | 328 (90.9) | 102 (90.3) | 10 (83.3) |
| | T-DM1 | 606 (91.3) | 329 (91.1) | 107 (94.7) | 9 (75.0) |
| | Chemotherapy | 600 (90.4) | 328 (90.9) | 100 (88.5) | 11 (91.7) |
| | Endocrine therapy | 253 (38.1) | 127 (35.2) | 42 (37.2) | 2 (16.7) |
| **T-DXd treatment** | | | | | |
| **BC status** | De novo stage IV | 250 (37.7) | 134 (37.1) | 42 (37.2) | 4 (33.3) |
| | Recurrent BC | 394 (59.3) | 215 (59.6) | 67 (59.3) | 8 (66.7) |
| **Duration of T-DXd treatment** | Median (range), month | 8.1 (0.03–35.4) | 8.3 (0.03–35.4) | 9.9 (0.7–29.4) | 7.2 (1.4–19.6) |
| **History of ILD in T-DXd treatment** | Yes | 155 (23.3) | 100 (27.7) | 22 (19.5) | 4 (33.3) |
| | None | 508 (76.5) | 261 (72.3) | 90 (79.6) | 8 (66.7) |
| | Unknown | 1 (0.2) | 0 (0.0) | 1 (0.9) | 0 (0.0) |
| **Reason for T-DXd discontinuation** | PD | 448 (67.5) | 223 (61.8) | 84 (74.3) | 5 (41.7) |
| | ILD | 146 (22.0) | 96 (26.6) | 20 (17.7) | 3 (25.0) |
| | AEs other than ILD | 34 (5.1) | 23 (6.4) | 6 (5.3) | 1 (8.3) |
| | Others | 36 (5.4) | 19 (5.3) | 3 (2.7) | 3 (25.0) |

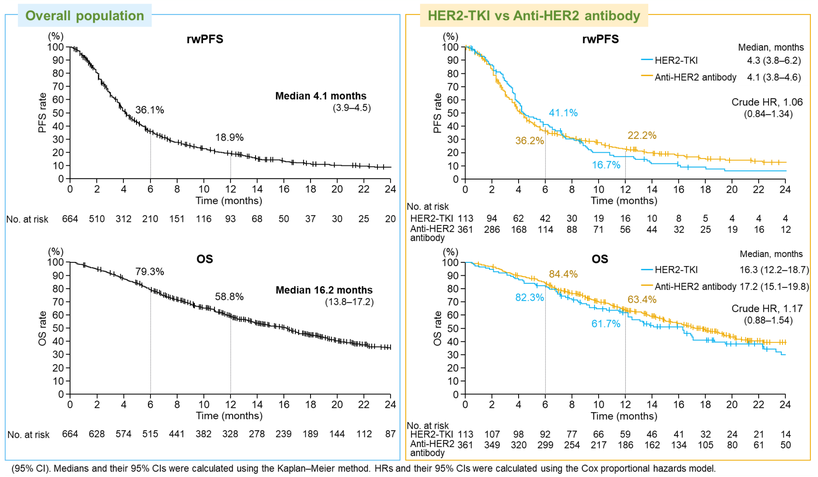
Data are shown as n (%) unless otherwise specified

### Table 2. Outcomes for 1st post–T-DXd treatment

| | All patients | 1st post–T-DXd treatment regimen: Anti-HER2 antibody | HER2-TKI | ADC | Chemo | Chemo + BEV | ET ± CDK | Others |
|---|---|---|---|---|---|---|---|---|
| | N = 664 | n = 361 | n = 113 | n = 12 | n = 64 | n = 52 | n = 49 | n = 13 |
| **rwPFS** | 4.1 (3.9–4.5) | 4.1 (3.8–4.6) | 4.3 (3.8–6.2) | 2.6 (1.0–4.7) | 2.8 (2.1–3.9) | 4.2 (3.0–5.4) | 6.5 (3.8–7.4) | 2.8 (1.0–7.3) |
| **rwTTF** | 3.8 (3.7–4.1) | 3.9 (3.6–4.3) | 4.2 (3.7–5.6) | 2.0 (0.3–3.1) | 2.5 (2.1–3.8) | 3.7 (2.6–4.8) | 5.6 (2.5–6.7) | 2.8 (1.4–7.3) |
| **rwTTNT** | 5.0 (4.6–5.5) | 5.1 (4.5–5.7) | 5.3 (4.4–6.8) | 3.0 (1.0–5.9) | 4.0 (3.5–4.5) | 5.5 (3.9–6.2) | 6.7 (4.8–10.1) | 4.4 (1.9–10.2) |
| **OS** | 16.2 (13.8–17.2) | 17.2 (15.1–19.8) | 16.3 (12.2–18.7) | 9.3 (4.3–NE) | 11.4 (5.9–19.2) | 8.2 (6.0–10.5) | 21.9 (16.9–NE) | 12.1 (5.1–NE) |

median (95% CI), months. Median and its 95% CI were calculated using the Kaplan-Meier method.

