



# Effectiveness of T-DXd Rechallenge for HER2+ Metastatic Breast Cancer: The EN-SEMBLE Nationwide Cohort Study

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- In the DESTINY-Breast09 trial, T-DXd plus pertuzumab as first-line treatment for HER2+ metastatic breast cancer (mBC) demonstrated a significant improvement in PFS with safety consistent with previous observations, although the incidence of nausea and interstitial lung disease (ILD)/pneumonitis was higher compared with trastuzumab, pertuzumab, and taxane.<sup>1</sup>
- T-DXd is expected to become the new first-line standard of care for HER2+ mBC, highlighting the increasing importance of discussions on subsequent therapies and T-DXd re-administration (rechallenge).

1. Tolaney SM, et al. *N Engl J Med*. 2025;394(6):551-562. doi: 10.1056/NEJMoa2508668.

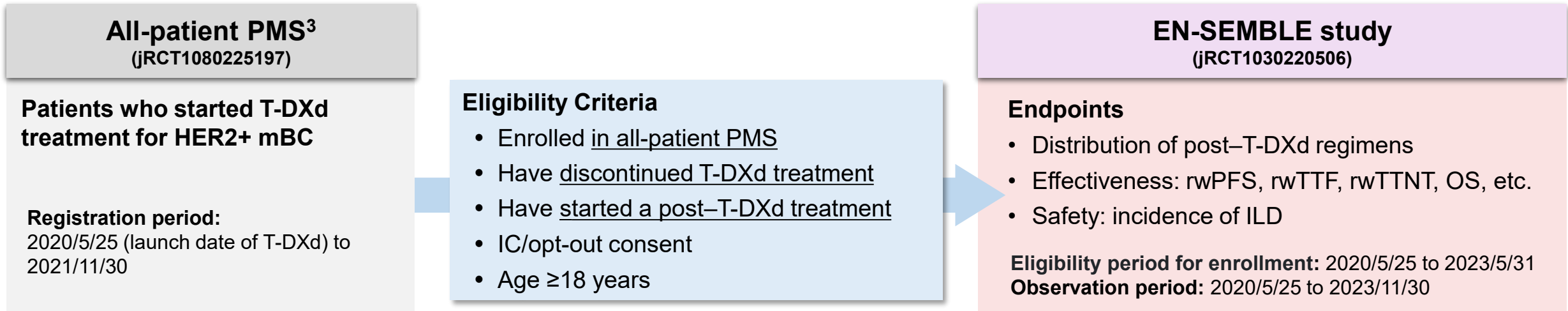
- EN-SEMBLE (jRCT1030220506) was a real-world, nationwide cohort study conducted in Japan to investigate the distribution and treatment outcomes of subsequent treatments after T-DXd discontinuation in patients with HER2+ mBC.<sup>2</sup>
- This analysis assessed the effectiveness and safety of T-DXd rechallenge in patients who received one intervening line of treatment following the T-DXd in the EN-SEMBLE study.

2. Nozawa K, et al. *ESMO Open*. 2025;10(8):105511. doi: 10.1016/j.esmooop.2025.105511.

# Study Design



**EN-SEMBLE Study: A nationwide cohort study using data from real-world settings in Japan (222 sites)**



3. Tsurutani J, et al. *Breast Cancer*. 2026;33(2):346-358. doi: 10.1007/s12282-025-01814-3

## T-DXd Rechallenge Subgroup Analysis

- Ad-hoc analysis of EN-SEMBLE study (data cutoff date: 2023/11/30).
- Patients who received T-DXd rechallenge as their second treatment following initial T-DXd were included in this analysis.
- For context, effectiveness outcomes were also determined in patients who did not receive T-DXd.

Abbreviations: IC, informed consent; ILD, interstitial lung disease; jRCT, Japan Registry of Clinical Trials; mBC, metastatic breast cancer; OS, overall survival; PMS, post-marketing surveillance; rwPFS, real-world progression-free survival; rwTTF; real-world time to treatment failure; rwTTNT, real-world time to next treatment.

## Outcomes of the post–T-DXd treatment, determined by T-DXd rechallenge subgroup analysis

### ● Effectiveness

- rwPFS, rwTTF, and OS
- ORR and BOR (assessed by the attending physician)

All assessed from the start of the T-DXd rechallenge or another second post–T-DXd treatment

