Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo





# Clinical Trial Designs and Results
## 5 DXd ADCs

Includes publicly disclosed pivotal trial topline results.

Compiled from previously disclosed materials

Each slide indicates the disclosure event of the data presented.

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# DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd

(SABCS 2025)

Daiichi-Sankyo

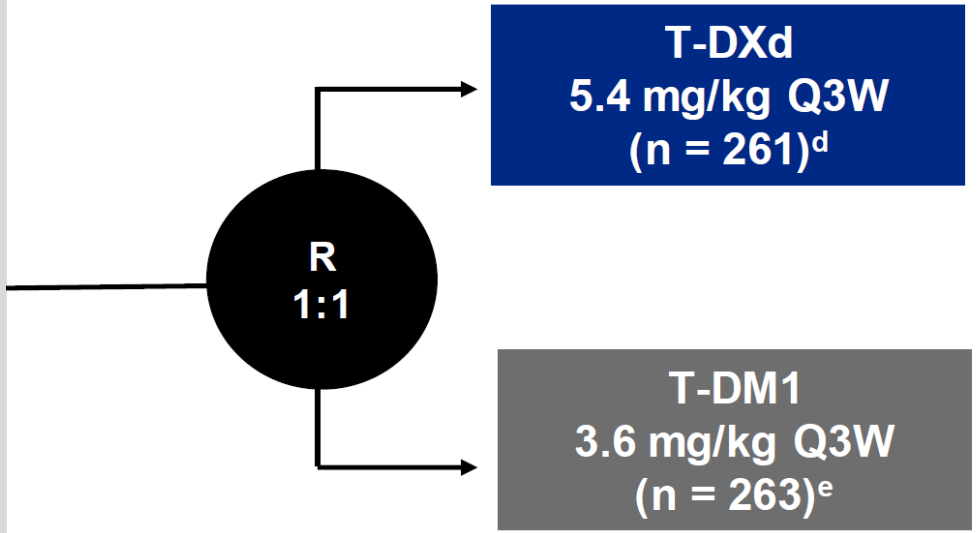
## An open-label, multicenter study (NCT03529110)

### Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer that has been previously treated with trastuzumab and a taxane[b]
- Could have clinically stable, treated brain metastases[c]
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment

### Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease




### Primary endpoint

- PFS (BICR)

### Key secondary endpoint

- OS

### Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

- At the time of data cutoff (May 21, 2021), 125 (48.6%) T-DXd patients and 214 (82.0%) T-DM1 patients had discontinued treatment
- Median follow up was 15.9 months
- BMs were measured at baseline by CT or MRI and lesions were monitored throughout the study

BICR, blinded independent central review; BM, brain metastasis; CT, computed tomography; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MRI, magnetic resonance imagining; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]Prior to protocol amendment, patients with stable, untreated BM were eligible. [d]4patients were randomly assigned but not treated. [e]2patients were randomly assigned but not treated.

ENHERTU®

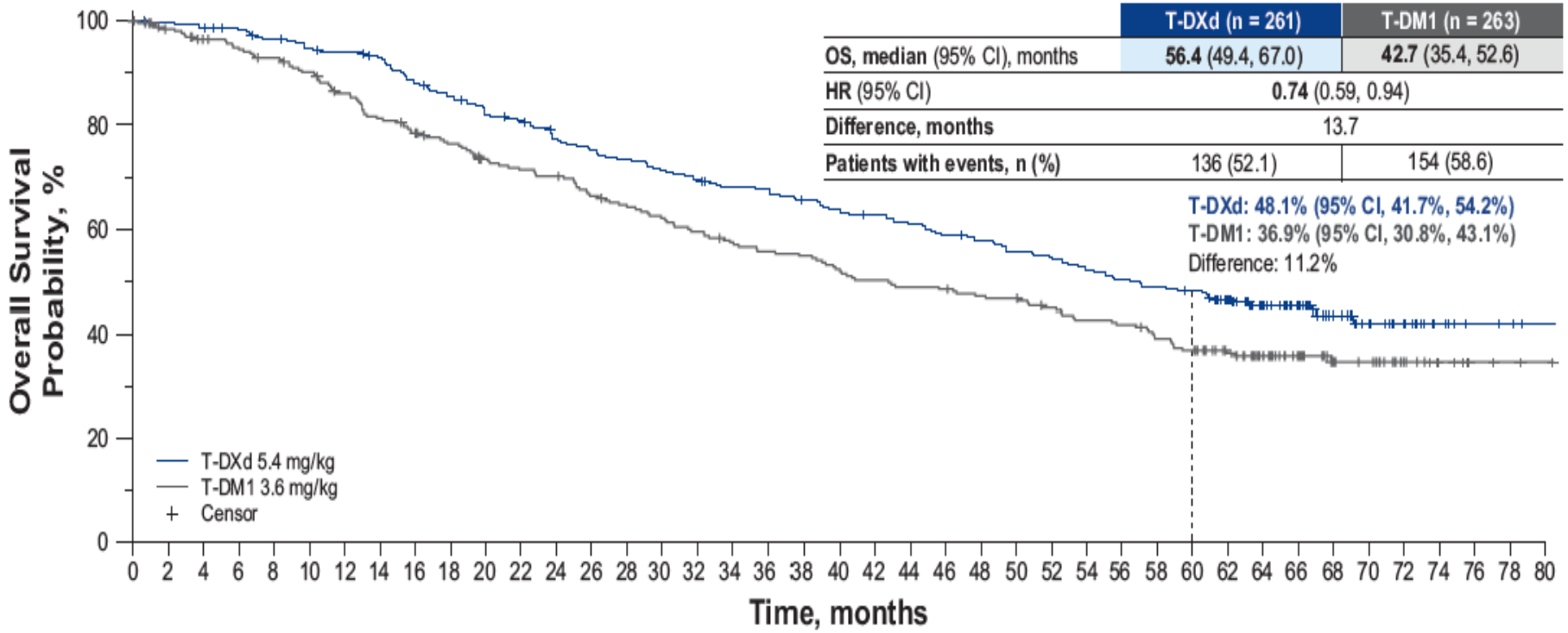
# Final Analysis for 2L Treatment in HER2+ Breast Cancer

DESTINY-Breast03 Ph3 (SABCS 2025)

Daiichi-Sankyo

## 5-year OS results reinforce the durability and sustainability of the efficacy and long-term safety of ENHERTU® leading to improved survival outcomes

**Efficacy : OS**




- Median PFS was 29.0 months in ENHERTU® group compared with 7.8 months in T-DM1 group; estimated 5-year PFS rate was 37.6% and 10.0%, respectively
- Median OS was 56.4 months in ENHERTU® group and 42.7 months in T-DM1 group; estimated 5-year OS rate was 48.1% and 36.9%, respectively
- No new safety signals were observed with longer follow-up
- The rate of adjudicated drug-related ILD was 17.5% with ENHERTU®; no grade 4 or grade 5 events were reported during the trial

Data cutoff: June 27, 2025

CI: confidence interval, HR: hazard ratio, ILD: interstitial lung disease, OS: overall survival, PFS: progression-free survival, SABCS: San Antonio Breast Cancer Symposium, T-DM1: trastuzumab emtansine, T-DXd: trastuzumab deruxtecan (ENHERTU®)

ENHERTU®

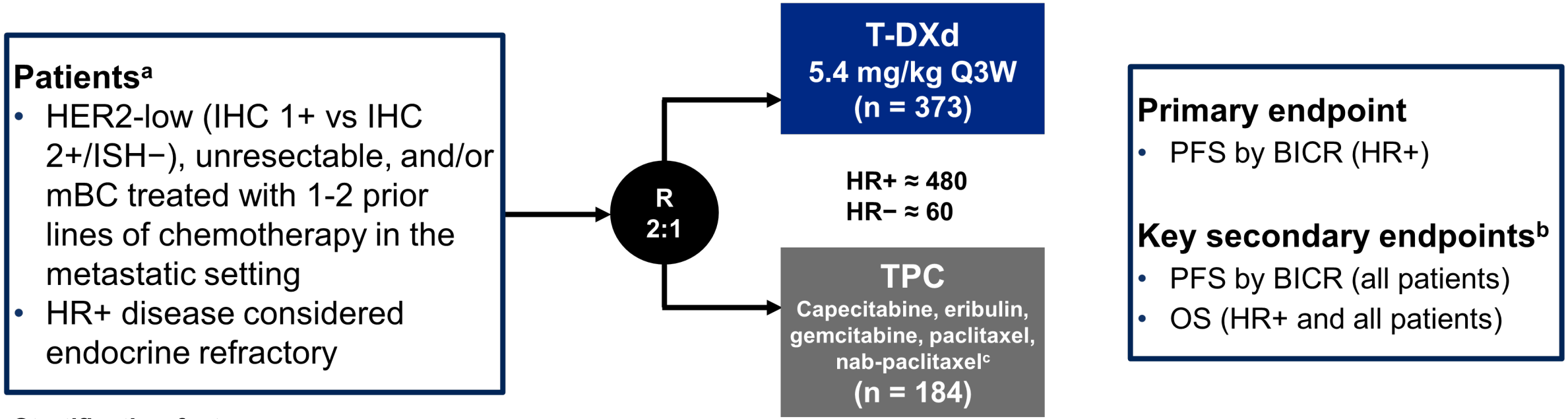
# First Randomized Phase 3 Study of T-DXd for HER2-low mBC

DESTINY-Breast04 Ph3 (ASCO 2022)

Daiichi-Sankyo

ASCO 2022 #LBA3 Plenary Session

## An open-label, multicenter study (NCT03734029)




**Primary endpoint**

- PFS by BICR (HR+)

**Key secondary endpoints[b]**

- PFS by BICR (all patients)
- OS (HR+ and all patients)

**Stratification factors**

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

ENHERTU®

# DESTINY-Breast04 data

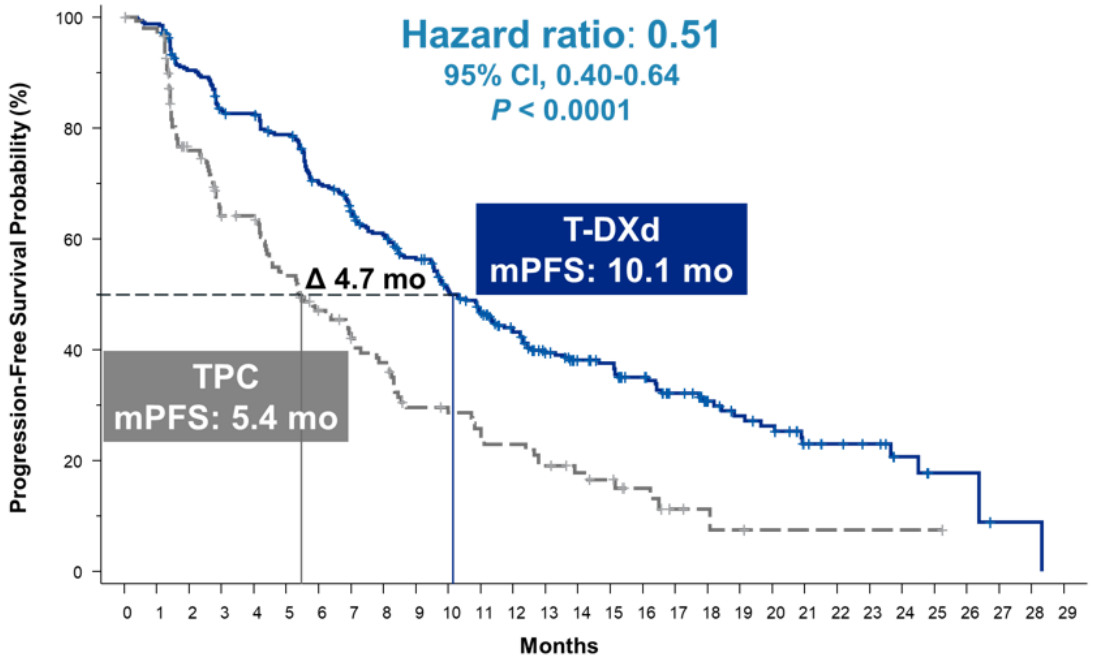
ASCO 2022 Highlights (Plenary Session)

Daiichi-Sankyo

## PFS in patients with HR+/HER2 low BC

- **49% reduction in the risk of disease progression or death** versus chemo, mPFS of **10.1m** compared to 5.4m with chemo

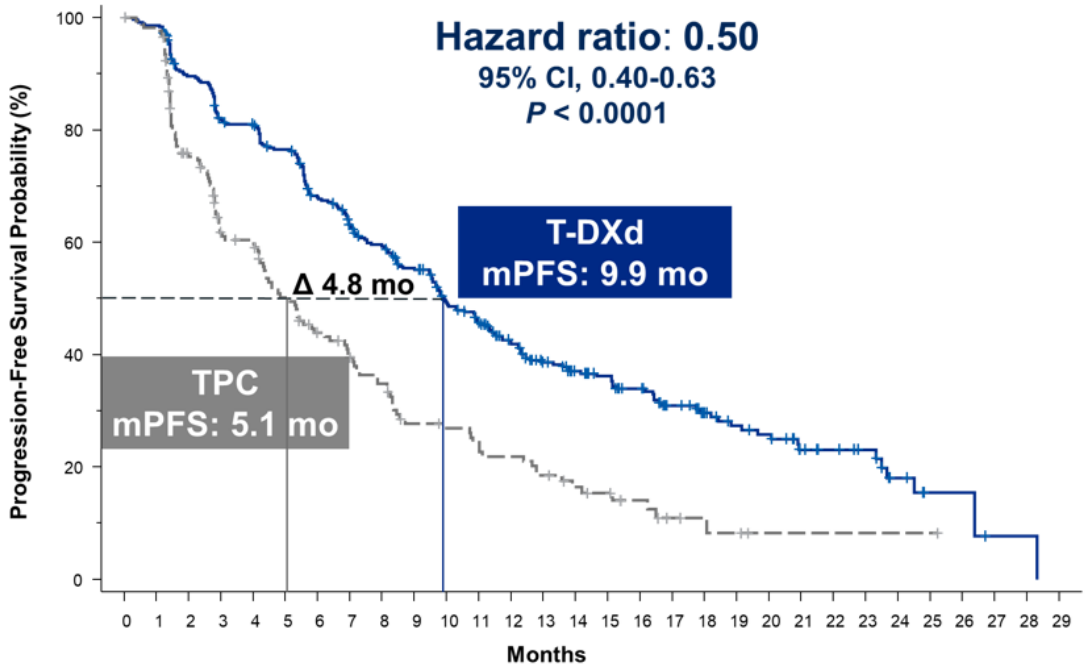
PFS（HR+）




## PFS in all patients with HR+ or HR-/HER2 low BC

- **50% reduction in the risk of disease progression or death** versus chemo, mPFS of **9.9m** compared to 5.1m with chemo

PFS (All patients)




BC: breast cancer, HR: hormone receptor, mPFS: median progression-free survival, PFS: progression-free survival, T-DXd: trastuzumab deruxtecan, TPC: treatment of physician's choice

ENHERTU®

# DESTINY-Breast04 data

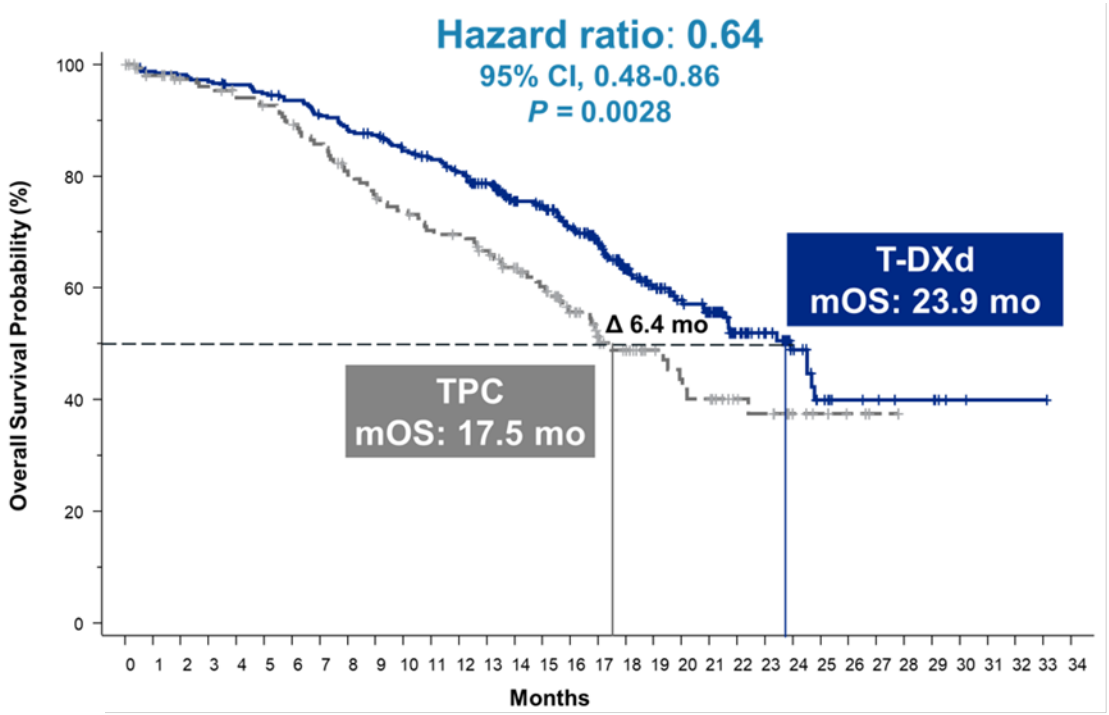
ASCO 2022 Highlights (Plenary Session)

Daiichi-Sankyo

## OS in patients with HR+/HER2 low BC

- **36% reduction in the risk of death** versus chemo, mOS of **23.9m** compared to 17.5m with chemo