### Figure 2. rwPFS and OS Kaplan–Meier curves from the time of the 1st post–T-DXd treatment




(95% CI). Medians and their 95% CIs were calculated using the Kaplan–Meier method. HRs and their 95% CIs were calculated using the Cox proportional hazards model.

### Table 3. Outcomes by subgroup based on reason for T-DXd discontinuation

| Reason for discontinuation of T-DXd | N | rwPFS: Median, months | rwPFS: Crude HR | rwTTNT: Median, months | rwTTNT: Crude HR | OS: Median, months | OS: Crude HR |
|---|---|---|---|---|---|---|---|
| **PD** | 448 | **3.5** (3.0–3.8) | **0.42** (0.34–0.51) | **4.2** (3.8–4.6) | **0.46** (0.37–0.56) | **12.0** (10.9–13.6) | **0.35** (0.27–0.45) |
| **AEs** (ILD/other than ILD) | 180 | **7.3** (5.7–10.3) | | **8.3** (6.2–11.3) | | **32.4** (22.3–NE) | |
| **ILD** | 146 | **7.2** (5.4–10.2) | **0.87** (0.54–1.39) | **7.8** (5.9–10.8) | **0.75** (0.48–1.19) | **32.4** (21.3–NE) | **0.79** (0.42–1.51) |
| **AEs other than ILD** | 34 | **10.2** (5.1–14.0) | | **11.3** (5.1–27.4) | | **NR** (19.8–NE) | |

(95% CI). Medians and their 95% CIs were calculated using the Kaplan–Meier method. HRs and their 95% CIs were calculated using the Cox proportional hazards model.

### Table 4. ILD in the 1st post–T-DXd treatment

| | N | ILD events: n (%) | ILD events: (95% CI) |
|---|---|---|---|
| **All patients** | 664 | 10 (1.5) | (0.7–2.8) |
| **History of ILD in T-DXd treatment** | | | |
| **Yes** | 155 | 5 (3.2) | (1.1–7.4) |
| **No** | 508 | 4 (0.8) | (0.2–2.0) |
| **Unknown** | 1 | 1 (100) | (2.5–100) |

Incidence of ILD, with the 95%CIs calculated using the Clopper–Pearson method.

### Table 5. Backgrounds for the patients with ILD in the 1st post–T-DXd treatment

| No. | History of ILD in T-DXd treatment: Yes/No | Worst grade[a] | Outcome[b] | 1st post–T-DXd treatment: Regimen | Time to onset of ILD (days) |
|---|---|---|---|---|---|
| 1 | Yes | Grade 2 | Non-recovery | Tmab + eribulin | 22 |
| 2 | Yes | Grade 1 | Non-recovery | Tmab | 255 |
| 3 | Yes | Grade 3 | Recovery | Tmab + PER + eribulin | 23 |
| 4 | Yes | Grade 3 | Recovery | Tmab + PER + eribulin | 39 |
| 5 | Yes | Grade 1 | Recovery | Eribulin | 161 |
| 6 | No | - | - | Tmab + PER + eribulin | 38 |
| 7 | No | - | - | Tmab + paclitaxel | 108 |
| 8 | No | - | - | Tmab + PER + docetaxel | 117 |
| 9 | No | - | - | Abemaciclib + fulvestrant | 134 |
| 10 | Unknown | - | - | Lapatinib + capecitabine | 100 |

[a]CTCAE grade decided by attending physician. [b]ILD status on the first day of the 1st post–T-DXd treatment.

## Summary of results

### Patient characteristics

- The median treatment line for the 1st post–T-DXd was the 5th regimen in the metastatic setting. (see Table 1).

### Distribution of post–T-DXd Treatment

- 73% of patients received any anti-HER2 therapy as the 1st post–T-DXd treatment (see Figure 1).

### Effectiveness

- Overall, the median rwPFS from the first post-T-DXd treatment was 4.1 months, and the median OS was 16.2 months. The rwPFS and OS results were numerically similar in anti-HER2 antibody and HER2-TKI-based therapies (see Table 2, Figure 2).
- Patients who discontinued T-DXd due to AEs had numerically better outcomes than those who discontinued due to PD (rwPFS: 7.3 months vs. 3.5 months; OS: 32.4 months vs. 12.0 months) (see Table 3).

### Incidence of ILD

- Out of 155 patients with a history of ILD in T-DXd treatment, recurrence of ILD was observed in 5 patients (3.2%) (see Table 4, 5).