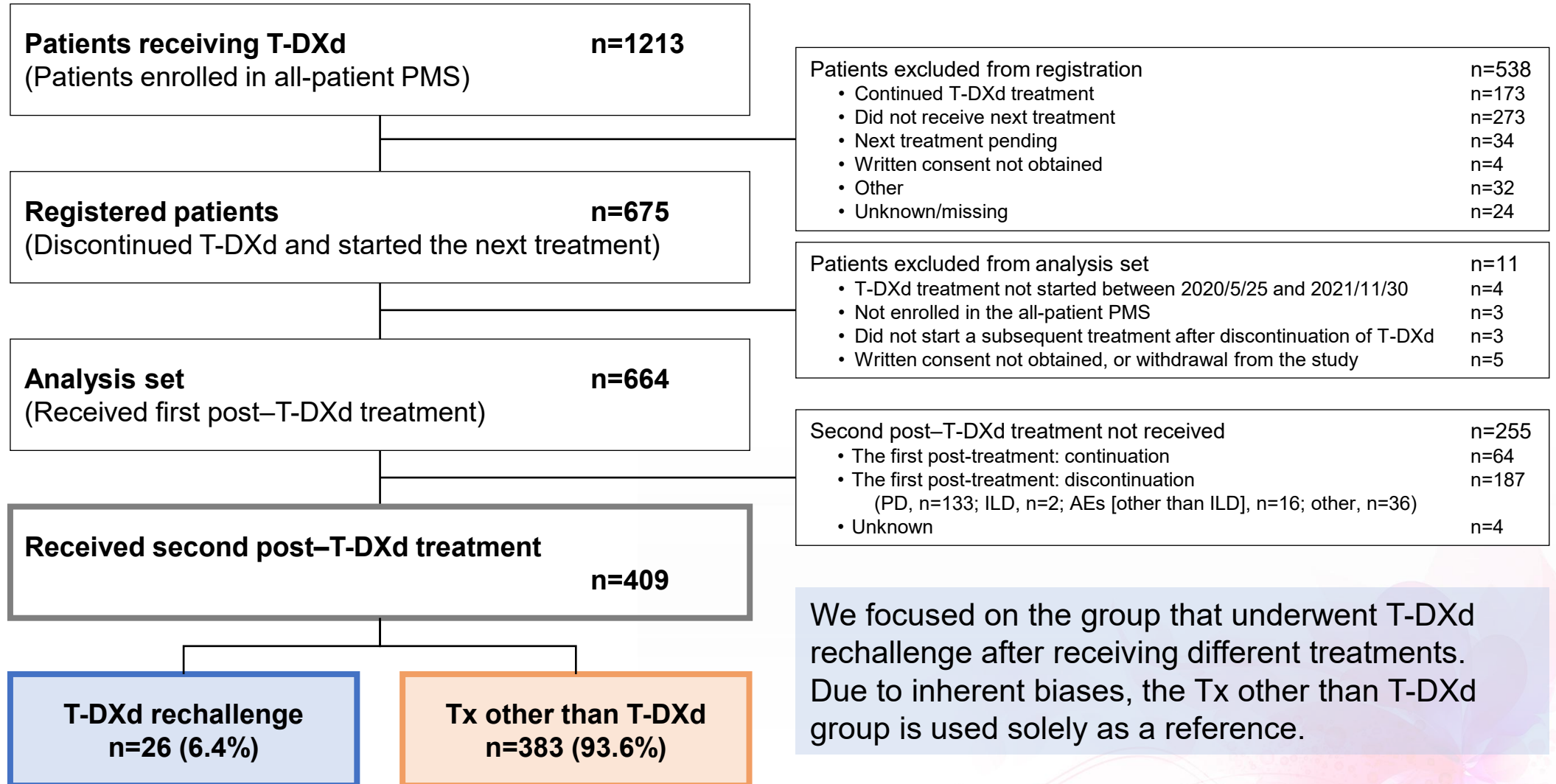
### ● Safety

- Incidence of ILD

- The timeline from the initial T-DXd treatments to the next treatment lines and T-DXd rechallenge were visualized using swimmer plots.

Abbreviations: BOR, best overall response; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; rwPFS, real-world progression-free survival; rwTTF, real-world time to treatment failure.

# Patient Disposition



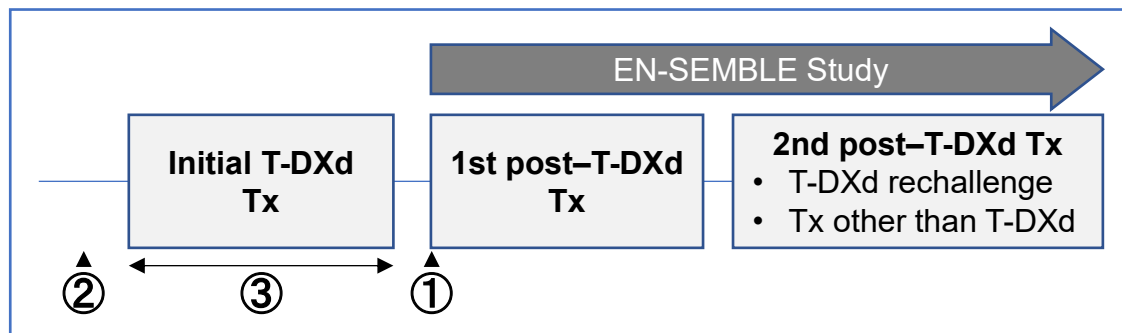
We focused on the group that underwent T-DXd rechallenge after receiving different treatments. Due to inherent biases, the Tx other than T-DXd group is used solely as a reference.

Abbreviations: AE, adverse event; ILD, interstitial lung disease; PD, progressive disease; PMS, post-marketing surveillance; Tx, treatment.

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# Patient Background 1

## Timing of the patient's background



### ① At the start of the first post-T-DXd treatment

	T-DXd rechallenge (n=26)	Tx other than T-DXd (n=383)
Age, years*	56.5 (50–67)	59.1 (51–68)
Hormone receptor positive	18 (69.2)	238 (62.1)
ECOG PS ≥2	3 (11.5)	22 (5.7)
Visceral metastasis	22 (84.6)	302 (78.9)
Brain metastasis	9 (34.6)	75 (19.6)

### ② Prior cancer therapy for mBC before initial T-DXd

	T-DXd rechallenge (n=26)	Tx other than T-DXd (n=383)
No. of prior regimens		
No. of lines*	4 (3–5)	3 (2–5)
≥3 lines	22 (84.6)	261 (68.1)
Prior regimens		
Anti-HER2 therapy	25 (96.2)	377 (98.4)
Trastuzumab	23 (88.5)	361 (94.3)
Pertuzumab	21 (80.8)	350 (91.4)
T-DM1	25 (96.2)	348 (90.9)
HER2-TKI	11 (42.3)	108 (28.2)
Chemotherapy	24 (92.3)	343 (89.6)
Endocrine therapy	13 (50.0)	153 (39.9)

Data are n (%) unless otherwise indicated. \*Median (Q1–Q3).