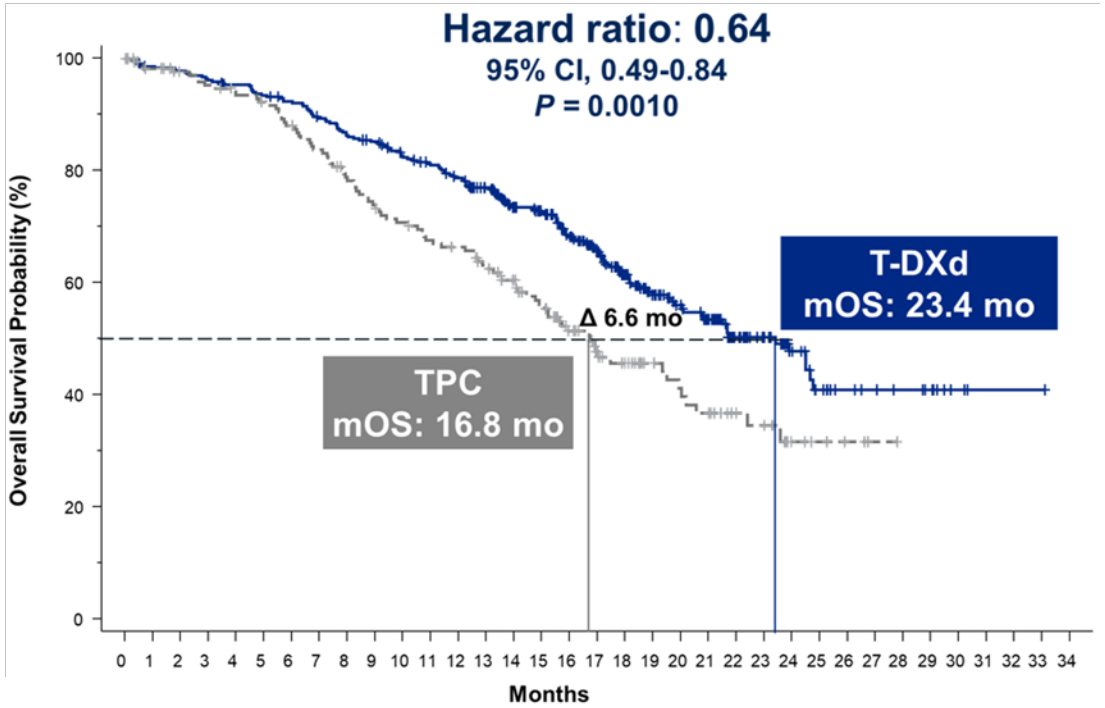
OS（HR+）




## OS in all patients with HR+ or HR-/HER2 low BC

- **36% reduction in the risk of death** versus chemo, mOS of **23.4m** compared to 16.8m with chemo

OS (All patients)




BC: breast cancer, HR: hormone receptor, mOS: median overall survival, OS: overall survival, T-DXd: trastuzumab deruxtecan, TPC: treatment of physician's choice

ENHERTU®

# DESTINY-Breast05 Study

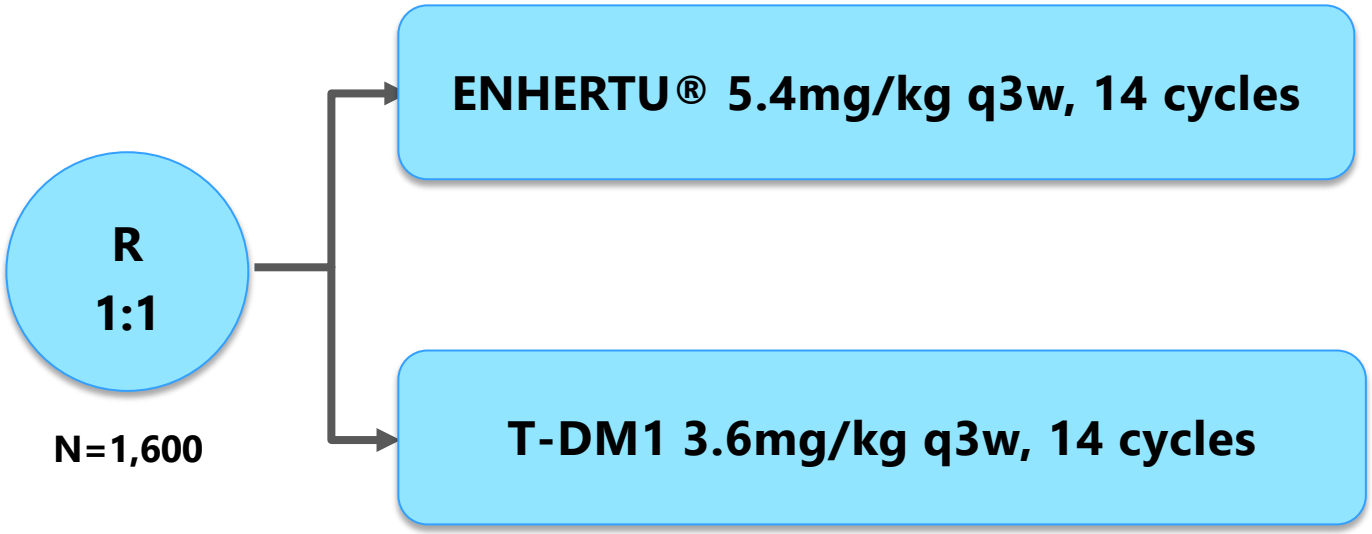
(ESMO 2025)

Daiichi-Sankyo

## Ph3 study of ENHERTU® vs. T-DM1 in high-risk HER2 positive participants with residual invasive BC following neoadjuvant therapy

**Key Eligibility Criteria**

- HER2 positive BC (IHC3+ or ISH+ as confirmed by a central laboratory) histologically
- Completion of neoadjuvant systemic chemotherapy and HER2-directed treatment
- Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes
- Pathologic evidence of residual invasive carcinoma in the breast and/or axillary lymph nodes following completion of neoadjuvant therapy meeting high-risk criteria




**Primary endpoint: IDFS,**

**Secondary endpoint: DFS, OS, DRFI, BMFI, safety and tolerability, PK, ADA**

ADA: anti-drug antibody, BC: breast cancer, BMFI: brain metastases-free interval, DFS: disease-free survival, DRFI: distant recurrence-free interval, IDFS: invasive disease-free survival, IHC: immunohistochemistry, ISH: in situ hybridization, OS: overall survival, pCR: pathological complete response, PK: pharmacokinetics, q3W: every 3 weeks, TLR: top line results

ENHERTU®

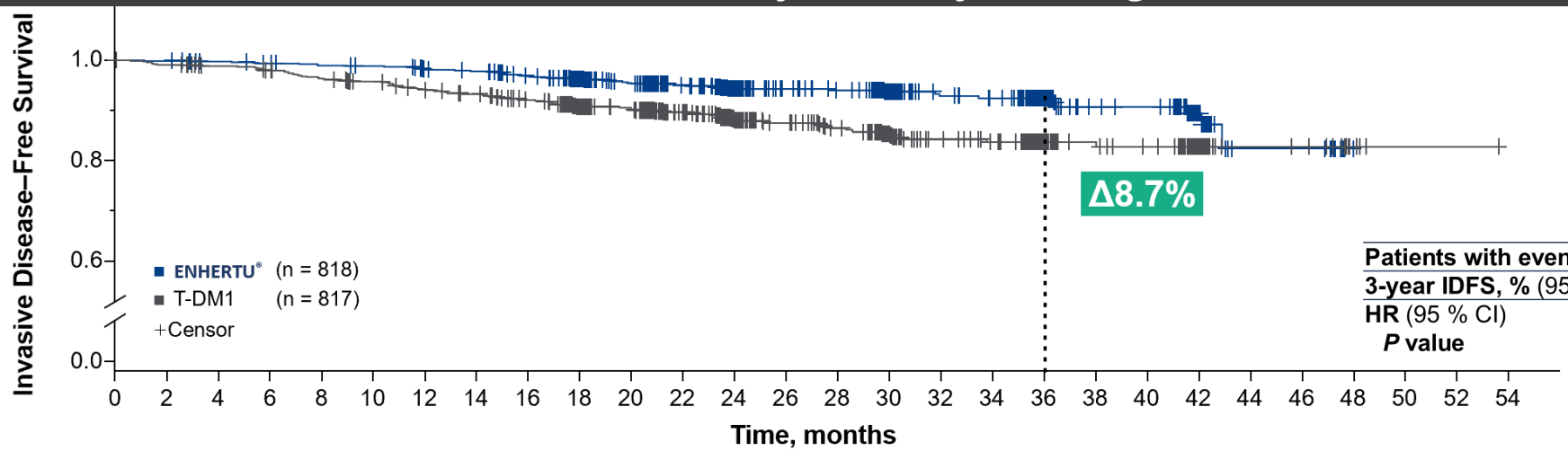
# Advancing ENHERTU® into Early HER2+ Breast Cancer

DESTINY-Breast05 Ph3 (ESMO 2025)

Daiichi-Sankyo

## ENHERTU® demonstrated a clinically meaningful and statistically significant benefit in patients with high-risk HER2 positive eBC following neoadjuvant therapy

### Efficacy: IDFS by investigator




| | T-DXd n = 818 | T-DM1 n = 817 |
|---|---|---|
| Patients with events, n (%) | **51** (6.2) | **102** (12.5) |
| 3-year IDFS, % (95% CI) | **92.4** (89.7-94.4) | **83.7** (80.2-86.7) |
| HR (95 % CI) | **0.47** (0.34-0.66) | |
| *P* value | **<0.0001**[b] | |

**Number at Risk:**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ENHERTU® | 818 | 788 | 781 | 776 | 771 | 768 | 758 | 753 | 731 | 684 | 634 | 544 | 440 | 380 | 370 | 275 | 218 | 212 | 129 | 92 | 90 | 46 | 14 | 14 | 0 | 0 | 0 | 0 |
| T-DM1 | 817 | 781 | 769 | 760 | 745 | 734 | 719 | 708 | 687 | 632 | 599 | 527 | 417 | 355 | 337 | 233 | 186 | 177 | 120 | 84 | 79 | 38 | 14 | 13 | 4 | 1 | 1 | 0 |

Data cutoff: July 2, 2025

- ENHERTU® showed a three-year IDFS rate of 92.4%, reduced the risk of invasive disease recurrence or death by 53 % (95CI: 0.34-0.66; p<0.0001) compared to T-DM1
- Clinically meaningful benefit was observed in additional secondary endpoints of DRFI (HR, 0.49 [95% CI, 0.34-0.71]) and BMFI (HR, 0.64 [0.35-1.17])
- The overall safety profiles of ENHERTU® and T-DM1 were generally manageable with no new safety signals

BC: breast cancer , BMFI: brain metastasis-free interval, CI: confidence interval, DRFI: distant recurrence-free interval, eBC: early-stage breast cancer, ESMO: European Society for Medical Oncology, HR: hazard ratio, IDFS: invasive disease-free survival, INV: investigator, T-DM1: trastuzumab emtansine

# DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

## PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

**Prior lines of therapy**

- ≥2 lines of ET ± targeted therapy for mBC
  **OR**
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    **OR**
  - Recurrence ≤24 months of starting adjuvant ET

**Stratification factors**

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

**T-DXd**
**5.4 mg/kg Q3W**
**(n=436)**

**HER2-low = 713**
**HER2-ultralow = 153†**

**TPC**
**(n=430)**

Options: capecitabine, nab-paclitaxel, paclitaxel

## ENDPOINTS

**Primary**

- PFS (BICR) in HER2-low

**Key secondary**

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

**Other secondary**

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+); †HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data); ‡to be presented separately
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
NCT04494425. Updated. April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

ENHERTU®

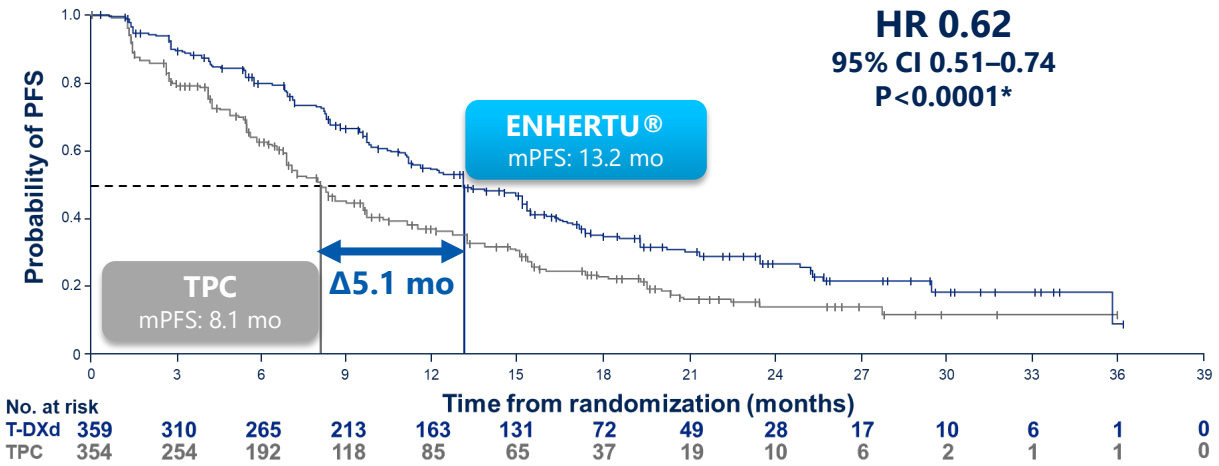
# Pioneered New Classifications of HER2

DESTINY-Breast06 Ph3 (ASCO 2024)

Daiichi-Sankyo

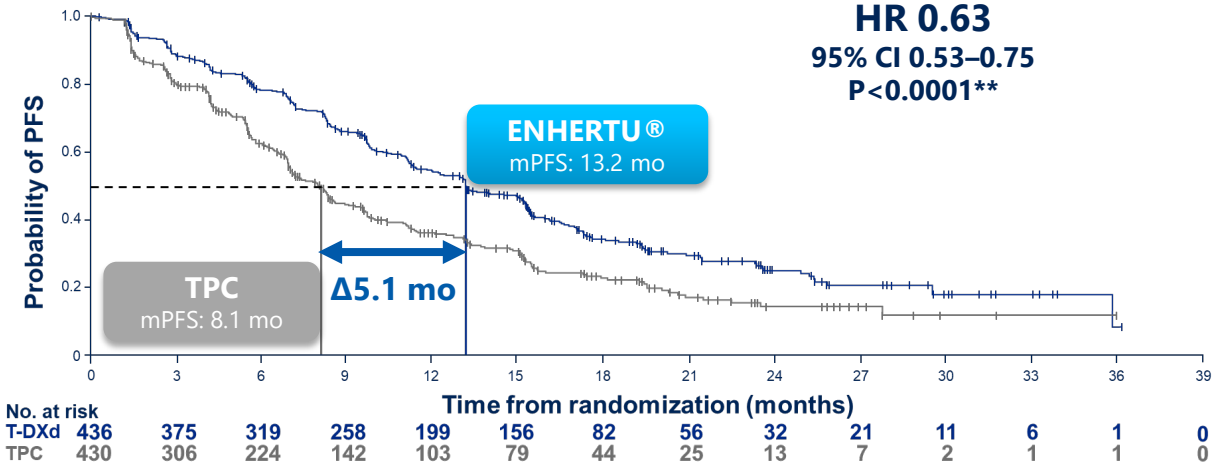
## ENHERTU® demonstrated efficacy in HER2 ultralow as well as HER2 low chemo naïve BC, and is approved in the US and EU

### PFS for HER2 low (BICR)




Data cutoff: March 18, 2024
*P-value of <0.05 required for statistical significance

### PFS for ITT（HER2 low and ultralow） (BICR)




Data cutoff: March 18, 2024
**P-value of <0.015 required for statistical significance

- ENHERTU® demonstrated a statistically significant and clinically meaningful improvement in PFS for chemo naïve HR positive, HER2 low and ultralow metastatic BC. No new safety concerns identified
- ENHERTU® is **approved to treat about 90 percent of people with mBC**

BC: breast cancer, BICR: blinded independent central review, CI: confidence interval, HR: hazard ratio, HR: hormone receptor, ITT: intention-to-treat, mPFS: median progression-free survival, PFS: progression-free survival, T-DXd: trastuzumab deruxtecan, ENHERTU®, TPC: treatment of physician's choice

ENHERTU®

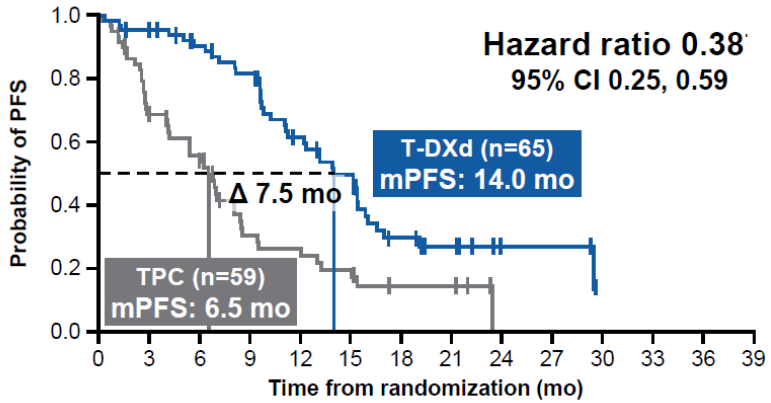
# PFS in Exploratory Subgroup Analysis

DESTINY-Breast06 (SABCS 2024)

## ENHERTU® improved PFS vs TPC regardless of time to progression on 1L endocrine therapy + CDK4/6i

**<TTP subgroups>**

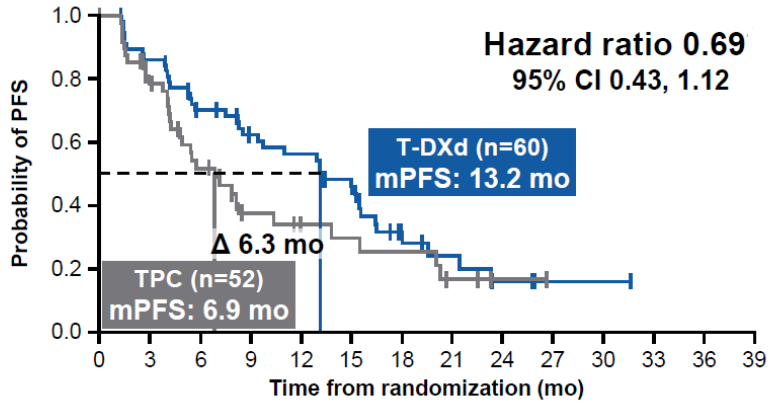
**<6-mo 1L TTP**




Number at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd | 65 | 61 | 53 | 47 | 32 | 25 | 12 | 8 | 3 | 3 | 0 |
| TPC | 59 | 38 | 30 | 14 | 12 | 9 | 4 | 4 | 0 | 0 | 0 |