### Abbreviations

ADC, antibody–drug conjugate; AEs, adverse events; BC, breast cancer; BEV, bevacizumab; CDK cyclin-dependent kinase; Chemo, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IC, informed consent; ILD, interstitial lung disease; jRCT, Japan Registry of Clinical Trials; LAP, lapatinib; LPI, last patient in; LPO, last patient out; mBC, metastatic breast cancer; NE, not estimable; NR, not reached; OS, overall survival; PD, progressive disease; PER, pertuzumab; PFS, progression-free survival; PMS, post-marketing surveillance; rw, real-world; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Tmab, trastuzumab; TTF, time to treatment failure; TTNT, time to next treatment.

### Acknowledgments

Under the guidance of the authors and in accordance with Good Publication Practice, medical writing and editorial support was provided by Elize Wolmarans, PhD, and Laura Halvorson, PhD, of ApotheCom, and was funded by Daiichi Sankyo.

### Declaration of interest

Kazuki Nozawa received lecturer fees from Daiichi Sankyo Co., Ltd. and Chugai Pharmaceutical Co., Ltd.
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# Supplementary Material

- List of Study Participating Sites
- rwPFS by Subgroups: Tmab + PER vs Tmab
- OS by Subgroups: Tmab + PER vs Tmab
- rwTTNT in the Overall Population
- rwTTNT by Subgroups: HER2-TKI vs Anti-HER2 antibody
- rwTTNT by Subgroups: Tmab + PER vs Tmab

HER2, human epidermal growth factor receptor 2; PER, pertuzumab; rw, real-word; TKI, tyrosine kinase inhibitor; Tmab, trastuzumab; TTNT, time to next treatment.

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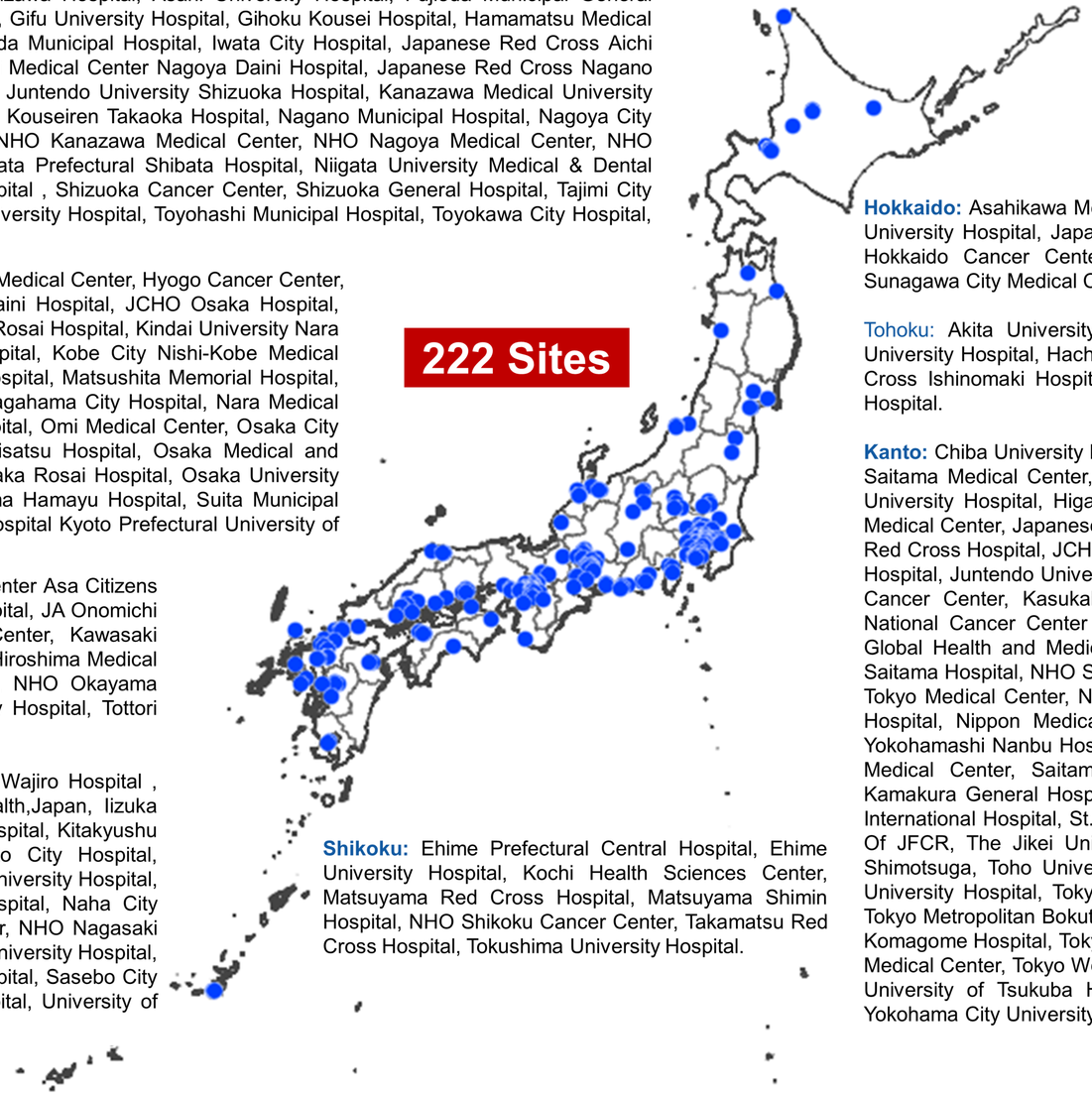
# Participating Study Sites