# Patient Background 2



## ③ Initial T-DXd treatment

	T-DXd rechallenge (n=26)	Tx other than T-DXd (n=383)
<b>mBC status</b>		
<i>De novo</i> stage IV	3 (11.5)	165 (43.1)
Recurrent breast cancer	21 (80.8)	209 (54.6)
DOT for initial T-DXd, months*	10.6 (8.5–14.6)	7.9 (5.5–12.8)
<b>BOR for initial T-DXd treatment</b>		
CR	4 (15.4)	10 (2.6)
PR	14 (53.8)	208 (54.3)
SD	5 (19.2)	122 (31.9)
PD	1 (3.8)	37 (9.7)
NE	2 (7.7)	6 (1.6)
ILD incidence related to initial T-DXd	4 (15.4)	95 (24.8)

	T-DXd rechallenge (n=26)	Tx other than T-DXd (n=383)
<b>Reason for discontinuation of initial T-DXd</b>		
PD	11 (42.3)	274 (71.5)
ILD	4 (15.4)	89 (23.2)
AEs other than ILD	6 (23.1)	9 (2.3)
Others	5 (19.2)	11 (2.9)
Interval between initial T-DXd discontinuation and 2nd post-treatment (T-DXd rechallenge or Tx other than T-DXd), months*	5.7 (3.7–11.4)	5.2 (3.5–8.4)

Data are n (%) unless otherwise indicated. \*Median (Q1–Q3).

Abbreviations: AE, adverse event; BOR, best overall response; CR, complete response; DOT, duration of treatment; ILD, interstitial lung disease; mBC, metastatic breast cancer; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; Tx, treatment.

# Survival Outcomes

## T-DXd rechallenge and Tx other than T-DXd



### Median follow-up

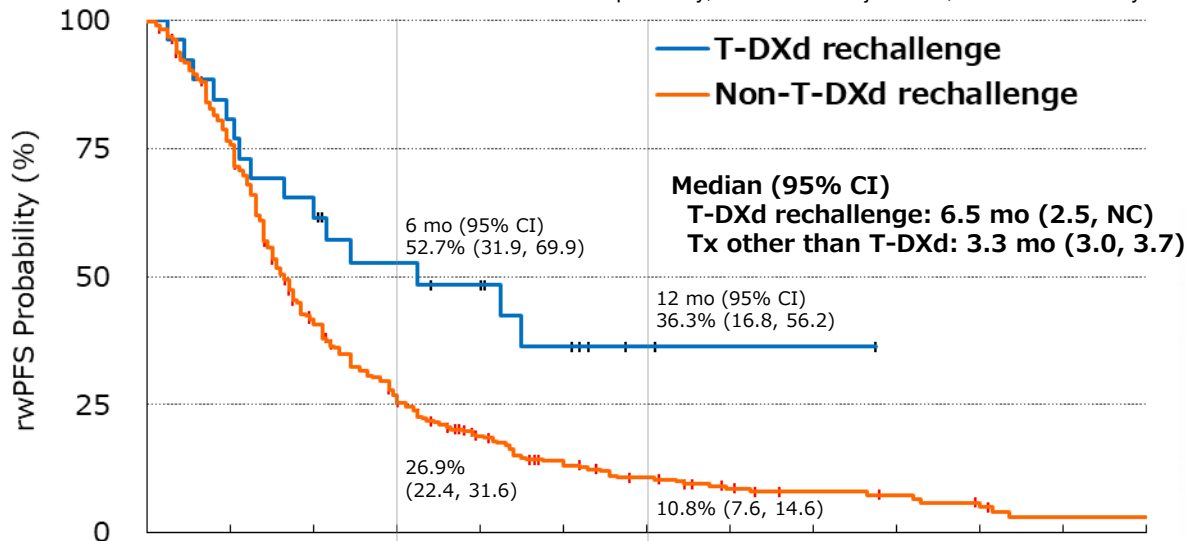
- **T-DXd rechallenge: 10.3 mo** (Q1-Q3, 4.6–12.9)  
(Status at DCO: 38.5% continuing, 61.5% discontinued, 0% unknown)
- **Tx other than T-DXd : 8.4 mo** (Q1-Q3, 4.6–13.7)  
(Status at DCO: 12.3% continuing, 87.5% discontinued, 0.3% unknown)

### rwTTF

	(95% CI)		
	6 mo	12 mo	Median
<b>T-DXd rechallenge</b> (n=26)	49.1% (28.8, 66.6)	32.6% (14.1, 52.6)	4.9 mo (3.0, NC)
<b>Tx other than T-DXd</b> (n=383)	25.0% (20.7, 29.6)	9.1% (6.2, 12.7)	3.2 mo (2.9, 3.5)

### rwPFS

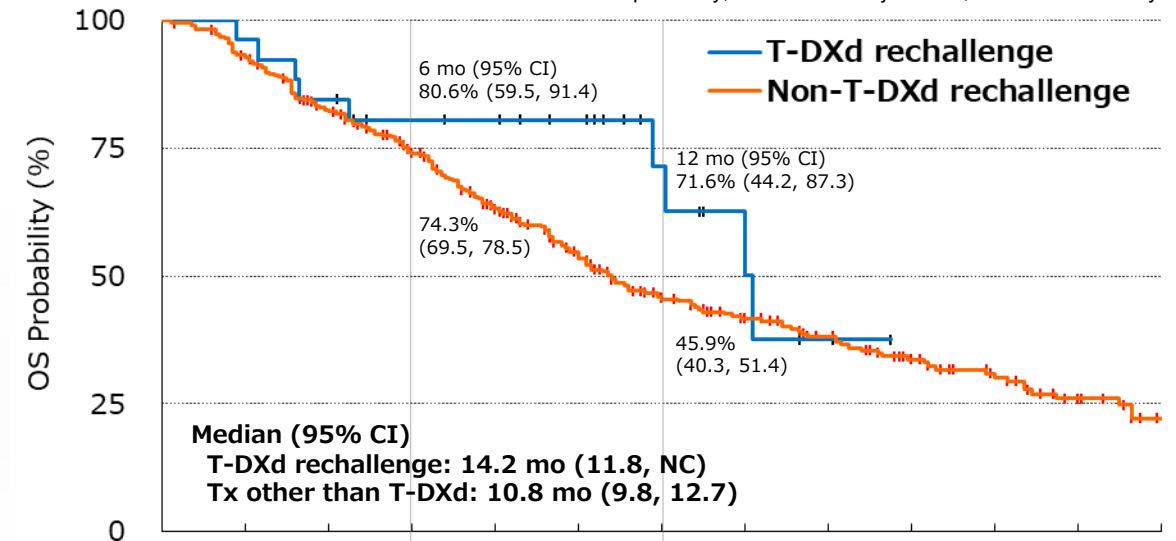
Descriptive only; no covariate adjustment; selection bias likely.