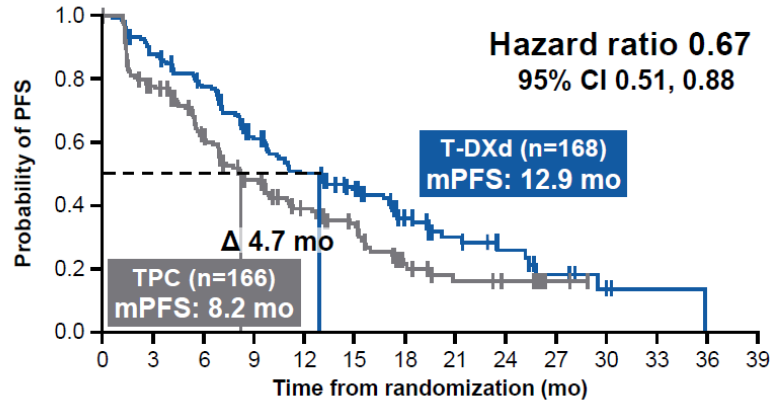
**6–12-mo 1L TTP**




Number at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd | 60 | 50 | 38 | 31 | 28 | 20 | 9 | 6 | 3 | 1 | 1 | 0 |
| TPC | 52 | 34 | 21 | 11 | 8 | 7 | 6 | 3 | 1 | 0 | 0 | 0 |

**>12-mo 1L TTP**




Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd | 168 | 146 | 125 | 94 | 74 | 59 | 28 | 17 | 11 | 6 | 2 | 1 | 0 |
| TPC | 166 | 114 | 86 | 62 | 44 | 33 | 14 | 8 | 6 | 2 | 0 | 0 | 0 |

- ENHERTU® demonstrated a clinically meaningful efficacy benefit vs TPC regardless of time to progression (TTP) on 1L ET + CDK4/6i (mPFS 12.9–14.0 mo with ENHERTU®)
  - ✓ This included patients with rapid (<6-mo) progression on 1L ET + CDK4/6i

CI: confidence interval, ET: endocrine therapy, mo: months, (m)PFS: (median) progression-free survival, PD: progressive disease, T-DXd: trastuzumab deruxtecan, TPC: treatment of physician's choice

ENHERTU®

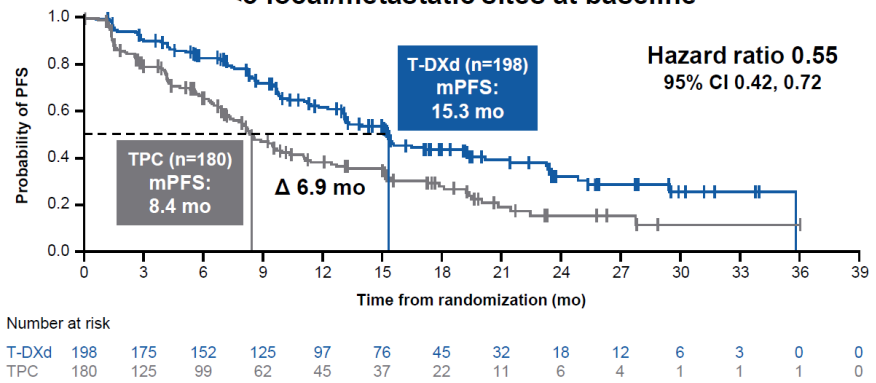
# PFS in Exploratory Subgroup Analysis

DESTINY-Breast06 (SABCS 2024)

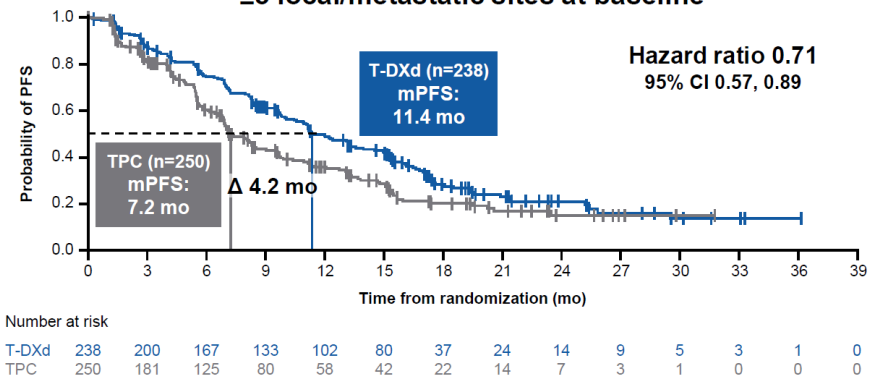
## PFS benefit with ENHERTU® was observed regardless of disease burden, with notable efficacy in patients with lower disease burden

<Disease burden subgroups>

<3 local/metastatic sites at baseline

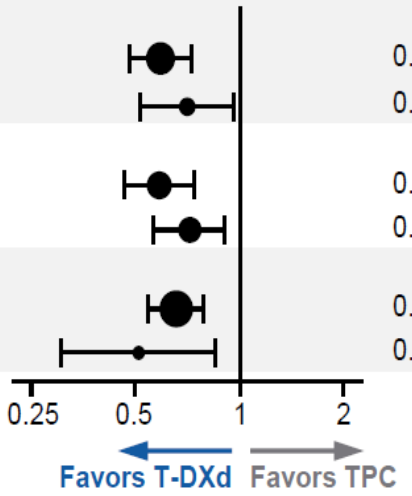



≥3 local/metastatic sites at baseline




Median PFS, mo (95% CI)

| | T-DXd | TPC | Hazard ratio (95% CI) |
|---|---|---|---|
| **Liver metastases** | | | |
| Yes (n=579) | 12.2 (10.4, 13.5) | 7.0 (6.4, 8.1) | 0.59 (0.48, 0.72) |
| No (n=287) | 16.5 (13.2, 19.4) | 11.3 (8.3, 15.2) | 0.70 (0.51, 0.96) |
| **Baseline tumor size** | | | |
| >Median (n=432) | 12.0 (9.9, 15.2) | 7.1 (6.5, 8.3) | 0.57 (0.45, 0.72) |
| ≤Median (n=434) | 15.0 (13.1, 16.1) | 9.7 (7.5, 13.2) | 0.71 (0.55, 0.90) |
| **Visceral disease** | | | |
| Yes (n=740) | 13.1 (11.1, 15.1) | 7.9 (6.9, 8.5) | 0.65 (0.55, 0.78) |
| No (n=126) | 23.3 (13.1, NE) | 11.3 (6.9, 15.7) | 0.51 (0.30, 0.85) |




- ENHERTU® also demonstrated efficacy regardless of disease burden, with notable efficacy in patients with lower disease burden (mPFS 15.0–23.3 mo with ENHERTU® )

CI: confidence interval, ET: endocrine therapy, mo: months, NE, not evaluable, (m)PFS: (median) progression-free survival, T-DXd: trastuzumab deruxtecan, TPC: treatment of physician's choice

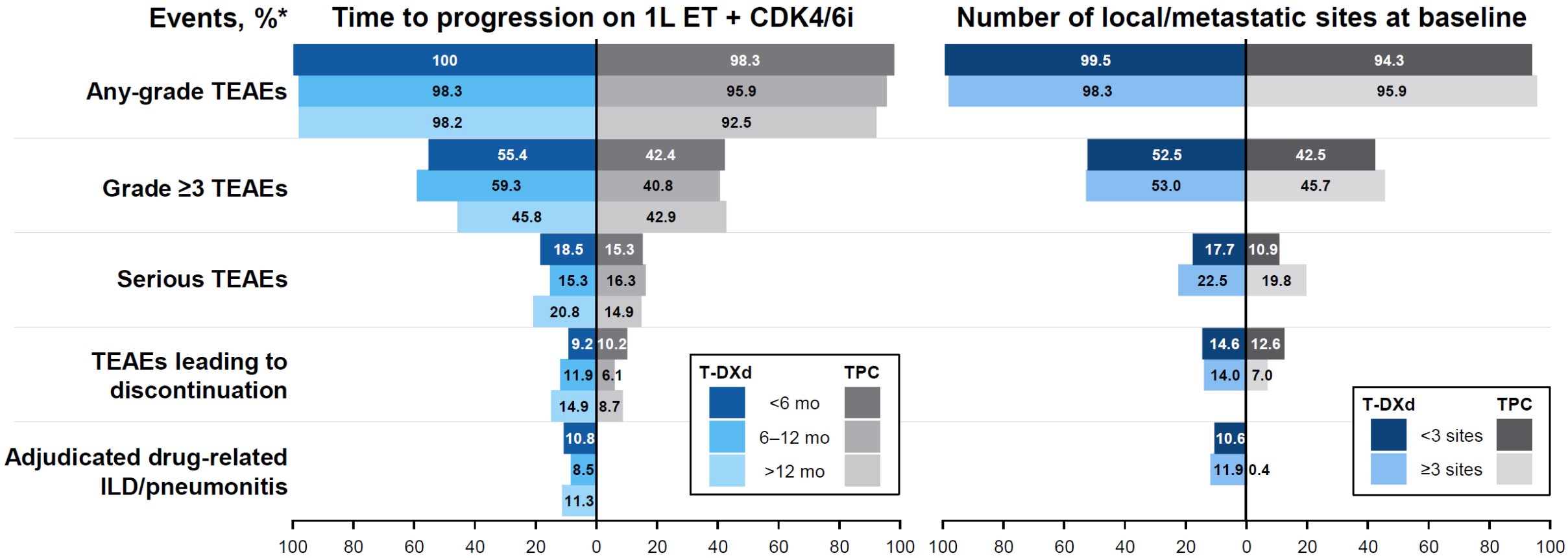
ENHERTU®

# Safety in Exploratory Subgroups

DESTINY-Breast06 (SABCS 2024)

Daiichi-Sankyo

## Safety profiles for ENHERTU® and TPC in TTP and disease burden subgroups in line with overall safety population†




*Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent cancer therapy (whichever occurs first); includes ILD/pneumonitis with an onset date or worsening on or after the date of first dose; †overall safety population (T-DXd vs TPC): any TEAEs, 98.8% vs 95.2%; Grade ≥3 TEAEs, 52.8% vs 44.4%; serious TEAEs, 20.3% vs 16.1%; TEAEs leading to discontinuation, 14.3% vs 9.4%; adjudicated drug-related ILD, 11.3% vs 0.2%

AE: adverse event, ET: endocrine therapy, ILD: interstitial lung disease, mo: months, T-DXd: trastuzumab deruxtecan, TEAE: treatment-emergent adverse event, TPC: treatment of physician's choice, TTP: time to progression

ENHERTU®

# More Advancements in HER2 Positive Breast Cancer

DESTINY-Breast09 Ph3 (ASCO 2025)

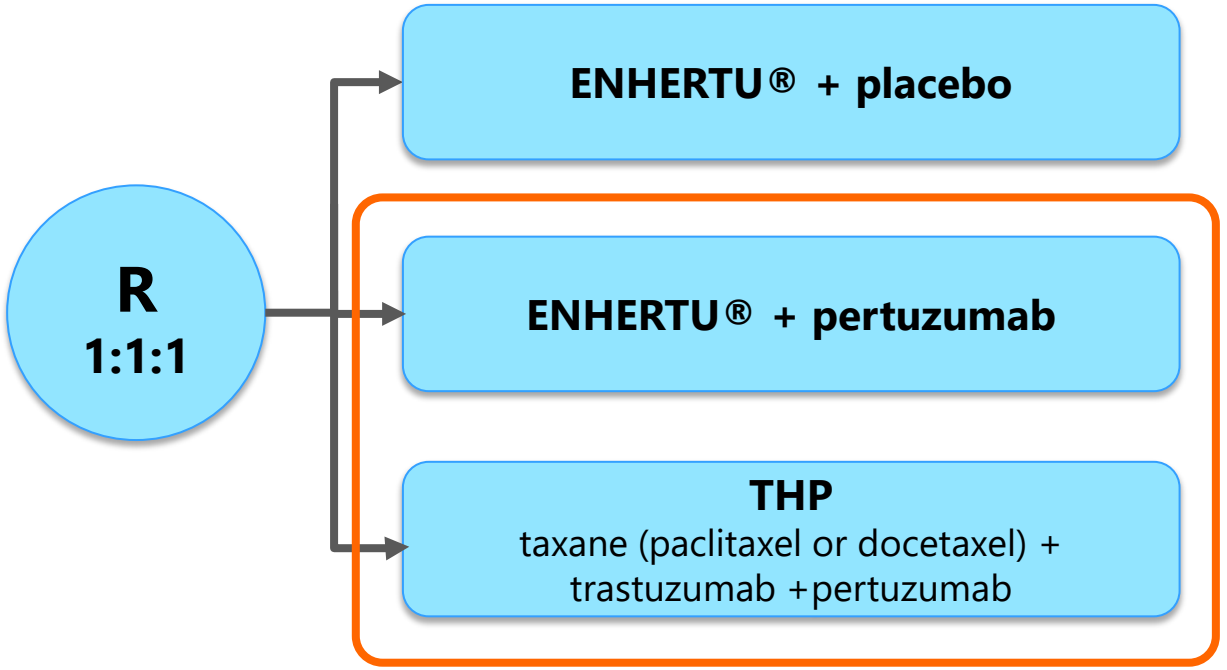
Daiichi-Sankyo

## DESTINY-Breast09 evaluates the efficacy and safety of ENHERTU® ± pertuzumab vs SOC in 1L HER2 positive mBC

### DESTINY-Breast09 Study Design

**Eligible Patient**

- HER2 positive advanced or metastatic breast cancer
- One prior line of ET for metastatic breast cancer permitted
- No other prior systemic treatment for metastatic breast cancer




**Primary endpoint**

- PFS (BICR)

**Secondary endpoints**

- OS
- PFS (investigator)
- ORR
- DOR
- PFS2
- Safety and tolerability

- At ASCO 2025, interim analysis results for the combination arm, ENHERTU® + pertuzumab, comparing to THP arm were presented (data cut-off: Feb 26, 2025)
- The arm assessing ENHERTU® monotherapy versus THP remains blinded to patients and investigators and will continue to the final PFS analysis

ASCO: American Society of Clinical Oncology, BC: breast cancer, BICR: blinded independent central review, DOR: duration of response, ORR: objective response rate, OS: overall survival, PFS: progression-free survival

ENHERTU®

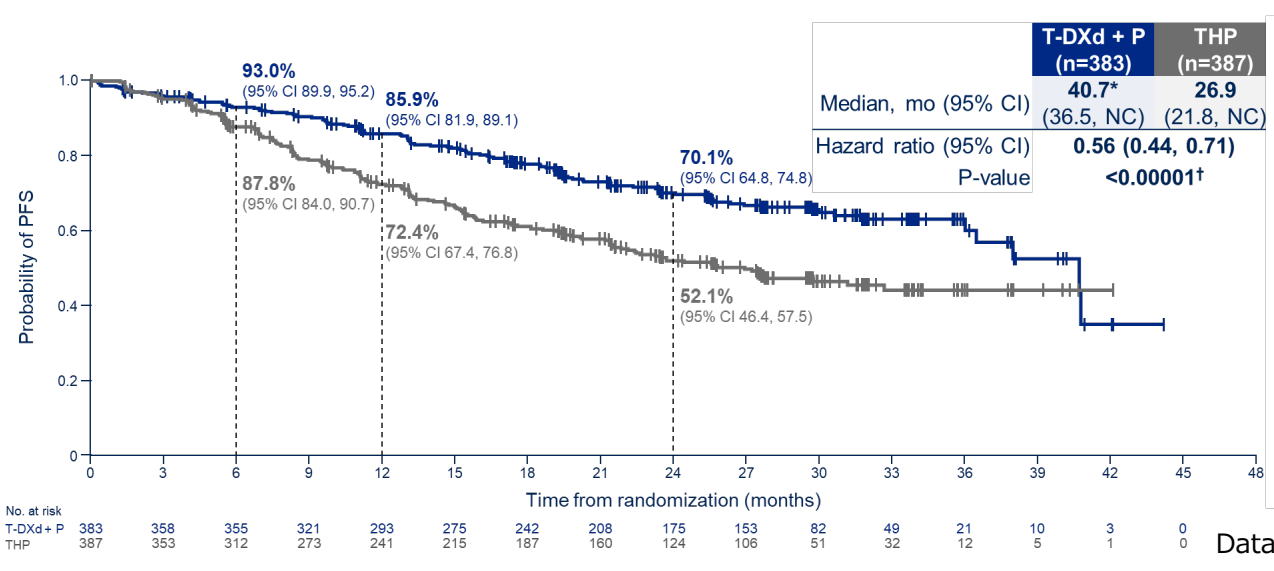
# Establish a New 1L Treatment for HER2 Positive BC

DESTINY-Breast09 Ph3 (ASCO 2025)