**Chubu:** Aichi Cancer Center, Aichi Medical University Hospital, Aizawa Hospital, Asahi University Hospital, Fujieda Municipal General Hospital, Fujita Health University Hospital, Fukui Red Cross Hospital, Gifu University Hospital, Gihoku Kousei Hospital, Hamamatsu Medical Center, Hamamatsu University Hospital, Ichinomiyanishi Hospital, Iida Municipal Hospital, Iwata City Hospital, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Japanese Red Cross Nagano Hospital, JCHO Chukyo Hospital, JCHO Mishima General Hospital, Juntendo University Shizuoka Hospital, Kanazawa Medical University Hospital, Kanazawa University Hospital, Kasugai Municipal Hospital, Kouseiren Takaoka Hospital, Nagano Municipal Hospital, Nagoya City University East Medical Center, Nagoya City University Hospital, NHO Kanazawa Medical Center, NHO Nagoya Medical Center, NHO Shinshu Ueda Medical Center, Niigata City General Hospital, Niigata Prefectural Shibata Hospital, Niigata University Medical & Dental Hospital, Ogaki Municipal Hospital, Seirei Hamamatsu General Hospital , Shizuoka Cancer Center, Shizuoka General Hospital, Tajimi City Hospital, Tokoname City Hospital, Toyama City Hospital, Toyama University Hospital, Toyohashi Municipal Hospital, Toyokawa City Hospital, Yaizu City Hospital.

**Kinki:** Aihara Hospital, Bellland General Hospital, Higashiosaka City Medical Center, Hyogo Cancer Center, Hyogo Medical University Hospital, Japanese Red Cross Kyoto Daini Hospital, JCHO Osaka Hospital, Kakogawa City Hospital, Kansai Medical University Hospital, Kansai Rosai Hospital, Kindai University Nara Hospital, Kitano Hospital, Kobe City Medical Center General Hospital, Kobe City Nishi-Kobe Medical Center, Kobe Minimally invasive Cancer Center, Kyoto University Hospital, Matsushita Memorial Hospital, Mie Prefectural General Medical Center, Mie University Hospital, Nagahama City Hospital, Nara Medical University Hospital, NHO Osaka National Hospital, Nippon Life Hospital, Omi Medical Center, Osaka City General Hospital, Osaka International Cancer Institute, Osaka Keisatsu Hospital, Osaka Medical and Pharmaceutical University Hospital, Osaka Red Cross Hospital, Osaka Rosai Hospital, Osaka University Hospital, Rinku General Medical Center, Shinko Hospital, Shirahama Hamayu Hospital, Suita Municipal Hospital, Sumitomo Hospital, Takarazuka City Hospital, University Hospital Kyoto Prefectural University of Medicine, Yao Municipal Hospital, Yokkaichi Municipal Hospital.

**Chugoku:** Fukuyama City Hospital, Hiroshima City North Medical Center Asa Citizens Hospital, Hiroshima Prefectural Hospital, JA Hiroshima General Hospital, JA Onomichi General Hospital, Kawasaki Medical School General Medical Center, Kawasaki Medical School Hospital, Matsue Red Cross Hospital, NHO Higashi-Hiroshima Medical Center, NHO Iwakuni Clinical Center, NHO Kure Medical Center, NHO Okayama Medical Center, NHO Yonago Medical Center, Okayama University Hospital, Tottori University Hospital, Yamaguchi University Hospital.