Month	0	2	4	6	8	10	12	14	16	18	20	22	24
No at risk													
T-DXd rechallenge	26	21	17	12	10	6	2	1	1	0	0	0	0
Tx other than T-DXd	383	286	142	91	55	35	26	17	12	10	7	3	3

### OS

Descriptive only; no covariate adjustment; selection bias likely.



Month	0	2	4	6	8	10	12	14	16	18	20	22	24
No at risk													
T-DXd rechallenge	26	25	22	18	17	14	8	4	2	0	0	0	0
Tx other than T-DXd	383	353	300	256	203	150	115	93	71	53	40	25	14

Medians and their 95% CIs were calculated using the Kaplan–Meier method.

Abbreviations: mo, month; NC, not calculated; OS, overall survival; rwPFS, real-world progression-free survival; rwTTF, real-world time to treatment failure; Tx, treatment.

# Tumor Response

(assessment by the attending physician)

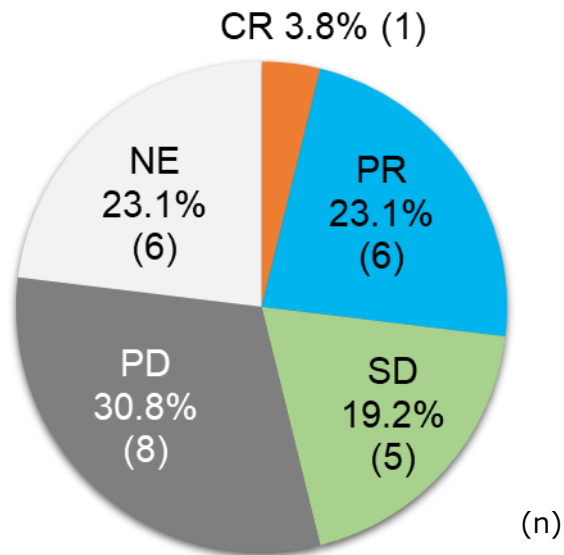


## T-DXd rechallenge (n=26)

**Objective response rate:**

26.9% (95% CI 11.6, 47.8)

**Best overall response:**

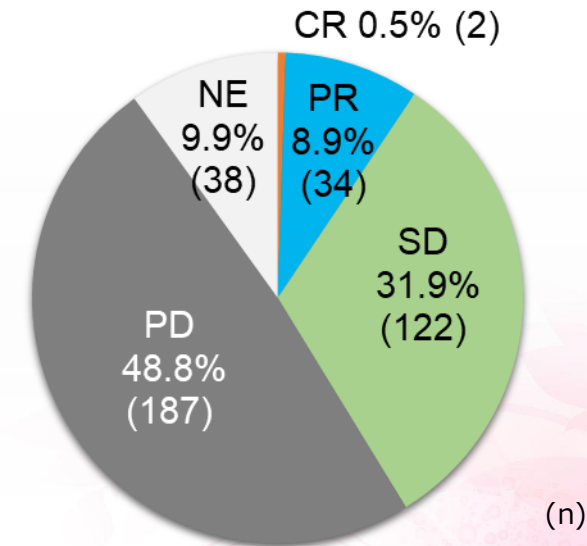


## Tx other than T-DXd (n=383)

**Objective response rate:**

9.4% (95% CI 6.7, 12.8)

**Best overall response:**



Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; Tx, treatment.