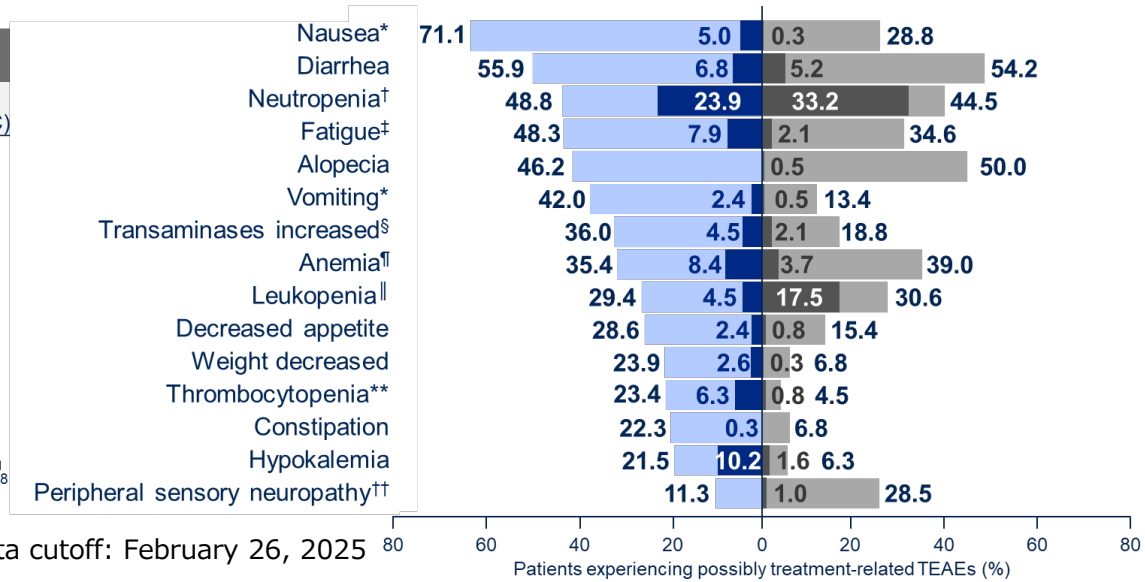
Daiichi-Sankyo

## ENHERTU® in combination with pertuzumab (T-DXd+P) showed statistically significant and clinically meaningful PFS in the 1L treatment of HER2+ mBC

### Antitumor Activity (PFS (BICR))




### Safety




Data cutoff: February 26, 2025

- mPFS in T-DXd+P arm was 40.7 mo versus 26.9 mo in THP arm with 44% reduction in the risk of disease progression or death
- Interim OS data showed an early trend favoring T-DXd+P compared to THP with HR 0.84 (95% CI 0.59-1.19) with 16% maturity
- T-DXd+P safety data were consistent with known profiles of individual treatments. The majority of ILD were low grade. There were two grade 5 ILD events (0.5%) in T-DXd+P
- Breakthrough Therapy Designation was granted by FDA in July 2025

ASCO: American Society of Clinical Oncology, BC: breast cancer, BICR: blinded independent central review, CI: confidence interval, FDA: U.S. Food and Drug Administration, ILD: interstitial lung disease, mBC: metastatic breast cancer, mo: month, mPFS: median progression-free survival, NC: not calculated, OS: overall survival, PFS: progression-free survival, T-DXd: trastuzumab deruxtecan, ENHERTU® , THP: taxane + trastuzumab +pertuzumab

ENHERTU®

# First Ph3 Study Demonstrated Benefit of ENHERTU® in Early Breast Cancer

DESTINY-Breast11 Ph3 (ESMO 2025)

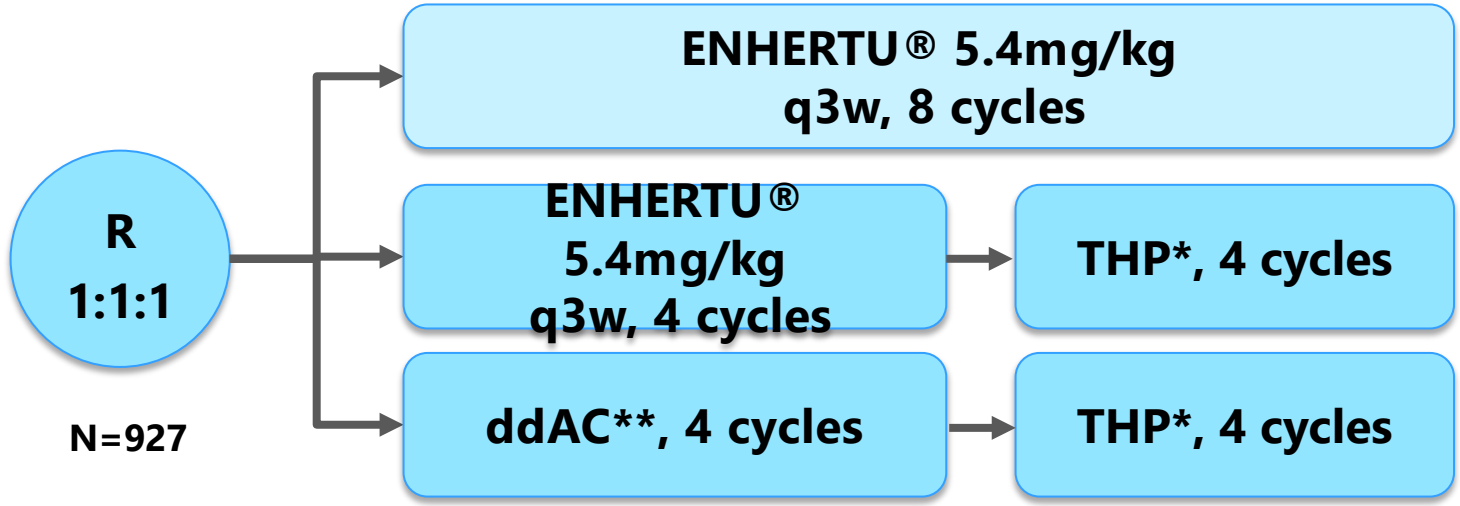
Daiichi-Sankyo

## ENHERTU® followed by THP demonstrated statistically significant and clinically meaningful improvement in pCR in high-risk HER2 positive eBC neoadjuvant setting

### DESTINY-Breast11 Study Design

**Eligible Patient**

- Histologically documented HER2 positive early BC
- Eligible for following clinical stage (based on mammogram or breast MRI assessment)
  - ✓ >T3 or N+ or inflammatory BC as determined by the AJCC staging system




* THP: paclitaxel qw + trastuzumab q3w + pertuzumab q3w
** ddAC: doxorubicin + cyclophosphamide q2w

Primary endpoint: pCR
Secondary endpoint: EFS, OS

- EFS was not mature at the time of this analysis, however, preliminary EFS data showed an early trend favoring ENHERTU®-THP therapy compared to ddAC-THP therapy
- Safety profile of ENHERTU®-THP therapy was consistent with the known profiles for each individual therapy, and showed an improvement compared to SOC
- Enrollment for ENHERTU® monotherapy arm was halted based on interim evaluation by IDMC

AJCC: American Joint Committee on Cancer, BC: breast cancer, eBC: early-stage breast cancer, EFS: event-free survival, HR: hormone receptor, IDMC: independent data monitoring committee, MRI: Magnetic Resonance Imaging, OS: overall survival, pCR: pathological complete response, qw: once weekly, q2w: every 2 weeks, q3w: every 3 weeks, TLR: top line results

ENHERTU®

# Advancing ENHERTU® into Early HER2+ Breast Cancer

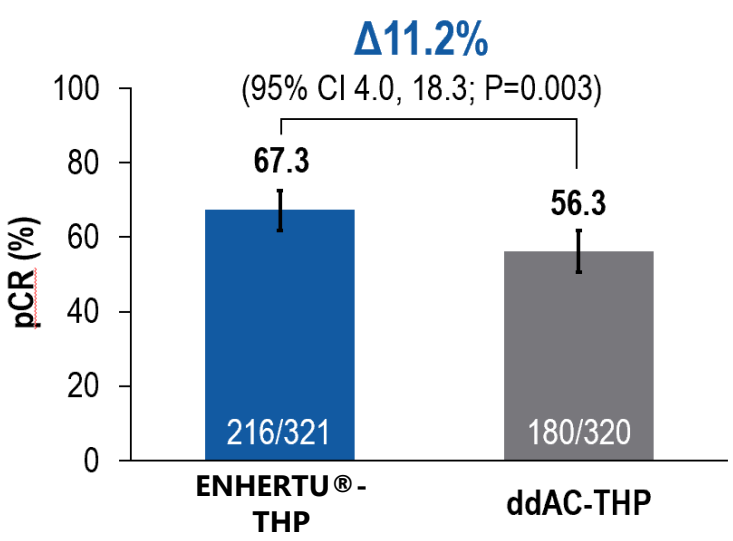
DESTINY-Breast11 Ph3 (ESMO 2025)

Daiichi-Sankyo

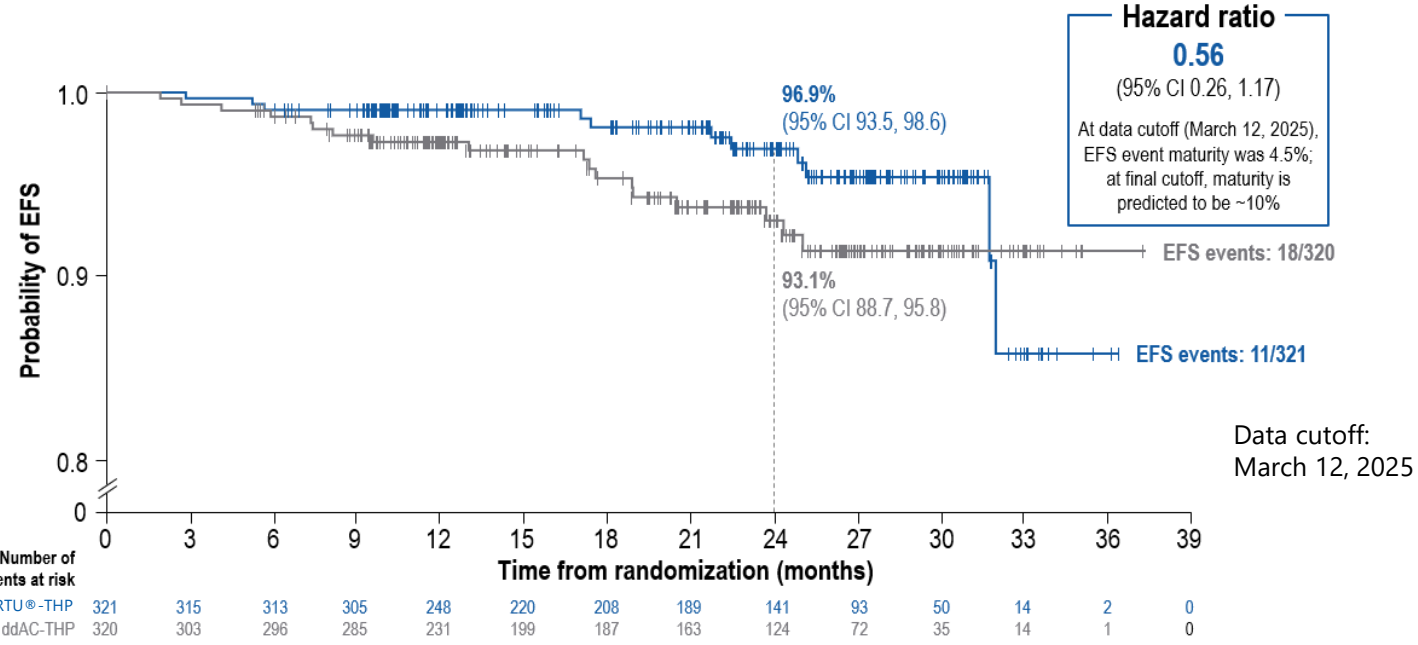
## ENHERTU® followed by THP showed statistically significant and clinically meaningful improvement in pCR rate in high-risk HER2 positive eBC neoadjuvant setting

### pCR

ITT population (primary endpoint)




### EFS




Data cutoff:
March 12, 2025

- ENHERTU®-THP arm showed 11.2% improvement in pCR rate compared to the ddAC-THP arm (95% CI 4.0-18.3)
- ENHERTU®-THP arm showed an early positive trend in EFS compared to the ddAC-THP arm (HR: 0.56; 95% CI 0.26-1.17)
- The safety profile of ENHERTU®-THP arm was favorable compared to the ddAC-THP arm, lower rates of Grade ≥3 AEs, serious AEs, and AEs leading to dose reductions/interruptions. ILD rates were low and similar between the two arms

AE: adverse event, BC: breast cancer, CI: confidence interval, ddAC: doxorubicin + cyclophosphamide, eBC: early-stage breast cancer, EFS: event-free survival, ESMO: European Society for Medical Oncology, HR: hazard ratio, ILD: interstitial lung disease, ITT: intention-to-treat, pCR: pathological complete response, THP: paclitaxel + trastuzumab + pertuzumab

ENHERTU®

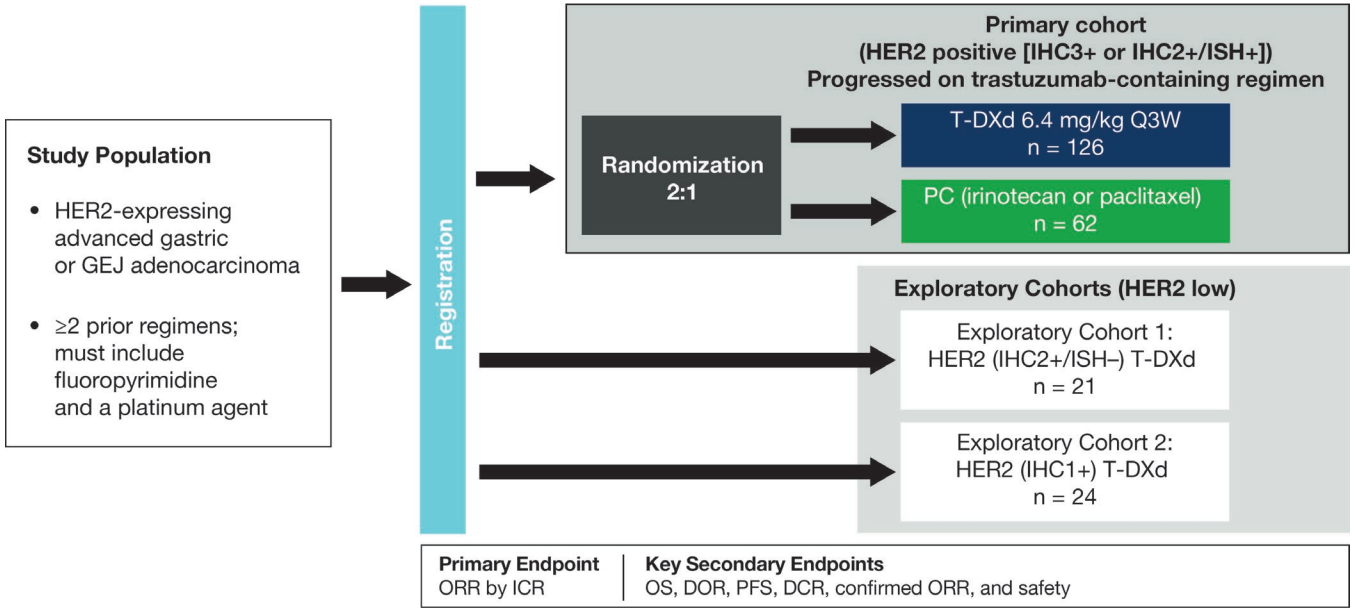
# Background and Study Design

DESTINY-Gastric01 (ASCO 2021)

Daiichi-Sankyo

- T-DXd is an antibody–drug conjugate comprising an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload (DXd)[1] approved in the United States and Japan for adult patients with advanced HER2+ gastric or GEJ adenocarcinoma[2,3]
- In the primary DESTINY-Gastric01 analysis, T-DXd exhibited statistically significant ORR and OS benefit vs standard chemotherapy
- Here, we present final OS results as well as updated efficacy and safety data
- Patients had a median of 2 prior lines of therapy (range, 2-9); 44.4% of patients had ≥3 previous lines
- As of June 3, 2020, 10 patients (8%) receiving T-DXd and no patients receiving PC remained on treatment

## DESTINY-Gastric01 Study Design




Key secondary endpoint of OS was to be statistically evaluated hierarchically if the primary endpoint was statistically significant

DCR, disease control rate; DOR, duration of response; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PC, physician's choice; PFS, progression-free survival; Q3W, every three weeks; T-DXd, trastuzumab deruxtecan.

1. Shitara K et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382:2419-2430. 2. Enhertu. Prescribing information. Daiichi Sankyo Inc.; 01/2021. 3. Enhertu. Summary of product characteristics. Daiichi Sankyo Co. LTD.; 2020.