**Kyusyu/Okinawa:** Fukuoka University Chikushi Hospital, Fukuoka Wajiro Hospital , Hospital of the University of Occupational and Environmental Health,Japan, Iizuka Hospital, JCHO Kurume General Hospital, Kagoshima University Hospital, Kitakyushu Municipal Medical Center, Kokura Memorial Hospital, Kumamoto City Hospital, Kumamoto Rosai Hospital, Kumamoto University Hospital, Kurume University Hospital, Nagasaki Prefecture Shimabara Hospital, Nagasaki University Hospital, Naha City Hospital, NHO Kyushu Cancer Center, NHO Kyushu Medical Center, NHO Nagasaki Medical Center, NHO Saga Hospital, Oita Prefectural Hospital, Oita University Hospital, Saga University Hospital, Sagara Hospital, Saiseikai Kumamoto Hospital, Sasebo City General Hospital, St. Mary's Hospital, Steel Memorial Yawata Hospital, University of the Ryukyus Hospital, Urasoe General Hospital.




**Shikoku:** Ehime Prefectural Central Hospital, Ehime University Hospital, Kochi Health Sciences Center, Matsuyama Red Cross Hospital, Matsuyama Shimin Hospital, NHO Shikoku Cancer Center, Takamatsu Red Cross Hospital, Tokushima University Hospital.

**Hokkaido:** Asahikawa Medical University Hospital, Asahikawa-Kosei General Hospital, Hokkaido University Hospital, Japanese Red Cross Kitami Hospital, KKR Sapporo Medical Center, NHO Hokkaido Cancer Center, NTT Medical Center Sapporo, Sapporo City General Hospital, Sunagawa City Medical Center, Teine Keijinkai Hospital, Tonan Hospital, Wakkanai City Hospital.

Tohoku: Akita University Hospital, Aomori Prefectural Central Hospital, Fukushima Medical University Hospital, Hachinohe City Hospital, Hoshi General Hospital Foundation, Japanese Red Cross Ishinomaki Hospital, Osaki Citizen Hospital, Tohoku Rosai Hospital, Tohoku University Hospital.

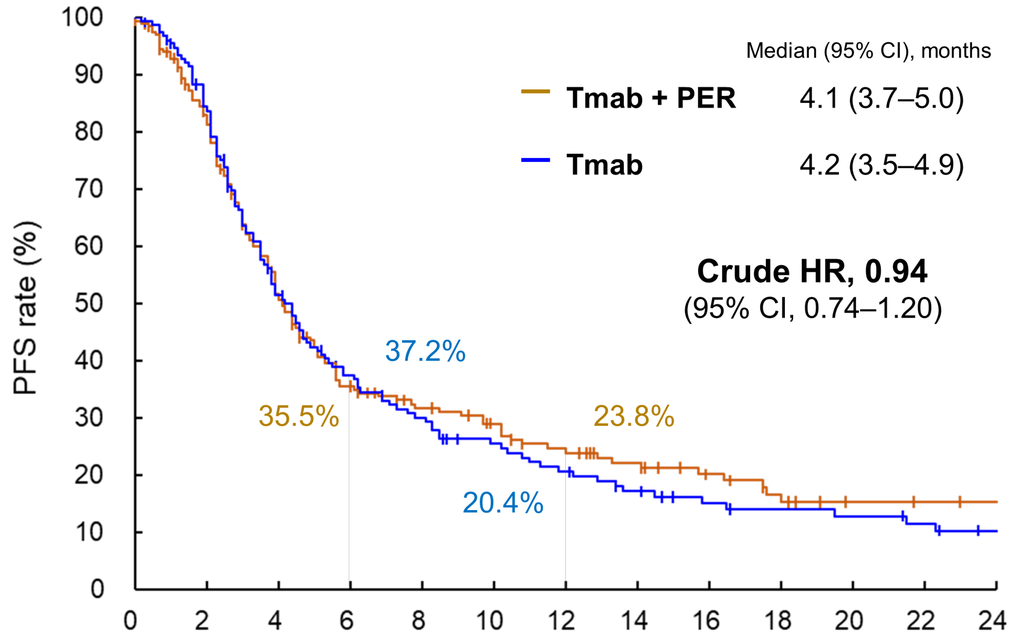
**Kanto:** Chiba University Hospital, Dokkyo Medical University Hospital, Dokkyo Medical University Saitama Medical Center, Fujisawa City Hospital, Funabashi Municipal Medical Center, Gunma University Hospital, Higashiyamato Hospital, Isesaki Municipal Hospital, Japanese Red Cross Medical Center, Japanese Red Cross Musashino Hospital, Japanese Red Cross Society Saitama Red Cross Hospital, JCHO Saitama Medical Center, Jichi Medical University, Juntendo University Hospital, Juntendo University Nerima Hospital, Juntendo University Urayasu Hospital, Kanagawa Cancer Center, Kasukabe Medical Center, Kitasato University Hospital, Kyoundo Hospital, National Cancer Center Hospital, National Cancer Center Hospital East, National Center for Global Health and Medicine, Nerima Hikarigaoka Hospital, NHO Chiba Medical Center, NHO Saitama Hospital, NHO Shibukawa Medical Center, NHO Takasaki General Medical Center, NHO Tokyo Medical Center, Nippon Medical School Hospital, Nippon Medical School Musashikosugi Hospital, Nippon Medical School Tamanagayama Hospital, Ofuna Chuo Hospital, Saiseikai Yokohamashi Nanbu Hospital, Saitama Medical Center, Saitama Medical University International Medical Center, Saitama Prefectural Cancer Center, Seirei Yokohama Hospital, Shonan Kamakura General Hospital, Shonan Memorial Hospital, Showa University Hospital, St. Luke's International Hospital, St. Marianna University School of Medicine, The Cancer Institute Hospital Of JFCR, The Jikei University School of Medicine Daisan Hospital, Tochigi Medical Center Shimotsuga, Toho University Omori Medical Center, Tokai University Hachioji Hospital, Tokai University Hospital, Tokyo Kyosai Hospital, Tokyo Medical University Hachioji Medical Center, Tokyo Metropolitan Bokutoh Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo Saiseikai Central Hospital, Tokyo Women's Medical University Adachi Medical Center, Tokyo Women's Medical University Yachiyo Medical Center, Toranomon Hospital, University of Tsukuba Hospital, Yatsu Hoken Hospital, Yokohama City University Hospital, Yokohama City University Medical Center, Yokohama Rosai Hospital.