# Swimmer Plot for Treatment Duration

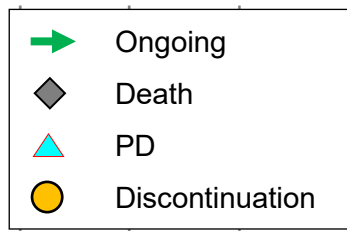
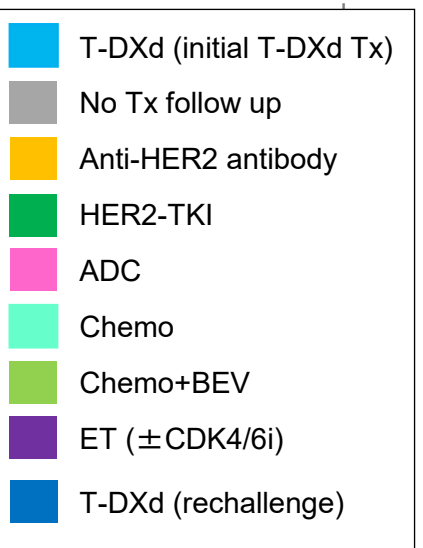
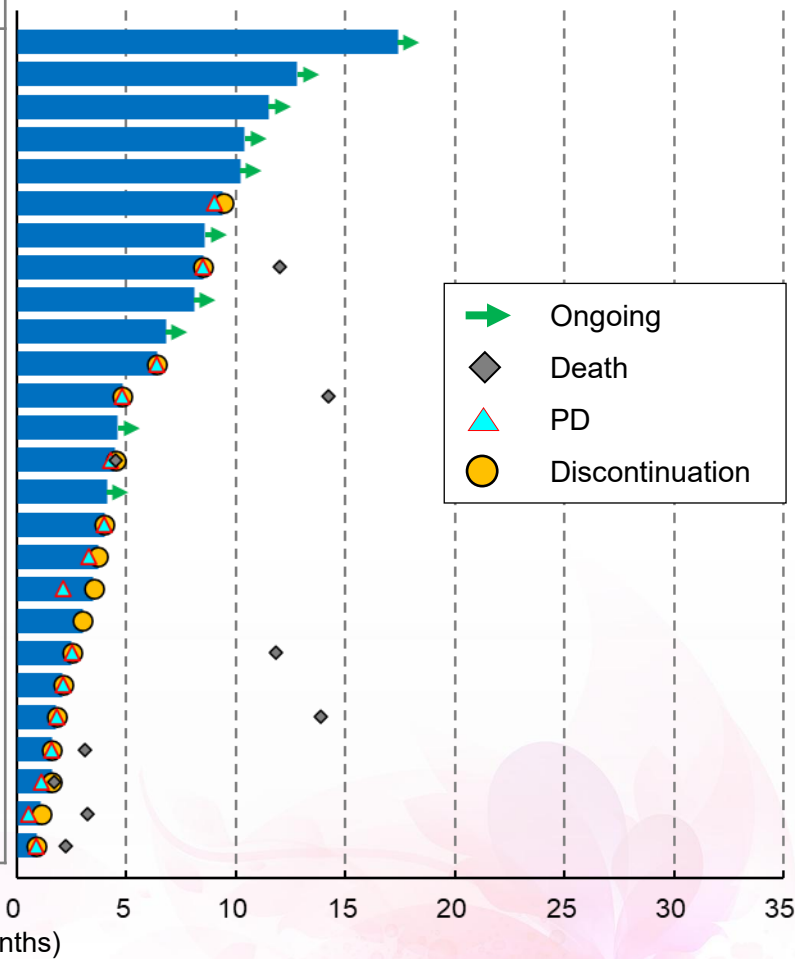
(T-DXd Rechallenge, n=26)



## ● Initial T-DXd Tx + 1st post Tx

Initial T-DXd Tx			T-DXd rechallenge	
DOT (mo)	BOR	Discontinuation reasons	DOT (mo)	BOR
5.5	PR	AE	17.5	NE
7.6	PR	AE	12.9	SD
10.6	NE	ILD	11.5	SD
15.2	PR	Others	10.4	NE
16.4	PR	ILD	10.2	PR
8.3	CR	Others	9.4	PR
1.4	NE	AE	8.6	PR
13.1	PR	AE	8.5**	PR
9.1	PR	AE	8.1	PR
23.8	SD	PD	6.8	NE
9.9	PR	ILD	6.4	PD
9.3	PR	PD	4.8	SD
13.6	PR	ILD	4.6	PR
9.1	SD	Others	4.5	SD
8.5	CR	AE	4.1	NE
5.2	PD	PD	4.0	PD
16.3	CR	Others	3.7	PD
22.8	SD	PD	3.5	PD
11.7	CR	Others	3.0	CR
14.6	PR	PD	2.5	NE
10.1	SD	PD	2.1*	PD
11.0	PR	PD	1.8	SD
13.6	PR	PD	1.6	PD
10.5	SD	PD	1.6	PD
15.0	PR	PD	1.2	PD
8.3	PR	PD	0.9	NE

## ● T-DXd rechallenge



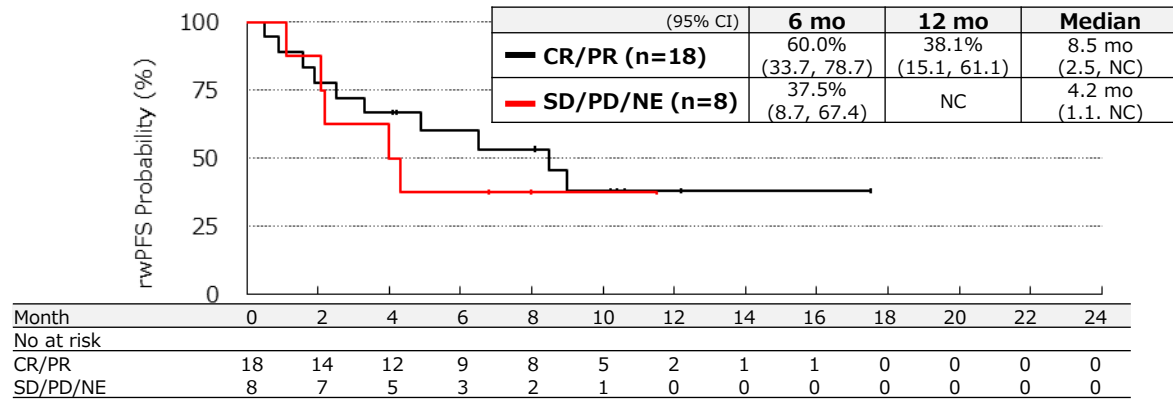
'AE' under Discontinuation reasons refers to AEs other than ILD. Median DOT for patients discontinuing initial T-DXd due to PD (\*) and for those discontinuing for reasons other than PD (\*\*).