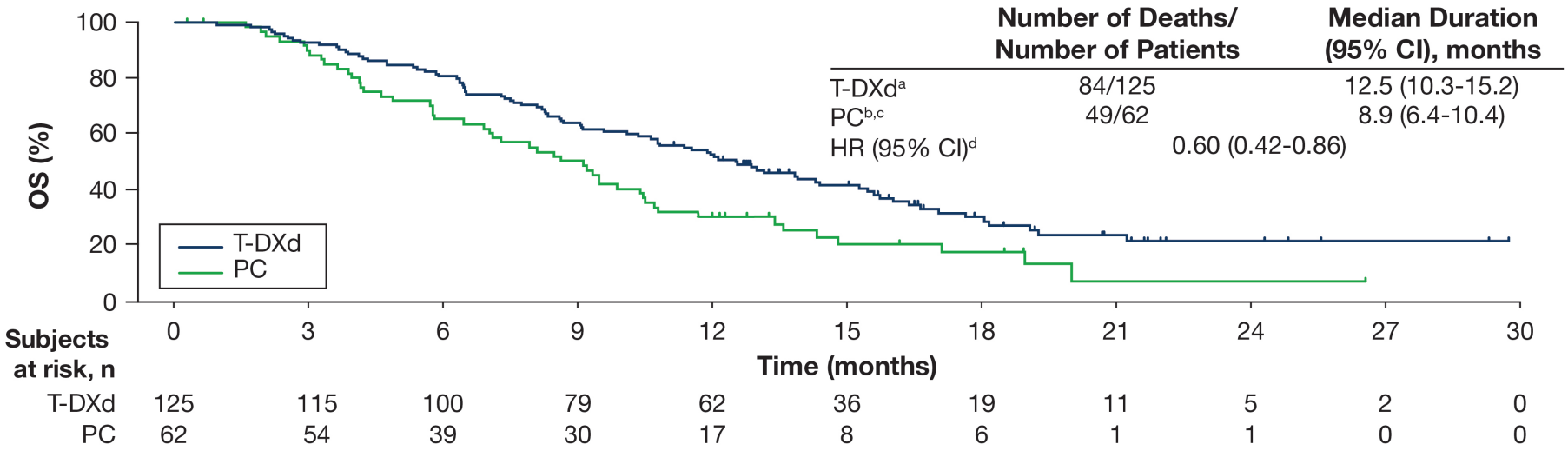
ENHERTU®

# Results: Overall Survival

DESTINY-Gastric01 (ASCO 2021)

Daiichi-Sankyo

## Kaplan-Meier Analysis of Overall Survival




As in the primary analysis (101 OS events; 54.0% maturity), in this updated analysis (133 OS events; 71.1% maturity), T-DXd showed superior antitumor activity compared to PC

HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

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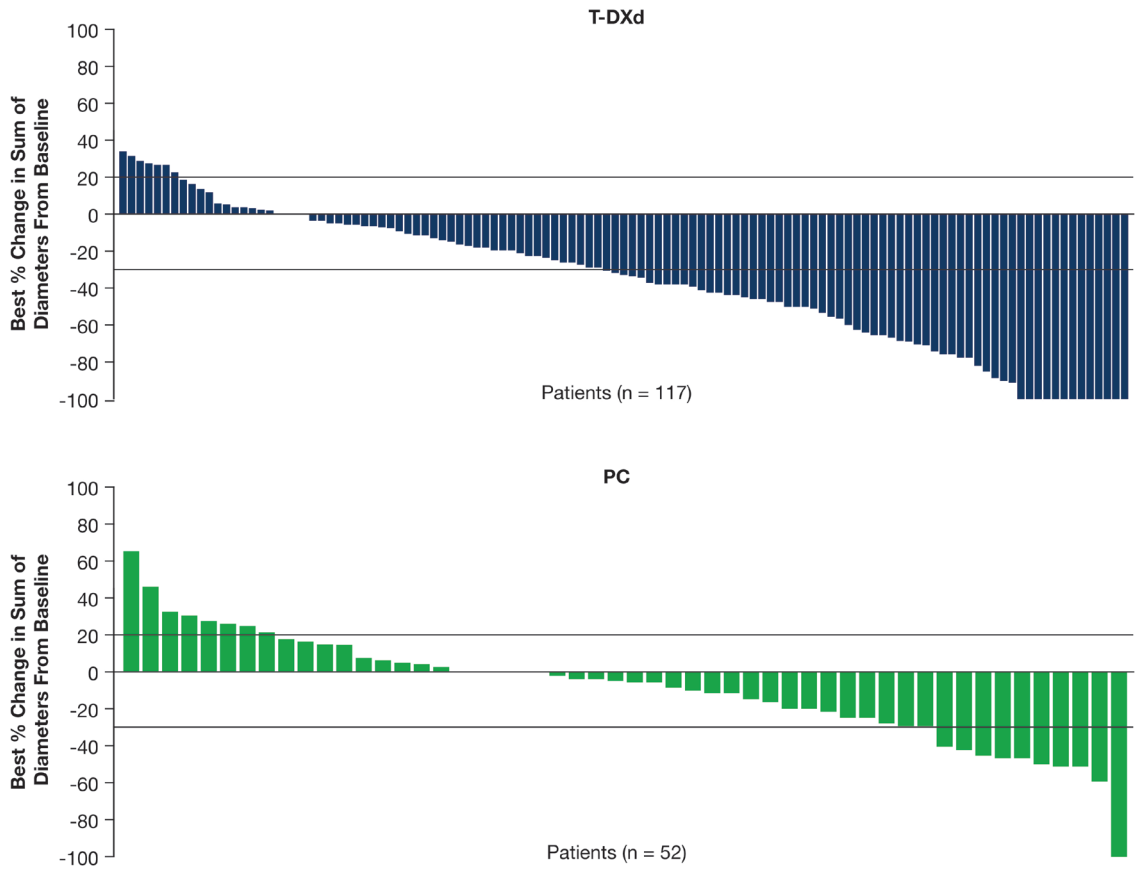
# Results: ORR and Other Efficacy Endpoints

DESTINY-Gastric01 (ASCO 2021)

Daiichi-Sankyo

| | T-DXd n = 119 | PC Overall n = 56 |
|---|---|---|
| ORR (CR + PR) by ICR, n (%)[a] | 61 (51.3)<br>95% CI, 41.9-60.5 | 8 (14.3)<br>95% CI, 6.4-26.2 |
| | *P* < 0.0001[b] | |
| CR | 11 (9.2) | 0 |
| PR | 50 (42.0) | 8 (14.3) |
| SD | 42 (35.3) | 27 (48.2) |
| PD | 14 (11.8) | 17 (30.4) |
| Not evaluable | 2 (1.7) | 4 (7.1) |
| Confirmed ORR (CR + PR) by ICR, n (%)[a] | 50 (42.0)<br>95% CI, 33.0-51.4 | 7 (12.5)<br>95% CI, 5.2-24.1 |
| CR | 10 (8.4) | 0 |
| PR | 40 (33.6) | 7 (12.5) |
| SD | 52 (43.7) | 28 (50.0) |
| PD | 14 (11.8) | 17 (30.4) |
| Not evaluable | 3 (2.5) | 4 (7.1) |
| Confirmed DCR (CR + PR + SD), n (%)[a] | 102 (85.7)<br>95% CI, 78.1-91.5 | 35 (62.5)<br>95% CI, 48.5-75.1 |
| Confirmed DOR, median, months | 12.5<br>95% CI, 5.6-NE | 3.9<br>95% CI, 3.0-4.9 |
| PFS, median, months | 5.6<br>95% CI, 4.3-6.9 | 3.5<br>95% CI, 2.0-4.3 |
| | *P* = 0.0003[c] | |
| TTR, median, months | 1.5<br>95% CI, 1.4-1.7 | 1.6<br>95% CI, 1.3-1.7 |

**Best Percentage Change from Baseline in Tumor Size for Individual**




CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; NE, not estimable; ORR, objective response rate; PC, physician's choice; PD, progressive disease; PFS, progression-free response; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTR, time to response. [a]Includes data for the response-evaluable set: all randomized patients who received ≥1 dose of study drug and had measurable tumors based on ICR at baseline. [b]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region. [c]Comparison between T-DXd and PC overall using stratified Log-rank test stratified by region.

ENHERTU®

# Study Design

DESTINY-Gastric02 (ESMO 2021)

Daiichi-Sankyo

An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer (NCT04014075)

## Key eligibility criteria

- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Centrally confirmed HER2 positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

→ **T-DXd 6.4 mg/kg Q3W N = 79[a]** →

## Primary endpoint

- Confirmed ORR by ICR

## Secondary endpoints[b]

- PFS by ICR
- OS
- DOR by ICR
- Safety and tolerability

- DESTINY-Gastric02 is the first study focused only on second-line T-DXd monotherapy in Western patients with HER2+ gastric/GEJ cancer who have progressed on a trastuzumab-containing regimen
  - It is the follow-on study to DESTINY-Gastric01, which evaluated T-DXd third-line or later in Asian patients[1]
- Patients were enrolled in Europe (Belgium, Great Britain, Italy, Spain) and the United States (data cutoff: April 9, 2021)

[a]Enrollment of 80 patients was planned; actual enrollment was 79 patients.
[b]Other secondary endpoints were ORR, PFS, and DOR by investigator assessment, pharmacokinetics, anti-drug antibodies, and patient-reported outcomes.

1. Shitara K et al. *N Engl J Med*. 2020;382:2419-30.

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; Q3W, every 3 weeks.

ENHERTU®

# Efficacy Endpoints

DESTINY-Gastric02 (ESMO 2021)

Daiichi-Sankyo

| | Patients (N = 79) |
|---|---|
| **Confirmed ORR[a], n (%)** | **30 (38)**<br>(95% CI, 27.3-49.6) |
| **Confirmed best overall response, n (%)** | |
| CR | **3 (3.8)** |
| PR | **27 (34.2)** |
| SD | **34 (43.0)** |
| PD | **13 (16.5)** |
| Not evaluable | **2 (2.5)** |
| **Median DOR,[b] months** | 8.1 (95% CI, 4.1-NE) |
| **Confirmed DCR[c], n (%)** | 64 (81.0)<br>(95% CI, 70.6-89.0) |
| **Median TTR, months** | 1.4 (95% CI, 1.4-2.6) |
| **Median PFS,[d] months** | 5.5 (95% CI, 4.2-7.3) |
| **Median follow up, months** | 5.7 (range, 0.7-15.2) |

Cutoff date: April 9, 2021.

[a]Primary endpoint. [b]Secondary endpoint analysis based on responders (n=30); 21 patients were censored (reasons: initiating new anticancer therapy, adequate tumor assessment no longer available, and ongoing without occurrence of progressive disease or death). [c]Exploratory endpoint. [d]Secondary endpoint analysis in the full analysis set based on 42 events (36 PD, 6 deaths).

BOR, best overall response; CR, complete response; DCR, disease control rate; mo, months; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

ENHERTU®

# Study Design

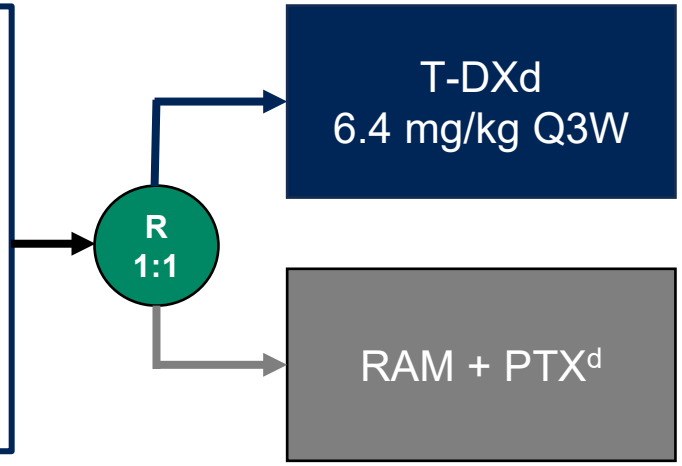
DESTINY-Gastric04 (ASCO2025)

Daiichi-Sankyo

## DESTINY-Gastric04: A Global, Multicenter, Randomized, Phase 3 Trial (NCT04704934)

**Patient Population**

- HER2+ (IHC 3+ or IHC 2+/ISH+)[a] GC/GEJA
- HER2 status confirmed locally or centrally[b] on a recent biopsy obtained after progression on trastuzumab
- ECOG PS 0 or 1
- No clinically active CNS metastases[c]




**Primary Endpoint**

- OS

**Secondary Endpoints**

- PFS (INV)[e]
- Confirmed ORR (INV)[e]
- DCR (INV)[e]
- DOR (INV)[e]
- Safety

**Exploratory Endpoints**

- PROs[f]

**Stratification factors**

- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excluding mainland China] vs Western Europe vs mainland China/rest of world)
- Time to progression on 1L therapy (<6 months vs ≥6 months)

1L, first-line; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-Dimension, 5-Level; FACT-Ga, Functional Assessment of Cancer Therapy-gastric; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; PTX, paclitaxel; Q3W, every 3 weeks; R, randomization; RAM, ramucirumab; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.

[a]As classified by the 2017 ASCO-CAP guidelines for HER2 testing in gastroesophageal adenocarcinoma. [b]Study protocol originally mandated HER2 status be determined centrally but was later amended to allow local determination. [c]Clinically active CNS metastases were defined as being untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants. Patients with clinically inactive CNS metastases could be enrolled. [d]RAM administered as 8 mg/kg on days 1 and 15 of each 28-day cycle and PTX administered as 80 mg/m$^2$ on days 1, 8, and 15 of each 28-day cycle. [e]Determined by investigator-based assessment on RECIST v1.1. [f]Based on EORTC EQ-5D-5L VAS and FACT-Ga subscales.

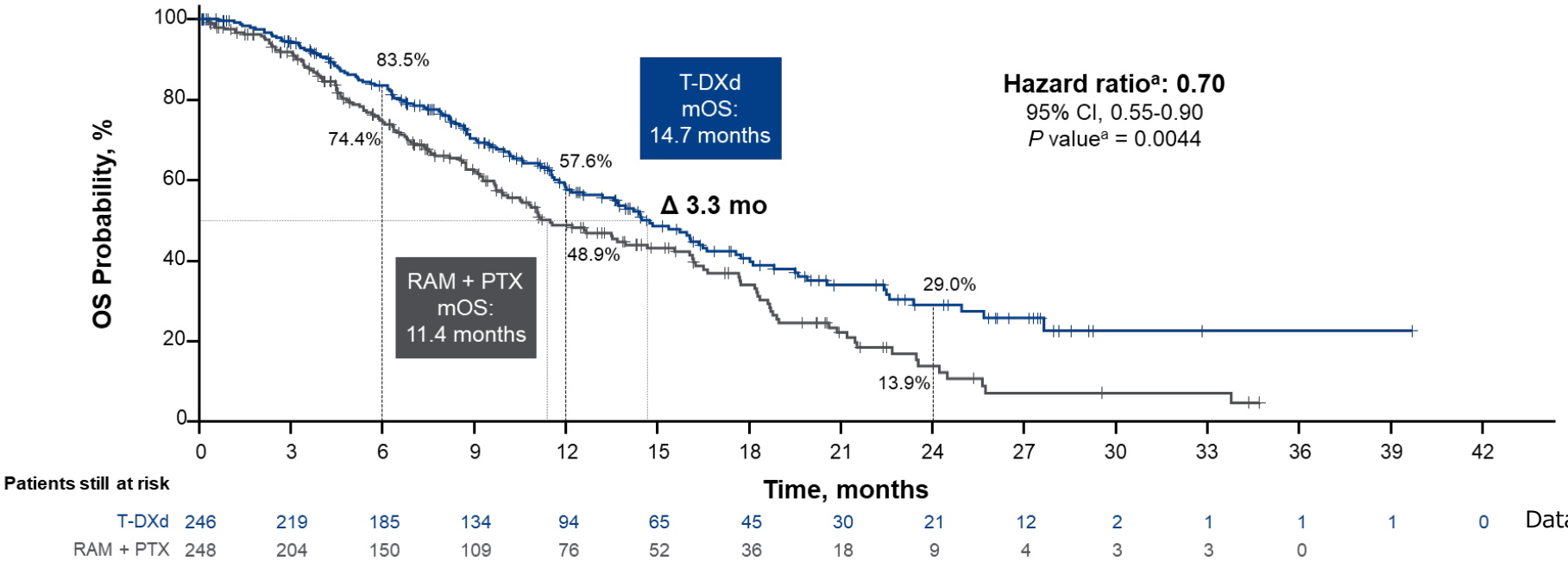
ENHERTU®

# For Earlier Treatment of HER2 Positive GC

DESTINY-Gastric04 Ph3 (ASCO 2025)

Daiichi-Sankyo

## DESTINY-Gastric04 establishes ENHERTU® as global 2L HER2+ SOC for patients with HER2+ mGC/GEJA




Data cutoff: October 24, 2024

- ENHERTU® demonstrated mOS 14.7 mo with 30% reduction in risk of death compared with ramucirumab plus paclitaxel combination therapy
- Improvement in mPFS (6.7 mo vs 5.6 mo), cORR (44.3% vs 29.1%), DCR (91.9% vs 75.9%), and mDOR (7.4 mo vs 5.3 mo) was also observed
- No new safety signals were identified. ILD/pneumonitis events in ENHERTU® arm were mainly low-grade, with no grade 4 or 5 events. Adjudicated as drug-related ILD occurred in 13.9 % (grade 3: 0.4%) of patients treated with ENHERTU®

ASCO: American Society of Clinical Oncology, CI: confidence interval, cORR: confirmed objective response rate, DCR: disease control rate, GC: gastric cancer, GEJA: gastroesophageal junction adenocarcinoma, ILD: interstitial lung disease, mDOR: median duration of response, mGC: metastatic gastric cancer, mo: month(s), mOS: median overall survival, mPFS: median progression free survival, OS: overall survival

aTwo-sided *P* value from stratified log-rank test and stratified Cox proportional hazards model adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+).