JCHO, Japan Community Healthcare Organization; NHO, National Hospital Organization.

# rwPFS by Subgroups

## Kaplan-Meier curves from the time of the 1st post–T-DXd treatment

### Tmab + PER vs Tmab




No. at risk

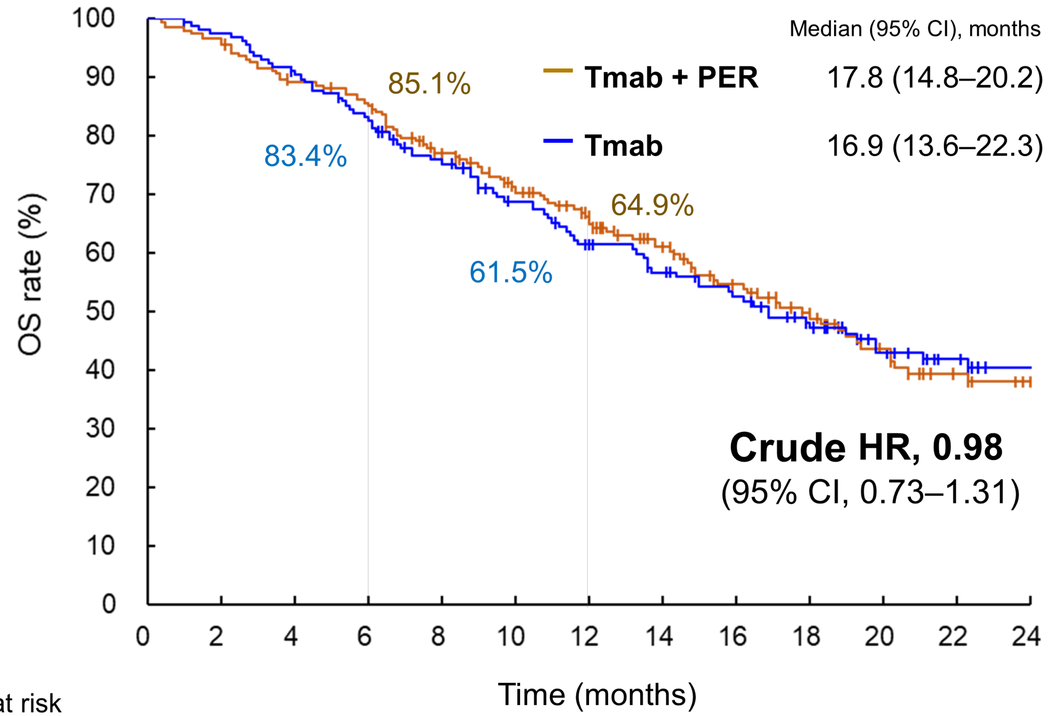
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tmab + PER | 203 | 157 | 93 | 62 | 48 | 40 | 31 | 25 | 18 | 13 | 8 | 7 | 6 |
| Tmab | 158 | 129 | 75 | 52 | 40 | 31 | 25 | 19 | 14 | 12 | 11 | 9 | 6 |

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PFS, progression-free survival;. PER, pertuzumab; rw, real-word; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Tmab, trastuzumab.