# rwPFS Stratified by Key Factors During Initial T-DXd Tx

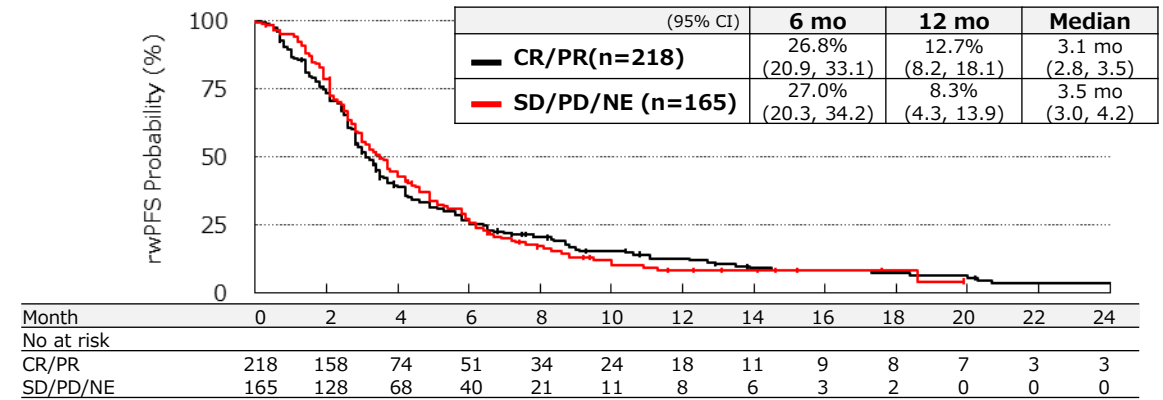


## Stratified by BOR during initial T-DXd treatment (CR/PR vs SD/PD/NE)

T-DXd rechallenge (n=26)

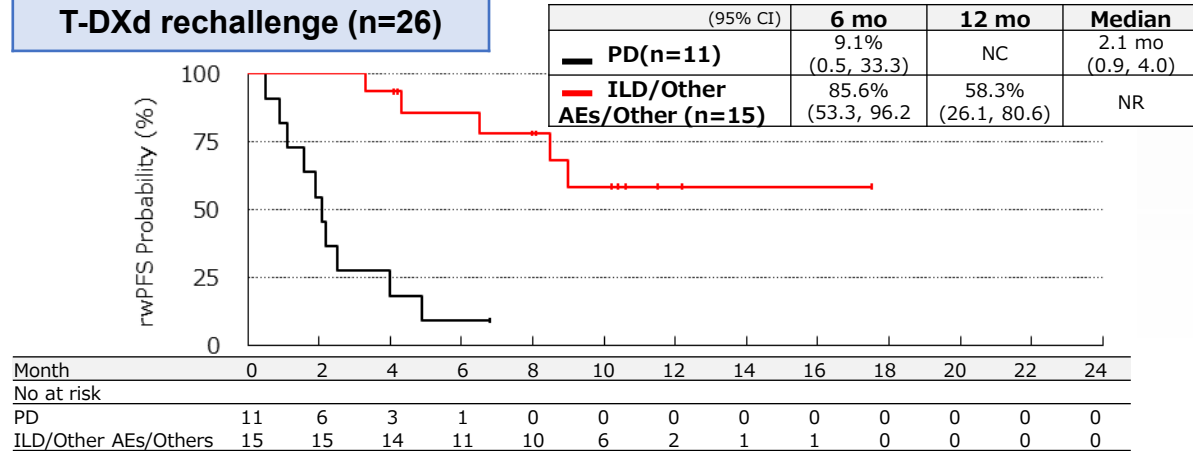


Tx other than T-DXd (n=383)

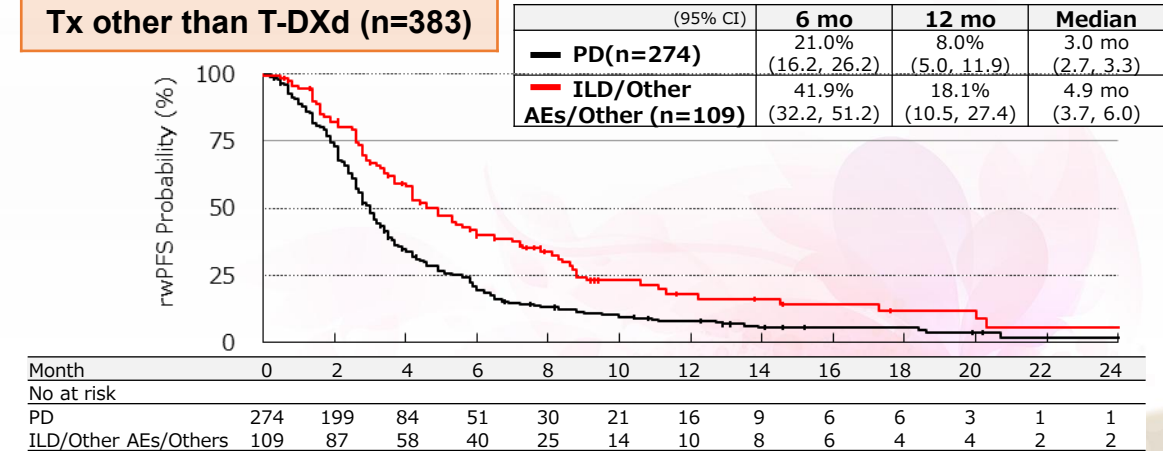


## Stratified by reason for initial T-DXd Tx discontinuation (PD vs ILD/Other AEs/Other)

T-DXd rechallenge (n=26)



Tx other than T-DXd (n=383)



Medians and their 95% CIs were calculated using the Kaplan-Meier method.

Abbreviations: AE, adverse event; BOR, best overall response; CR, complete response; ILD, interstitial lung disease; NC, not calculated; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; Tx, treatment.