ENHERTU®

# Study Design

DESTINY-Lung01 (ESMO 2021)

Daiichi-Sankyo

## Multicenter, international, 2-cohort phase 2 trial (NCT03505710)

### Key eligibility criteria

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]



Cohort 1: HER2-overexpressing[c] (IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg q3w
N = 49

Cohort 1a: HER2-overexpressing[c] (IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg q3w
N = 41



**Cohort 2: *HER2*-mutated T-DXd 6.4 mg/kg q3w N = 42**

**Cohort 2 expansion: *HER2*-mutated T-DXd 6.4 mg/kg q3w N = 49**

### Primary end point

- Confirmed ORR by ICR[d]

### Secondary end points

- DOR
- PFS
- OS
- DCR
- Safety

### Exploratory end point

- Biomarkers of response

**Data cutoff: May 3, 2021**

- 91 patients with *HER2*m NSCLC were enrolled and treated with T-DXd
- 15 patients (16.5%) remain on treatment to date
- 76 patients (83.5%) discontinued, primarily for progressive disease (37.4%) and adverse events (29.7%)

[a]Patients with asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll [b]*HER2* mutation documented solely from a liquid biopsy could not be used for enrolment [c]HER2 overexpression without known *HER2* mutation was assessed by local assessment of archival tissue and centrally confirmed [d]Per RECIST v1.1

DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

ENHERTU®

# Confirmed ORR, Best Overall Response, and DoR

DESTINY-Lung01 (ESMO 2021)

Daiichi-Sankyo

| | Patients (N = 91) |
|---|---|
| **Confirmed ORR[a], n (%)** | **50 (54.9)**<br>(95% CI, 44.2-65.4) |
| **Best overall response, n (%)** | |
| CR | **1 (1.1)** |
| PR | **49 (53.8)** |
| SD | **34 (37.4)** |
| PD | **3 (3.3)** |
| Not evaluable | **4 (4.4)** |
| **DCR, n (%)** | 84 (92.3)<br>(95% CI, 84.8-96.9) |
| **Median DoR, months** | 9.3 (95% CI, 5.7-14.7) |
| **Median follow up, months** | 13.1 (range, 0.7-29.1) |

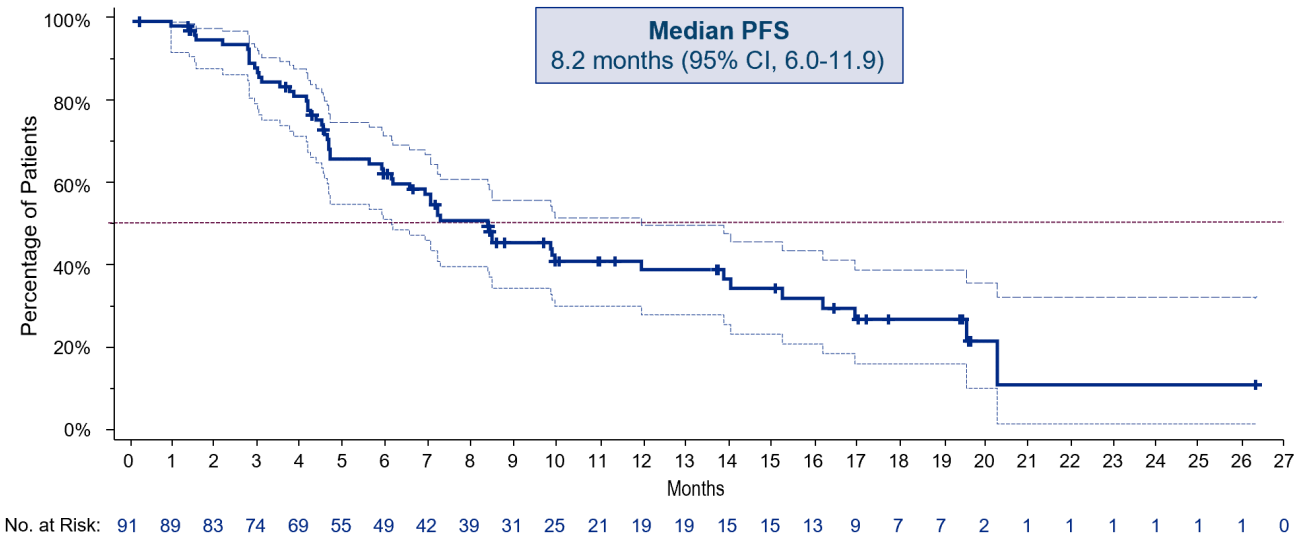
[a]Primary endpoint

CR, complete response; DoR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

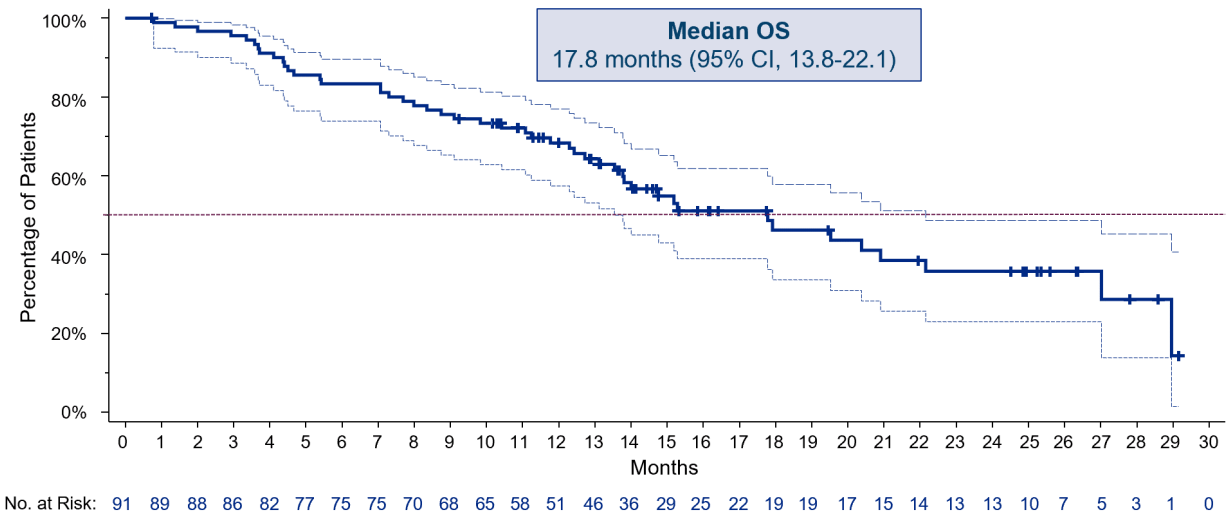
ENHERTU®

# Progression-free Survival and Overall Survival

DESTINY-Lung01 (ESMO 2021)




Median follow-up was 13.1 months (range, 0.7-29.1)
PFS assessed by ICR using RECIST v1.1., the median was based on Kaplan-Meier estimate, and 95% CI for median was computed using the Brookmeyer-Crowley method, and dashed lines indicate the 95% CI. Of 91 patients, 41 had progressive disease and 15 had died by the data cutoff date. Data for 35 patients were censored as indicated by tick marks; patients were censored if they discontinued treatment.




Median follow-up was 13.1 months (range, 0.7-29.1 months)
Dashed lines indicate the 95% CI. Of 91 patients, 47 had died by the data cutoff date. Data for 44 patients were censored as indicated by tick marks; patients were censored if they discontinued treatment.

ENHERTU®

# Study Design

DESTINY-Lung02 (WCLC 2023)

Daiichi-Sankyo

Blinded, randomized, multicenter, international, noncomparative, phase 2 trial (NCT04644237)

## Background

- T-DXd 5.4 mg/kg and 6.4 mg/kg showed robust antitumor activity in multiple cancer types; however, T-DXd 5.4 mg/kg has not been evaluated in patients with previously treated *HER2*-mutant (*HER2*m) mNSCLC
- DESTINY-Lung02 assessed the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with *HER2*m mNSCLC
  - In the interim analysis, T-DXd showed deep and durable responses and an acceptable and generally manageable safety profile[1]
- Herein, we report the **primary analysis results** of DESTINY-Lung02

## Statistical considerations

- Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper-Pearson CI of confirmed ORR of a T-DXd dose with the benchmark ORR of 26.4% (upper limit of the ORR 95% CI in the ramucirumab plus docetaxel arm of the REVEL trial)[2]
- The study was not powered to statistically compare between arms

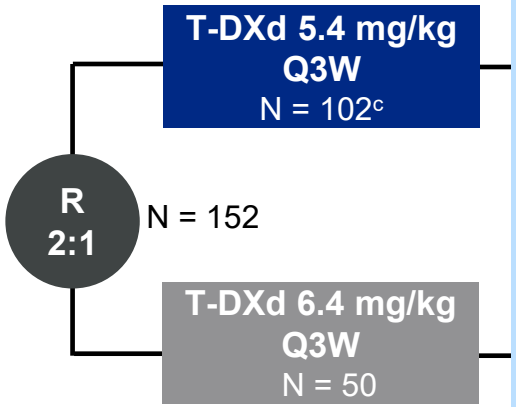
**Key Eligibility Criteria[a]**

- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

**Stratification Factor:**

- Prior anti–PD-(L)1 treatment

## Study Design




**Primary Endpoint**

- Confirmed ORR by BICR

**Secondary Endpoints**

- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

***Patients and investigators were blinded to the dose level***

**Primary analysis data cutoff: 23 December 2022**

BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator assessment; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan.
[a]Patients with stable baseline brain metastases (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) were eligible. [b]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [c]1 patient randomly assigned to the T-DXd 5.4 mg/kg arm did not receive treatment as the patient discontinued due to COVID-19 before cycle 1 day 1.

1. Goto K et al. *Annals of Oncol*. 2022;33 (suppl_7): S808-S869 2. Garon EB et al. *Lancet*. 2014;384:665-73.

ENHERTU®

# Baseline Characteristics and Efficacy Summary

DESTINY-Lung02 (WCLC 2023)

Daiichi-Sankyo

## Baseline Characteristics

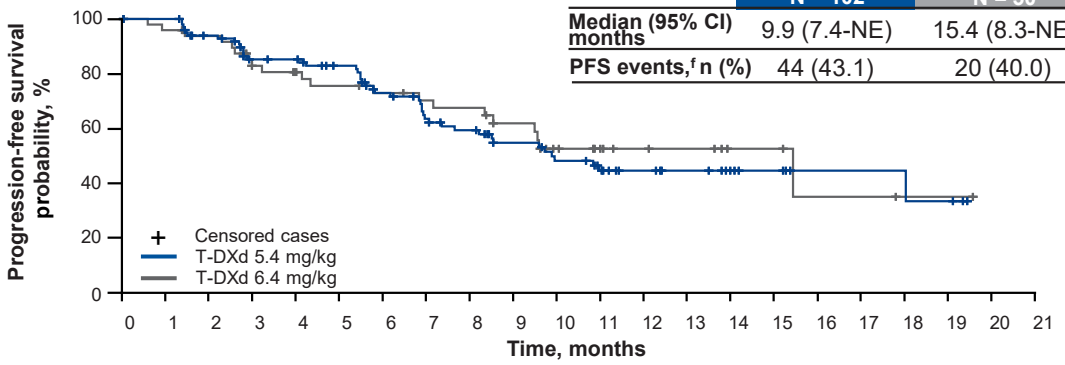
In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:

- **Median age** was 59.4 years (range, 31-84) and 61.3 years (range, 28-86)
- Most patients were **female** (63.7% and 68.0%), **from Asia** (61.8% and 60.0%), had **never smoked** (53.9% and 58.0%), and **received prior anti–PD-(L)1 therapy** (73.5% and 78.0%)
- *HER2* mutations were primarily in the **kinase domain** (97.1% and 100%)
- **Baseline CNS metastasis** was present in 34.3% and 44.0% of patients
- **Median prior lines of treatment** was 2 (range, 1-12) and 2 (range, 1-7)

| Efficacy summary | T-DXd 5.4 mg/kg N = 102 | T-DXd 6.4 mg/kg N = 50 |
|---|---|---|
| **Confirmed ORR,[a] n (%)** [95% CI] | **50 (49.0)** [39.0-59.1] | **28 (56.0)** [41.3-70.0] |
| CR \| PR | 1 (1.0) \| 49 (48.0) | 2 (4.0) \| 26 (52.0) |
| SD \| PD | 45 (44.1) \| 4 (3.9) | 18 (36.0) \| 2 (4.0) |
| Non-evaluable[b] | 3 (2.9) | 2 (4.0) |
| **DCR,[c] n (%)** [95% CI] | 95 (93.1) [86.4-97.2] | 46 (92.0) [80.8-97.8] |
| **Median DoR,[d,e] months (95% CI)** | 16.8 (6.4-NE) | NE (8.3-NE) |
| **Median TTIR,[d] months (range)** | 1.8 (1.2-7.0) | 1.6 (1.2-11.2) |
| **Median follow-up, months (range)** | 11.5 (1.1-20.6) | 11.8 (0.6-21.0) |

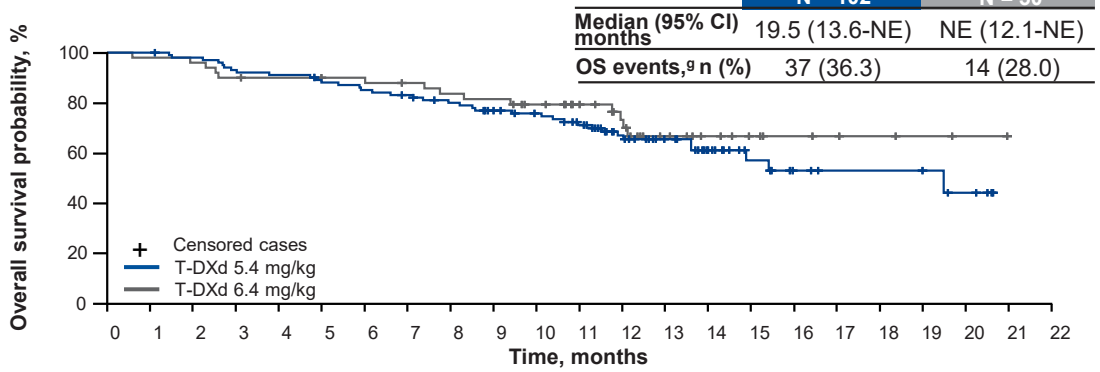
**PFS**

| | T-DXd 5.4 mg/kg N = 102 | T-DXd 6.4 mg/kg N = 50 |
|---|---|---|
| Median (95% CI) months | 9.9 (7.4-NE) | 15.4 (8.3-NE) |
| PFS events,[f] n (%) | 44 (43.1) | 20 (40.0) |




**OS**

| | T-DXd 5.4 mg/kg N = 102 | T-DXd 6.4 mg/kg N = 50 |
|---|---|---|
| Median (95% CI) months | 19.5 (13.6-NE) | NE (12.1-NE) |
| OS events,[g] n (%) | 37 (36.3) | 14 (28.0) |



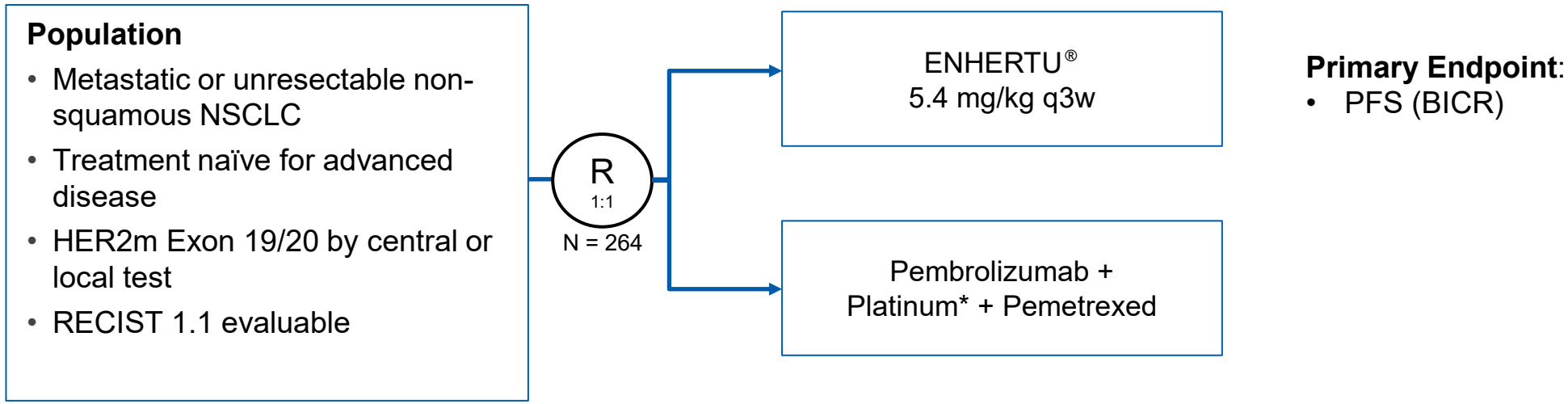

BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTIR, time to initial response. [a]Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1. [b]3 patients were non-evaluable at 5.4 mg/kg (1 patient never received treatment due to COVID-19; 2 patients discontinued before first tumor assessment); 2 patients were non-evaluable at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment). [c]Proportion of patients with confirmed CR, PR, or SD assessed by BICR. [d]Assessed by BICR. [e]60.0% and 75.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored. [f]56.9% and 60.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored. [g]63.7% and 72.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored.

# Study Design

DESTINY-Lung04 (WCLC 2026)

## DESTINY-Lung04

Ph3 study of T-DXd as 1L treatment of NSCLC harboring HER2 exon 19 or 20 mutations




**Primary Endpoint**:
- PFS (BICR)

Prespecified subgroups include: HER2 co-amplification; PD-L1 status (≥1%)
* Investigator choice of cisplatin or carboplatin

ENHERTU®

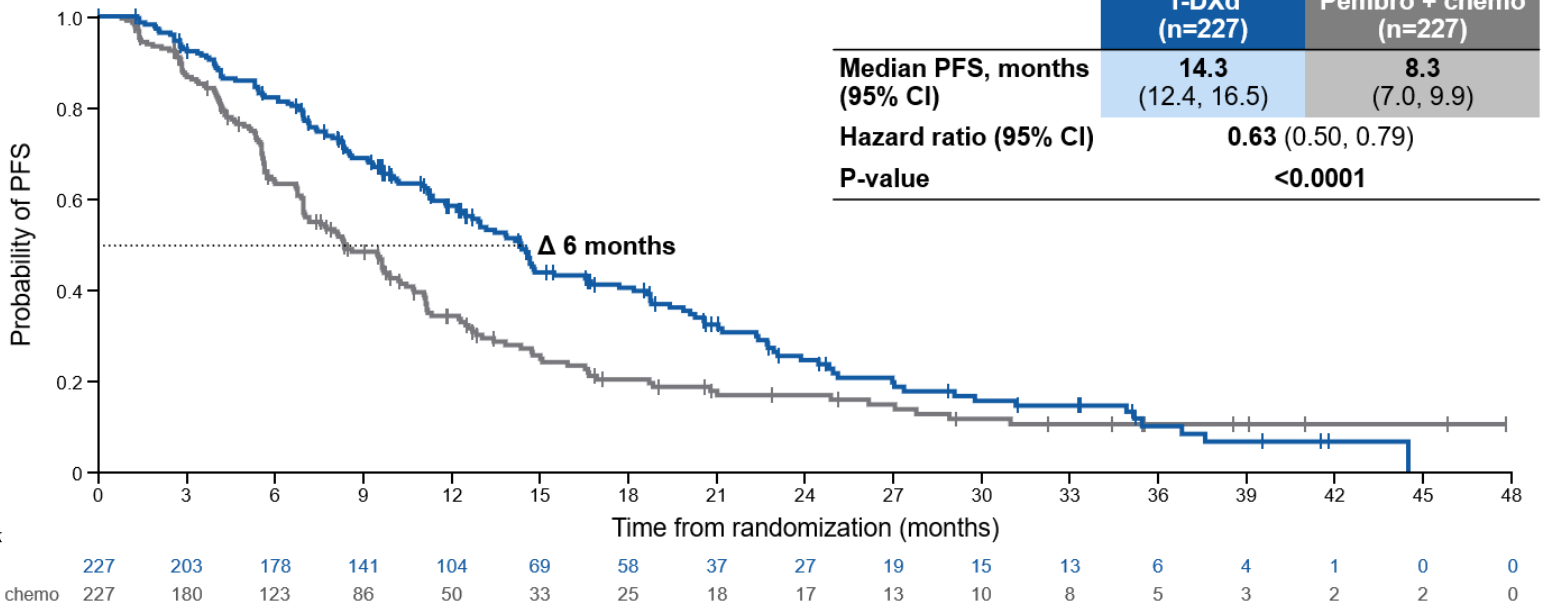
# Expand Enhertu® into 1L HER2 mutant NSCLC