# OS by Subgroups

## Kaplan-Meier curves from the time of the 1st post–T-DXd treatment

### Tmab + PER vs Tmab




No. at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tmab + PER | 203 | 196 | 179 | 170 | 144 | 124 | 106 | 90 | 72 | 53 | 41 | 30 | 25 |
| Tmab | 158 | 153 | 141 | 129 | 110 | 93 | 80 | 72 | 62 | 52 | 39 | 31 | 25 |

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PER, pertuzumab; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Tmab, trastuzumab.

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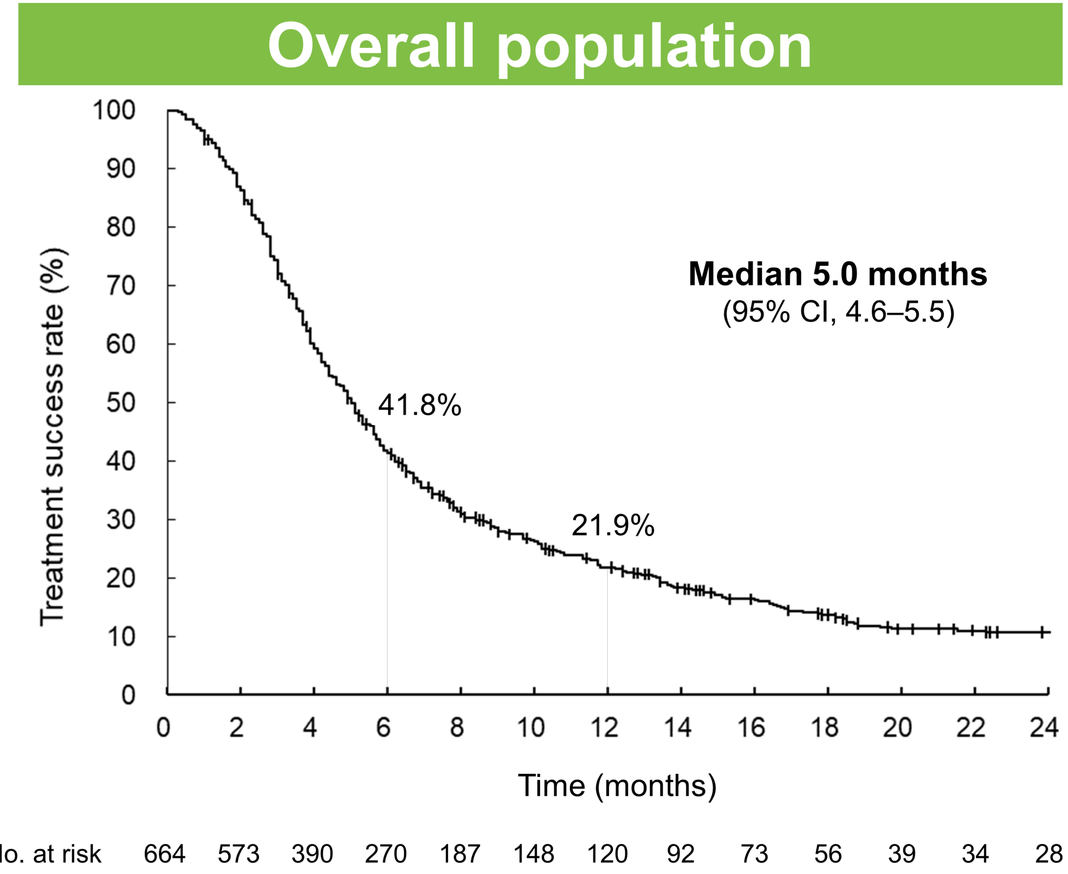
# rwTTNT in the Overall Population