# ILD Incidence



Among the 26 patients who underwent T-DXd rechallenge:

- No incidence of ILD was recorded during the T-DXd rechallenge period.
- Four patients had experienced ILD during their initial T-DXd treatment. These four patients did not experience a recurrence of ILD during their subsequent treatment or the T-DXd rechallenge.

Abbreviation: ILD, interstitial lung disease.

# Limitations



- The findings are based on a small sample size.
- This was an observational study conducted in clinical practice, and although subject to many treatment selection biases, statistical adjustment has not been performed.
- Rechallenge with T-DXd in patients who experienced ILD was evaluated in only four patients, and the safety analysis was insufficient.

Abbreviation: ILD, interstitial lung disease.

# Summary of Results



**The real-world outcomes for 26 patients with HER2+ mBC who received T-DXd rechallenge after one intervening treatment following the T-DXd were examined.**

1. The rechallenge group achieved numerically longer rwPFS, rwTTF, and OS, as well as numerically higher ORR. Additionally, despite receiving a later line of treatment, a higher proportion of patients in the rechallenge group were continuing to receive the treatment at the data cutoff.
2. Patients whose reason for discontinuation of initial T-DXd treatment was not due to PD may benefit more in terms of treatment outcomes of T-DXd rechallenge.
3. No ILD events occurred during the rechallenge, including in four patients with a history of ILD related to initial T-DXd.

# Conclusion

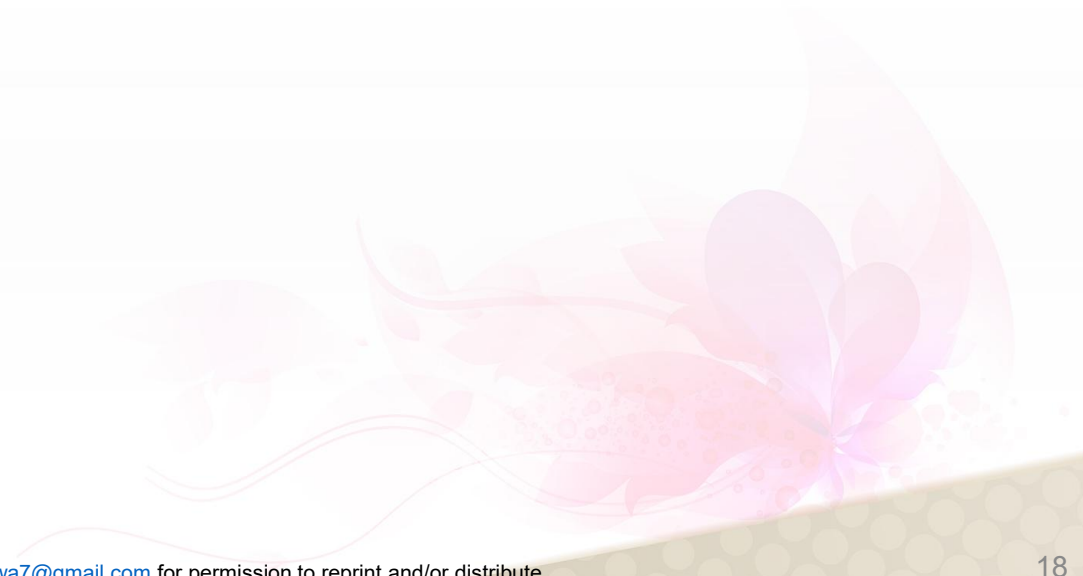


- These results suggest that patients with HER2+ mBC may benefit from T-DXd rechallenge after one intervening therapy, particularly those who discontinued their initial T-DXd treatment without PD due to AEs including, but not limited to ILD.
- No ILD events were observed during the rechallenge, including in four patients who had previously experienced ILD related to the initial T-DXd treatment.



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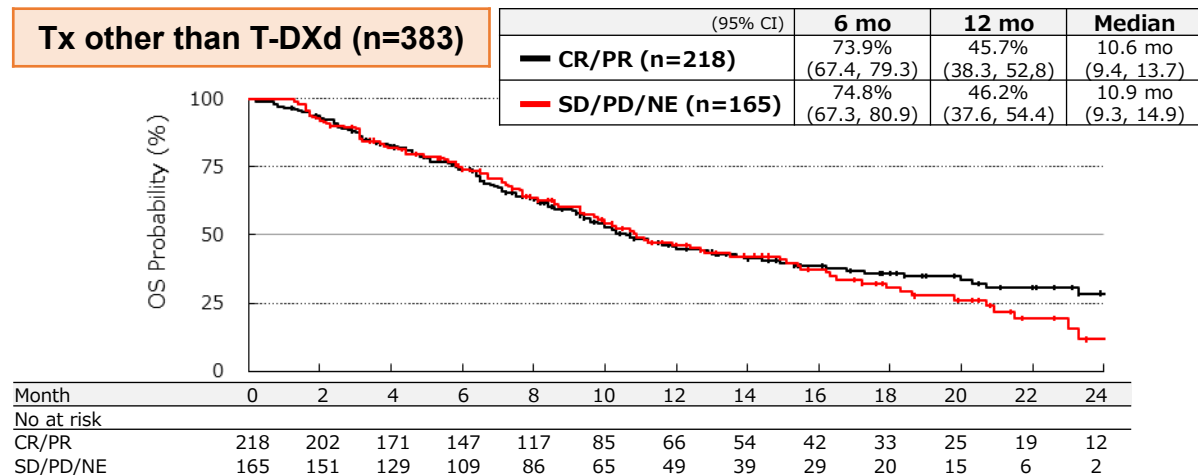
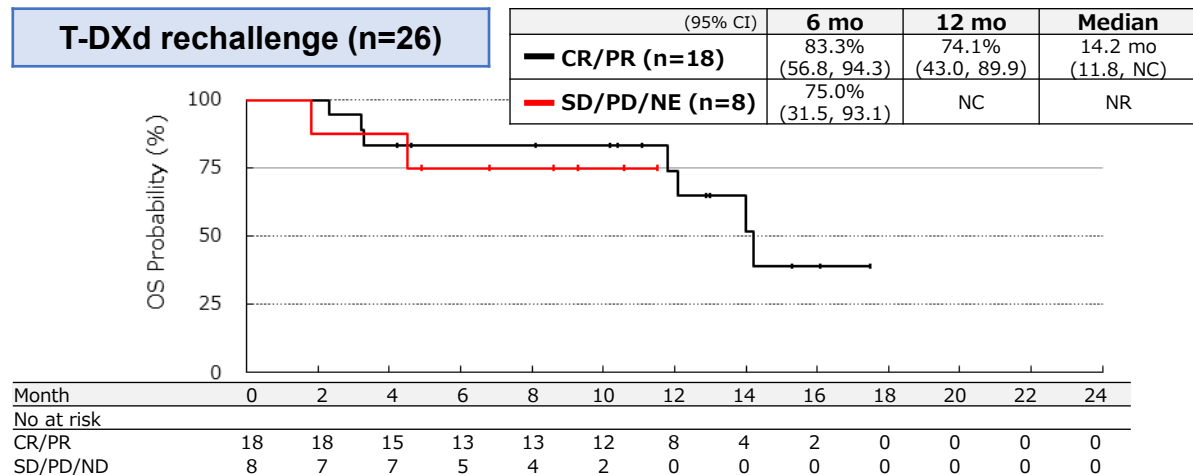
Abbreviations: ILD, interstitial lung disease; mBC, metastatic breast cancer; PD, progressive disease.