DESTINY-Lung04 Ph3 (WCLC 2026)

Daiichi-Sankyo

## DESTINY-Lung04 demonstrated a statistically significant and clinically meaningful PFS improvement vs. SOC pembrolizumab + doublet chemo

### PFS (BICR): primary endpoint




| | T-DXd (n=227) | Pembro + chemo (n=227) |
|---|---|---|
| Median PFS, months (95% CI) | **14.3** (12.4, 16.5) | **8.3** (7.0, 9.9) |
| Hazard ratio (95% CI) | **0.63** (0.50, 0.79) | |
| P-value | **<0.0001** | |

Data cutoff: June 9, 2026

- First and only randomized Ph3 trial to demonstrate superior efficacy over pembrolizumab + doublet chemo in the 1L setting.
- Supports Enhertu® as a novel, future 1L treatment option for patients with HER2 mutant NSCLC
- Safety profile was consistent with known profile with no new safety concerns
- DESTINY-Lung04 demonstrated a positive risk-benefit profile
- Data will be shared with global regulatory authorities

BICR: blinded independent central review, CI: confidence interval, NSCLC: non-small cell lung cancer, OS: overall survival, PFS: progression-free survival, SOC: standard of care, T-DXd: trastuzumab deruxtecan

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# study design

DESTINY-Lung05 (WCLC 2025)

Daiichi-Sankyo

## Patient population*

- Aged ≥18 years
- Metastatic nonsquamous NSCLC
- Locally or centrally confirmed activating *HER2* exon 19 or 20 mutation†
- Disease progression on or after ≥1 prior anticancer therapy‡
- RECIST 1.1-evaluable lesion
- WHO or ECOG performance status 0–1
- Patients with previously treated CNS metastases were allowed if asymptomatic / neurologically stable§

→

**T-DXd 5.4 mg/kg every 3 weeks**

Treatment continued until disease progression per RECIST 1.1, unacceptable toxicities, or trial discontinuation

→

## Key endpoints

**Primary:** Confirmed ORR by ICR¶

**Secondary:**

- Confirmed ORR by INV¶
- DOR, DCR, PFS by ICR/INV¶
- OS
- CNS-PFS by ICR¶
- Safety

**Exploratory:**

- Best percentage change from baseline in the sum of diameters of target lesions

*Approximately 80 patients were planned for enrollment, with 72 patients enrolled at data cutoff; †based on a pre-existing tissue test result from a local laboratory or prospective central confirmation of the HER2 tissue mutation test result (retrospective central confirmation was performed for those enrolled based on existing local HER2 mutation results); ‡treatment with prior HER2-directed therapy, except for pan-HER class tyrosine kinase inhibitors, and prior treatment with an antibody-drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor were not allowed; §patients with asymptomatic CNS disease at baseline were eligible if they did not need ongoing corticosteroid or anticonvulsant treatments, had recovered from acute radiotherapy toxicity, and ≥2 weeks had passed since whole-brain radiotherapy; ¶per RECIST 1.1

CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; INV, investigator assessed; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization

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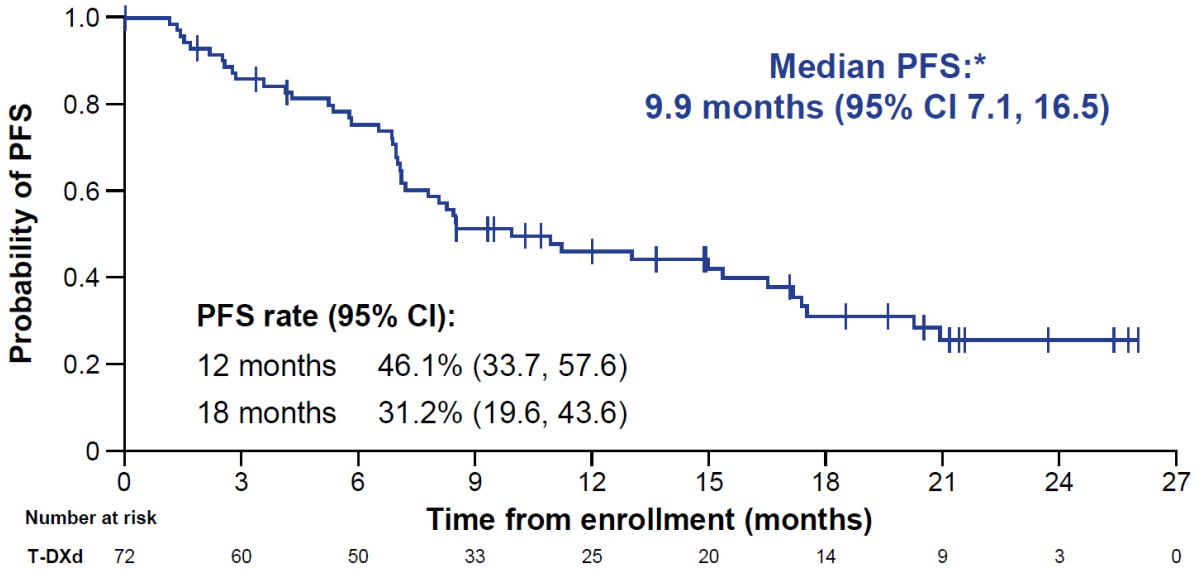
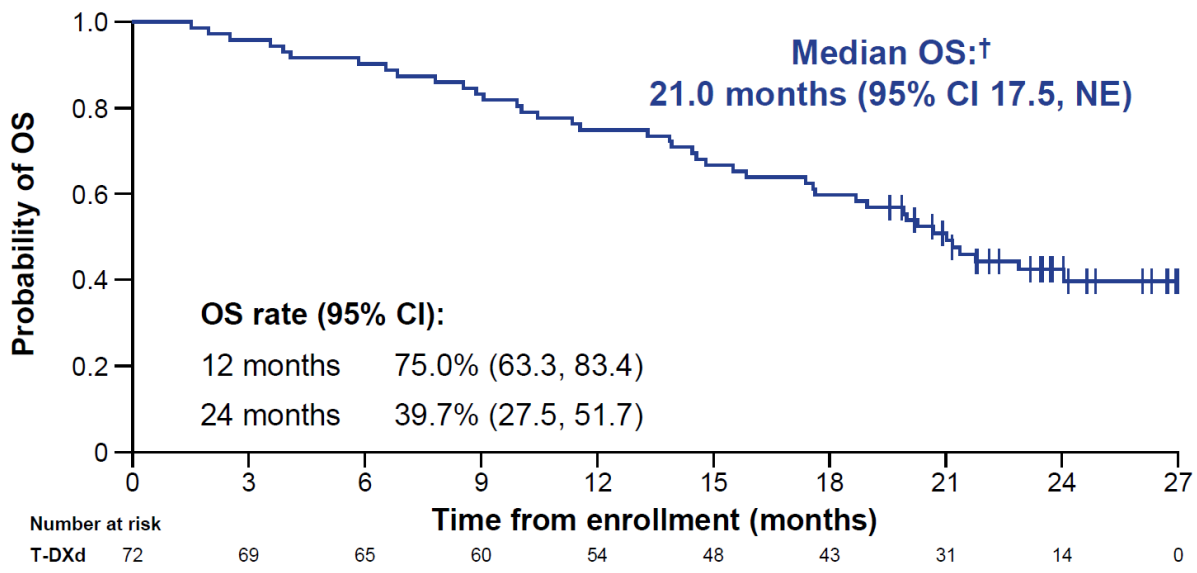
# Kaplan-Meier estimates of PFS by ICR and OS

DESTINY-Lung05(WCLC 2025)




Symbols indicate a censored observation. PFS was assessed by ICR per RECIST 1.1 *Progression events that did not occur within two missed visits of the last evaluable assessment or enrollment date were censored; †patients not known to have died at the time of analysis were censored at the last recorded date on which they were known to be aliveCI, confidence interval; ICR, independent central review; NE, not evaluable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

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# study design

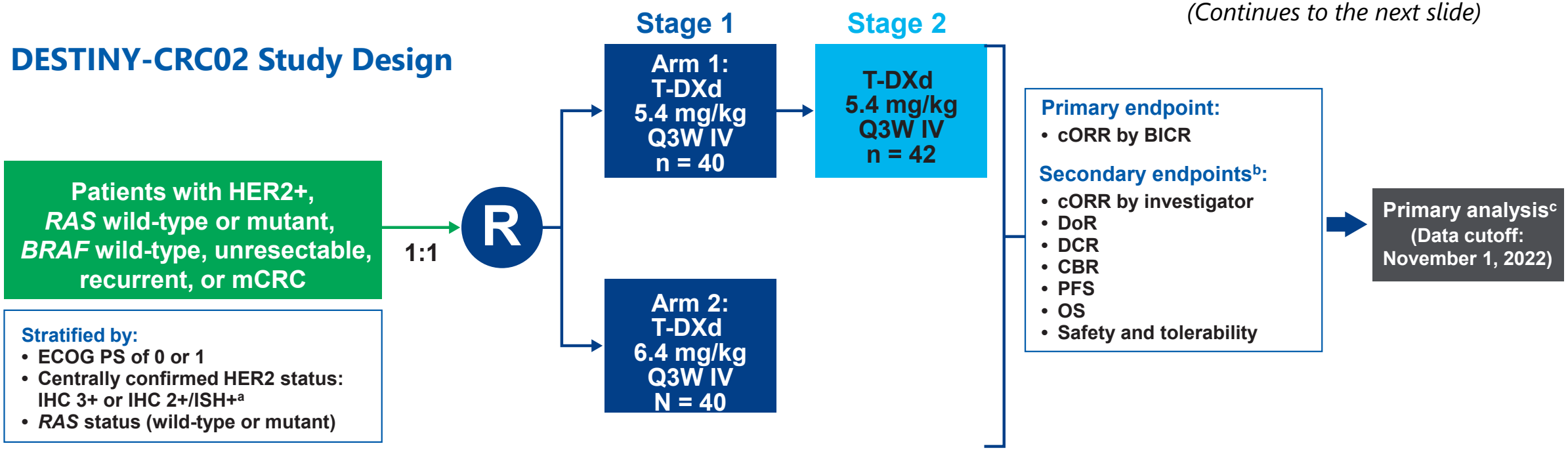
DESTINY-CRC02 (ASCO2023)

Daiichi-Sankyo

- DESTINY-CRC02 is a randomized, 2-stage, 2-arm, multicenter, global, Ph2 study in patients with mCRC

*(Continues to the next slide)*

## DESTINY-CRC02 Study Design




**This study was not powered to statistically compare the two arms.**

**Source: Raghav et al., ASCO 2023, Oral Presentation #3501**

BICR, blinded independent central review; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RAS, rat sarcoma; T-DXd, trastuzumab deruxtecan. Both investigators and patients were blind to treatments.

[a]HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (IUO). [b]Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. [c]Primary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

ENHERTU®

# ENHERTU® showed promising efficacy in HER2+ mCRC

## - Primary analysis of Ph2 DESTINY-CRC02 (ASCO2023)

*(Continued)*

- Promising antitumor activity was observed at both 5.4 mg/kg and 6.4 mg/kg doses

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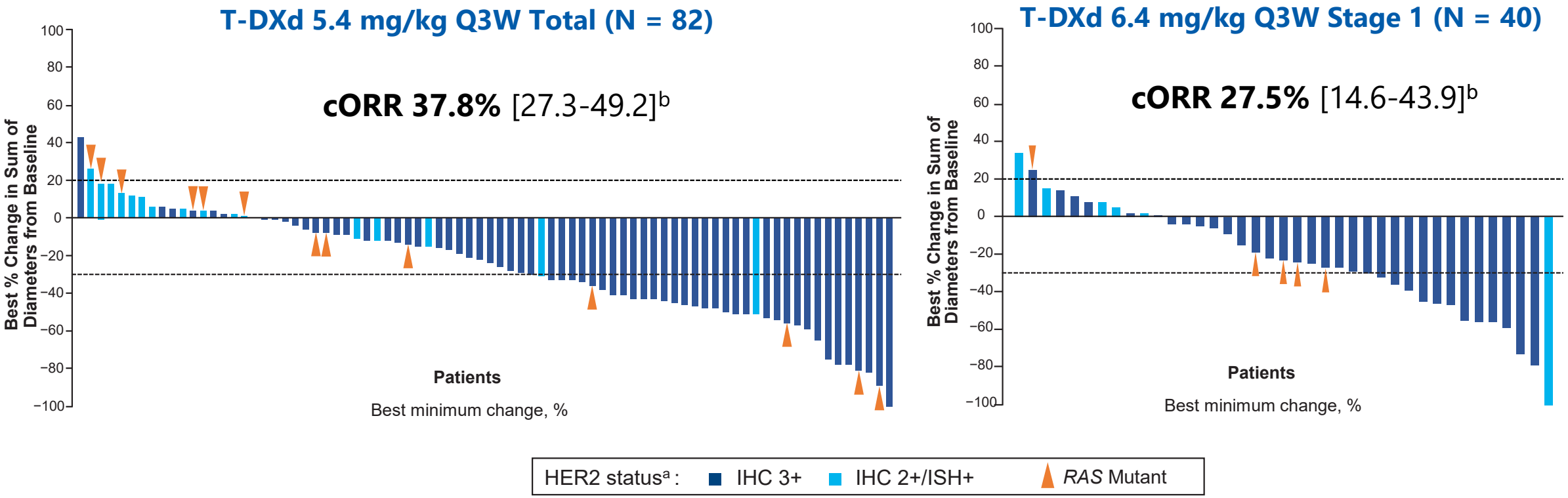


**Source: Raghav et al., ASCO 2023, Oral Presentation #3501**

cORR, confirmed objective response rate; IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; Q3W, every 3 weeks; RAS, rat sarcoma; T-DXd, trastuzumab deruxtecan. Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.

[A] HER2 status was assessed by central laboratory. [b] 95% confidence interval.

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# DESTINY-PanTumor02 interim results showed potential of ENHERTU® as a new treatment option in HER2-exp tumors

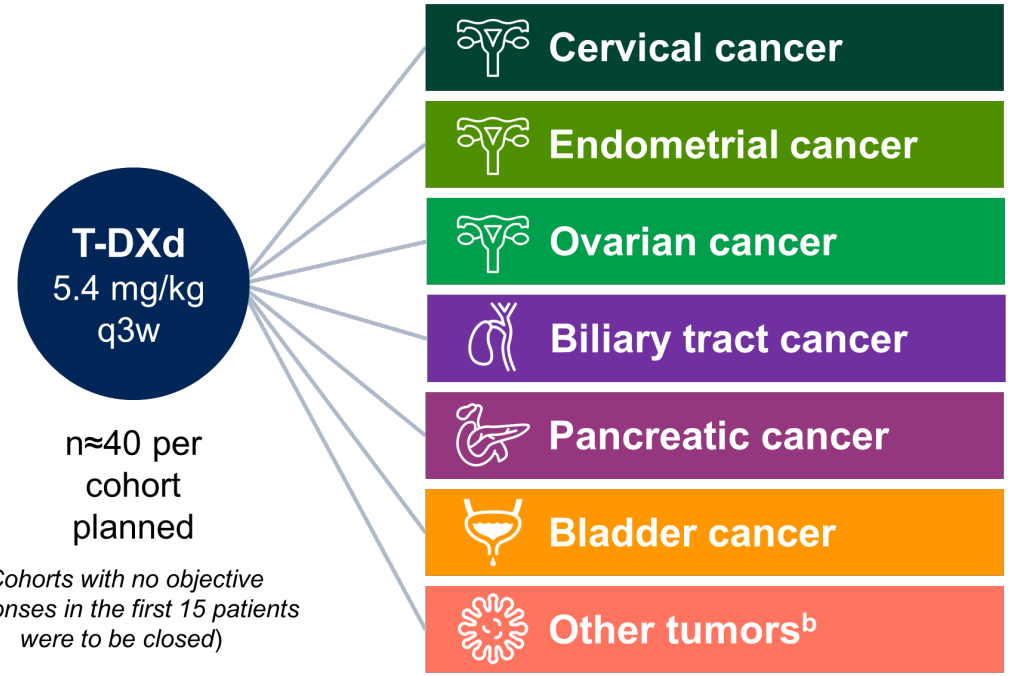
ASCO 2023

Daiichi-Sankyo

- DESTINY-PanTumor02 is an open-label, multicenter study, in HER2-expressing advanced solid tumors not eligible for curative therapy

*(Continues to the next slide)*

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Herceptest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1




n≈40 per cohort planned

(*Cohorts with no objective responses in the first 15 patients were to be closed*)

**Primary endpoint**

- Confirmed ORR (investigator)[c]

**Secondary endpoints**

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

**Data cut-off for analysis:**

- Nov 16, 2022

**Source: Meric-Bernstam et al., ASCO 2023, Oral Presentation #3000**

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. [c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1. 2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization. 1. Hofmann M, et al. Histopathology 2008;52(7):797–805.