## Kaplan-Meier curves from the time of the 1st post–T-DXd treatment

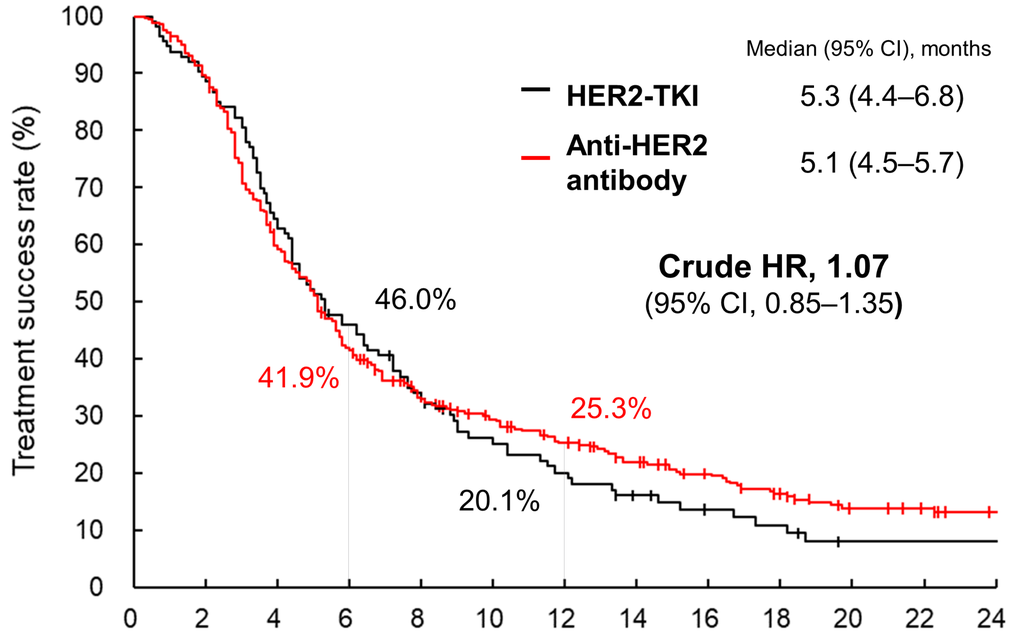



pts, patients; rw, real-world; T-DXd, trastuzumab deruxtecan; TTNT, Time to next treatment.

# rwTTNT by Subgroups

## Kaplan-Meier curves from the time of the 1st post–T-DXd treatment

### HER2-TKI vs Anti-HER2 antibody




No. at risk

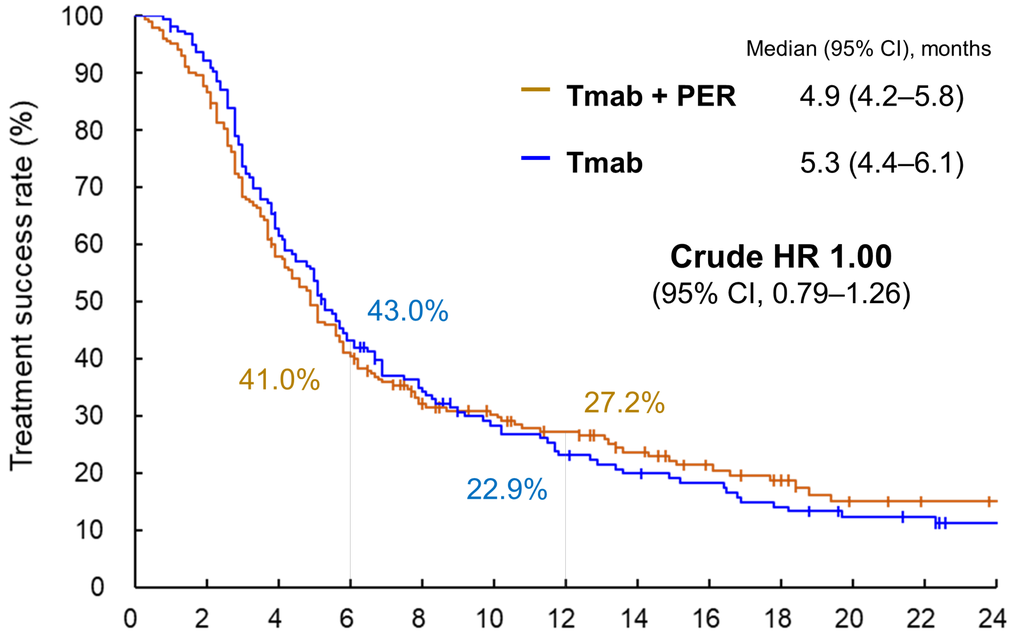
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HER2-TKI | 113 | 100 | 72 | 51 | 36 | 25 | 20 | 14 | 10 | 8 | 4 | 4 | 4 |
| Anti-HER2 antibody | 361 | 323 | 212 | 148 | 106 | 87 | 72 | 58 | 46 | 34 | 24 | 21 | 16 |

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PER, pertuzumab; rw, real-world; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Tmab, trastuzumab; TTNT, time to next treatment.

# rwTTNT by Subgroups

## Kaplan-Meier curves from the time of the 1st post–T-DXd treatment

### Tmab + PER vs Tmab




No. at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tmab + PER | 203 | 178 | 116 | 82 | 57 | 50 | 42 | 33 | 24 | 17 | 11 | 9 | 8 |
| Tmab | 158 | 145 | 96 | 66 | 49 | 37 | 30 | 25 | 22 | 17 | 13 | 12 | 8 |

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PER, pertuzumab; rw, real-world; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Tmab, trastuzumab; TTNT, time to next treatment.