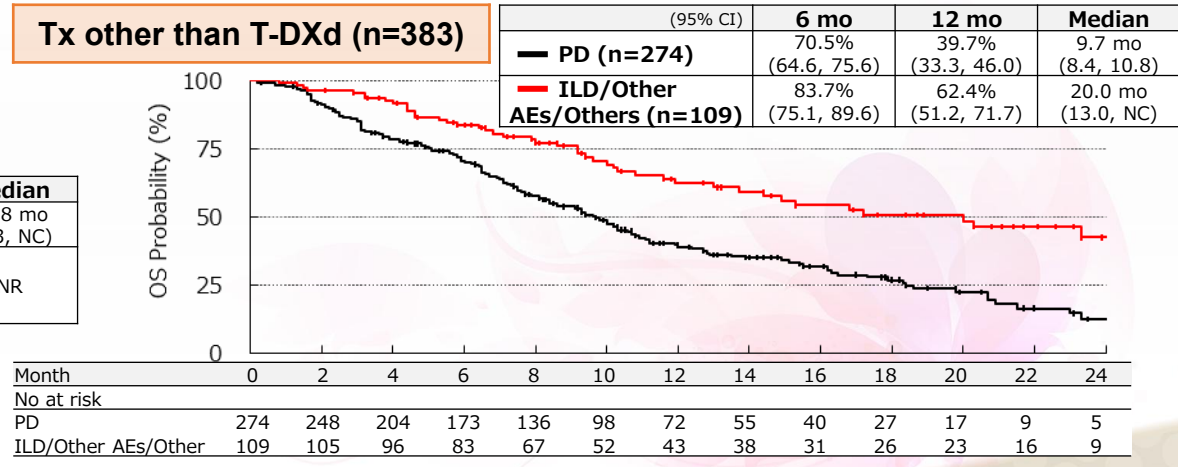
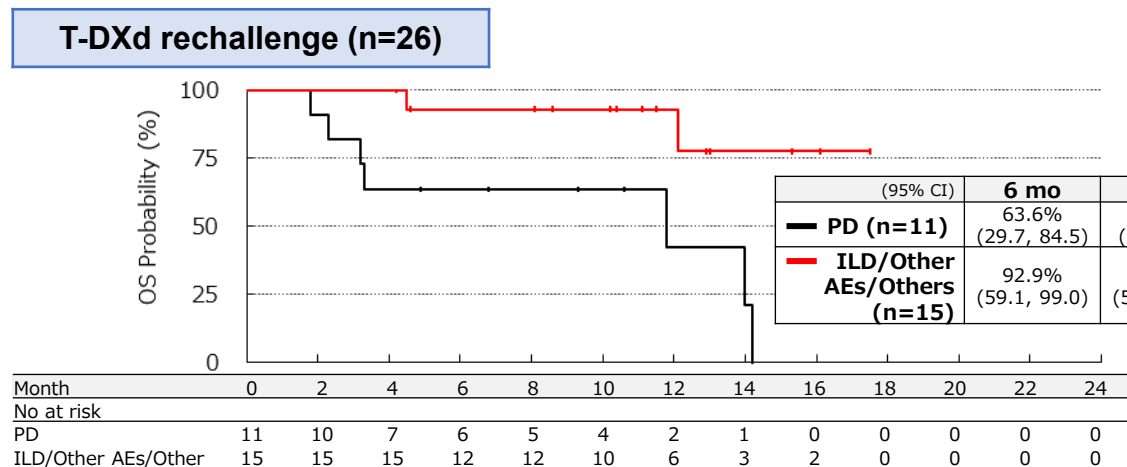
# OS Stratified by Key Factors during Initial T-DXd Tx



## Stratified by BOR during initial T-DXd treatment (CR/PR vs SD/PD/NE)



## Stratified by reason for initial T-DXd Tx discontinuation (PD vs ILD/Other AEs/Other)



Medians and their 95% CIs were calculated using the Kaplan-Meier method.

Abbreviations: AE, adverse event; BOR, best overall response; CR, complete response; ILD, interstitial lung disease; NC, not calculated; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; Tx, treatment.