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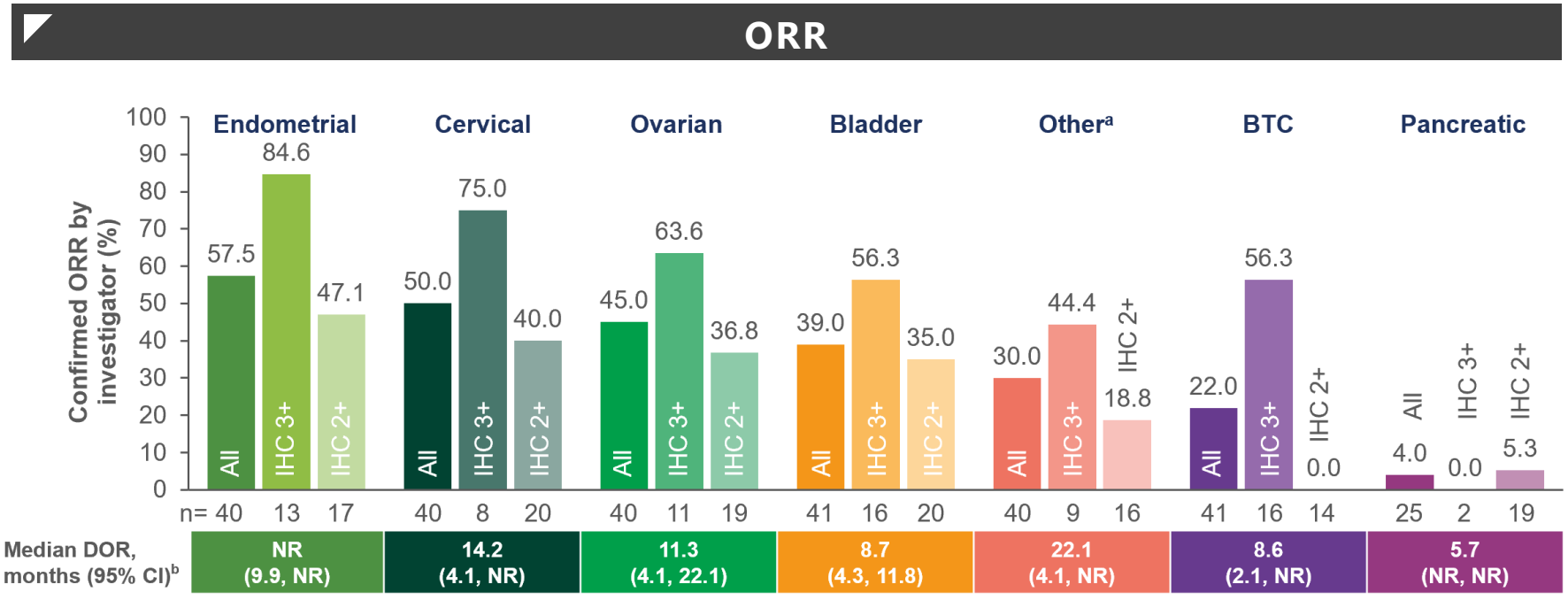
# DESTINY-PanTumor02

ESMO 2023

Daiichi-Sankyo

## DESTINY-PanTumor02 demonstrated clinically meaningful and durable responses across a broad range of HER2 expressing advanced solid tumors




| | All patients (N=267) | IHC 3+ (n=75) | IHC 2+ (n=125) |
|---|---|---|---|
| ORR, % (95% CI) | 37.1 (31.3, 43.2) | 61.3 (49.4, 72.4) | 27.2 (19.6, 35.9) |
| Median DOR, months (95% CI)[b] | 11.3 (9.6, 17.8) | 22.1 (9.6, NR) | 9.8 (4.3, 12.6) |

- All patients: ORR 37.1% and median DOR 11.3months
- Patients with IHC 3+: ORR 61.3% and median DOR 22.1months
- Durable responses led to clinically meaningful PFS & OS
- The safety profile was consistent with the known profile with grade 5 ILD 1.1%
- **Plan to file** with DESTINY-PanTumor02 study data **within FY2023** for a potential **tumor agnostic therapy** in previously treated patients with HER2 expressing solid tumors in the US

Analysis of ORR by investigator was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. a Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer; b includes patients with a confirmed objective response only,

BTC: biliary tract cancer, CI: confidence interval, DOR: duration of response, IHC: immunohistochemistry, ILD: interstitial lung disease, NR: not reached, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, T-DXd: trastuzumab deruxtecan (ENHERTU®)

DATROWAY®

# TROPION-Lung01: Study design

ESMO 2023

Daiichi-Sankyo

## TROPION-Lung01 Study Design

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

### Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

**Without actionable genomic alterations[a]**

- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

**With actionable genomic alterations**

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

**Dato-DXd**
6 mg/kg Q3W
(N=299)

**Docetaxel**
75 mg/m$^2$ Q3W
(N=305)

### Dual Primary Endpoints

- PFS by BICR
- OS

### Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

**Stratified by:** histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

Enrollment period: 19 February 2021 to 7 November 2022.
BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.
[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs non-squamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.

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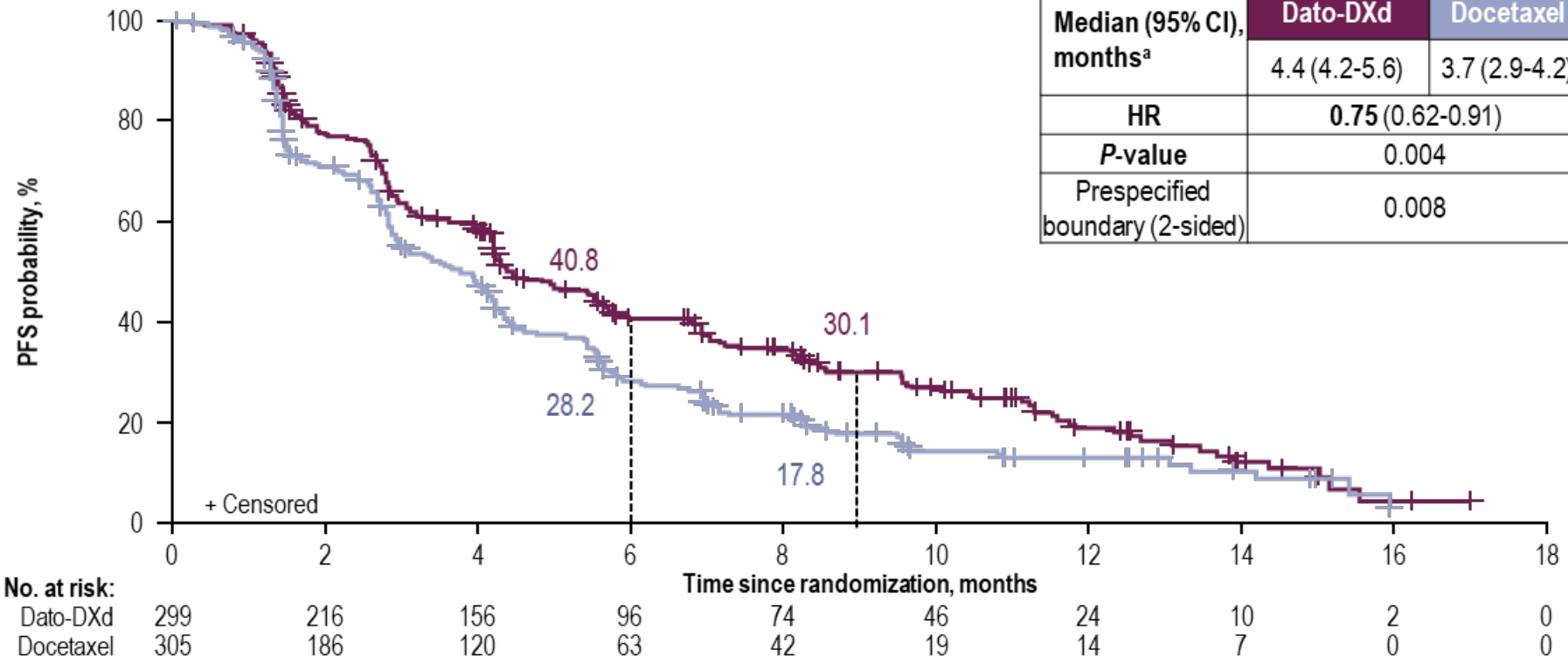
# TROPION-Lung01: PFS (ITT)

ESMO 2023

Daiichi-Sankyo

## Progression-Free Survival: ITT

| Median (95% CI), months[a] | Dato-DXd | Docetaxel |
|---|---|---|
| | 4.4 (4.2-5.6) | 3.7 (2.9-4.2) |
| HR | **0.75** (0.62-0.91) | |
| *P*-value | 0.004 | |
| Prespecified boundary (2-sided) | 0.008 | |




| | Dato-DXd | Docetaxel |
|---|---|---|
| **ORR** (95% CI), %[b] | **26.4** (21.5-31.8) | **12.8** (9.3-17.1) |
| **DOR** (95% CI), mo | **7.1** (5.6-10.9) | **5.6** (5.4-8.1) |

CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Median PFS follow-up was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and docetaxel, respectively. [b]Included 4 CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

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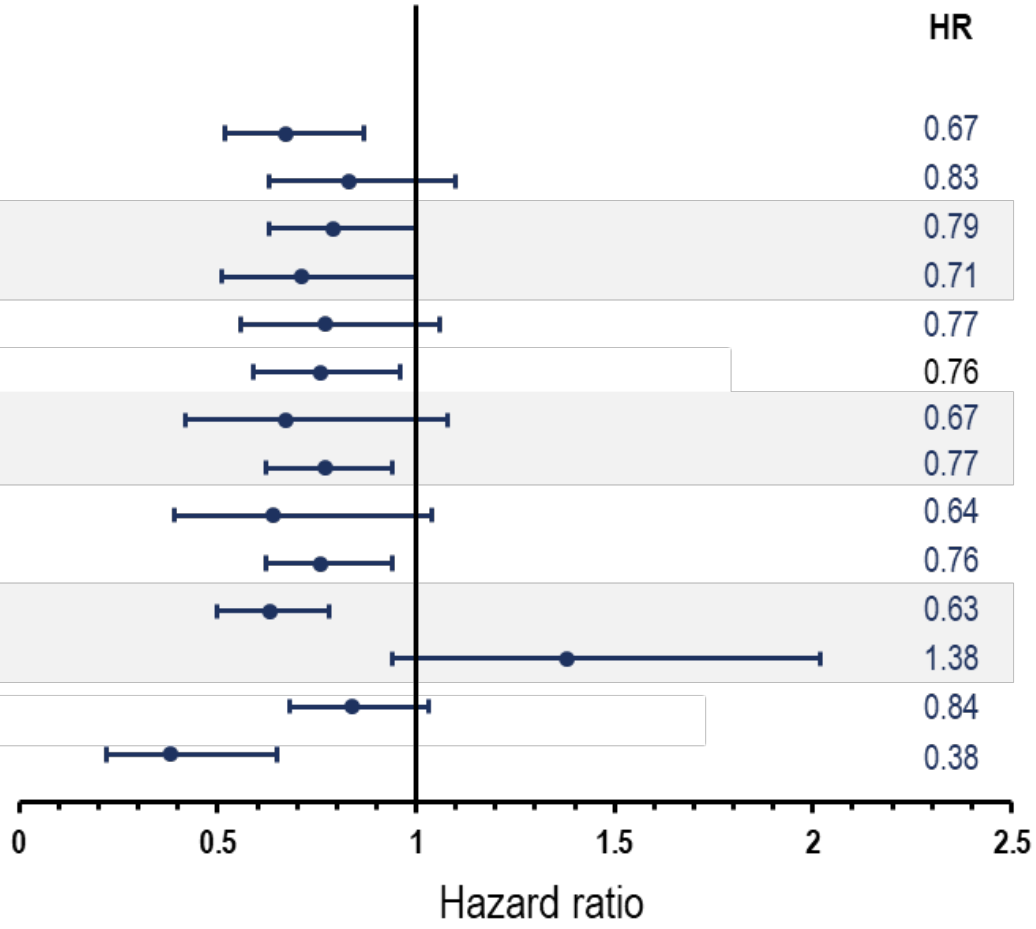
# TROPION-Lung01: PFS in key subgroups

ESMO 2023

Daiichi-Sankyo

## PFS in Key Subgroups

| | | Events/n | | HR |
|---|---|---|---|---|
| | | Dato-DXd | Docetaxel | |
| Age at randomization | <65 years | 118/162 | 115/155 | 0.67 |
| | ≥65 years | 95/137 | 103/150 | 0.83 |
| Sex | Male | 136/183 | 158/210 | 0.79 |
| | Female | 77/116 | 60/95 | 0.71 |
| Race | Asian | 76/119 | 82/120 | 0.77 |
| | Non-Asian | 131/172 | 129/177 | 0.76 |
| Smoking status | Never | 36/61 | 33/52 | 0.67 |
| | Former/current | 177/238 | 184/251 | 0.77 |
| Brain metastasis at baseline | With | 33/50 | 31/47 | 0.64 |
| | Without | 180/249 | 187/258 | 0.76 |
| Histology | Non-squamous | 156/229 | 168/232 | 0.63 |
| | Squamous | 57/70 | 50/73 | 1.38 |
| Actionable genomic alterations[a] | Absent | 189/252 | 184/255 | 0.84 |
| | Present | 24/47 | 34/50 | 0.38 |




[a]Regardless of histology.

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# TROPION-Lung01: PFS by histology

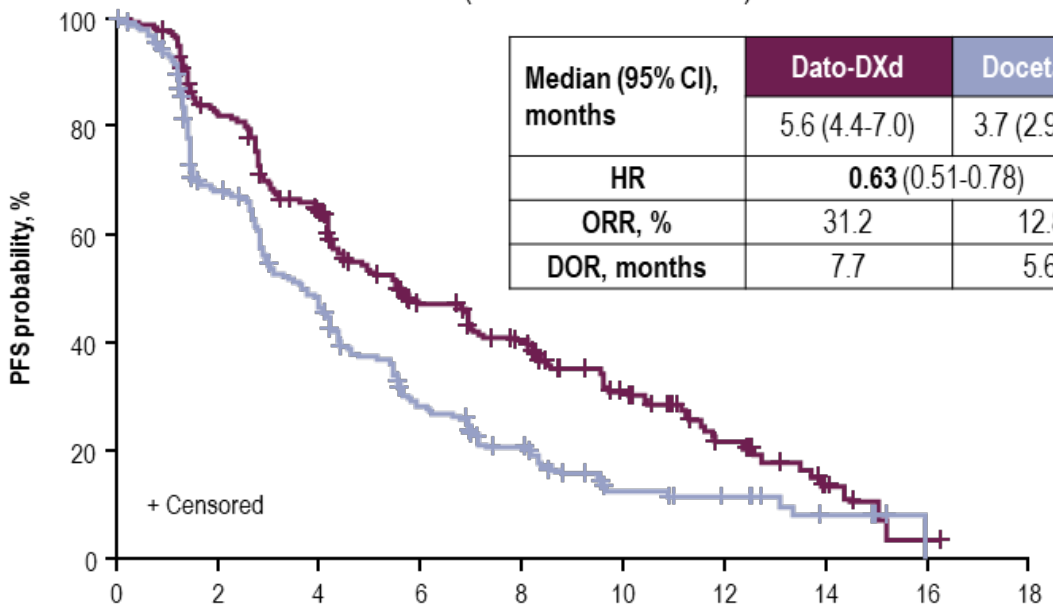
ESMO 2023

Daiichi-Sankyo

## PFS by Histology

### Non-squamous

(with and without AGAs)

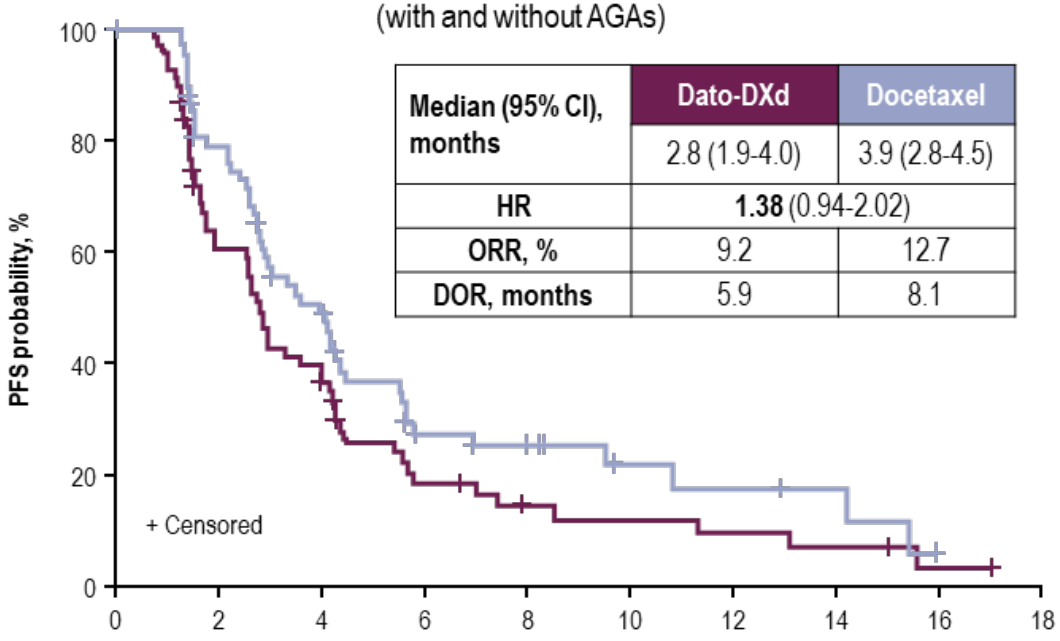



| Median (95% CI), months | Dato-DXd | Docetaxel |
|---|---|---|
| | 5.6 (4.4-7.0) | 3.7 (2.9-4.2) |
| HR | **0.63** (0.51-0.78) | |
| ORR, % | 31.2 | 12.8 |
| DOR, months | 7.7 | 5.6 |

| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 229 | 178 | 134 | 86 | 68 | 41 | 20 | 7 | 1 | 0 |
| Docetaxel | 232 | 135 | 90 | 50 | 32 | 14 | 10 | 4 | 0 | 0 |

### Squamous

(with and without AGAs)




| Median (95% CI), months | Dato-DXd | Docetaxel |
|---|---|---|
| | 2.8 (1.9-4.0) | 3.9 (2.8-4.5) |
| HR | **1.38** (0.94-2.02) | |
| ORR, % | 9.2 | 12.7 |
| DOR, months | 5.9 | 8.1 |

| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 70 | 38 | 22 | 10 | 6 | 5 | 4 | 3 | 1 | 0 |
| Docetaxel | 73 | 51 | 30 | 13 | 10 | 5 | 4 | 3 | 0 | 0 |

**PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)**

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response ratel PFS, progression-free survival.
Squamous subset included 3 patients with AGAs

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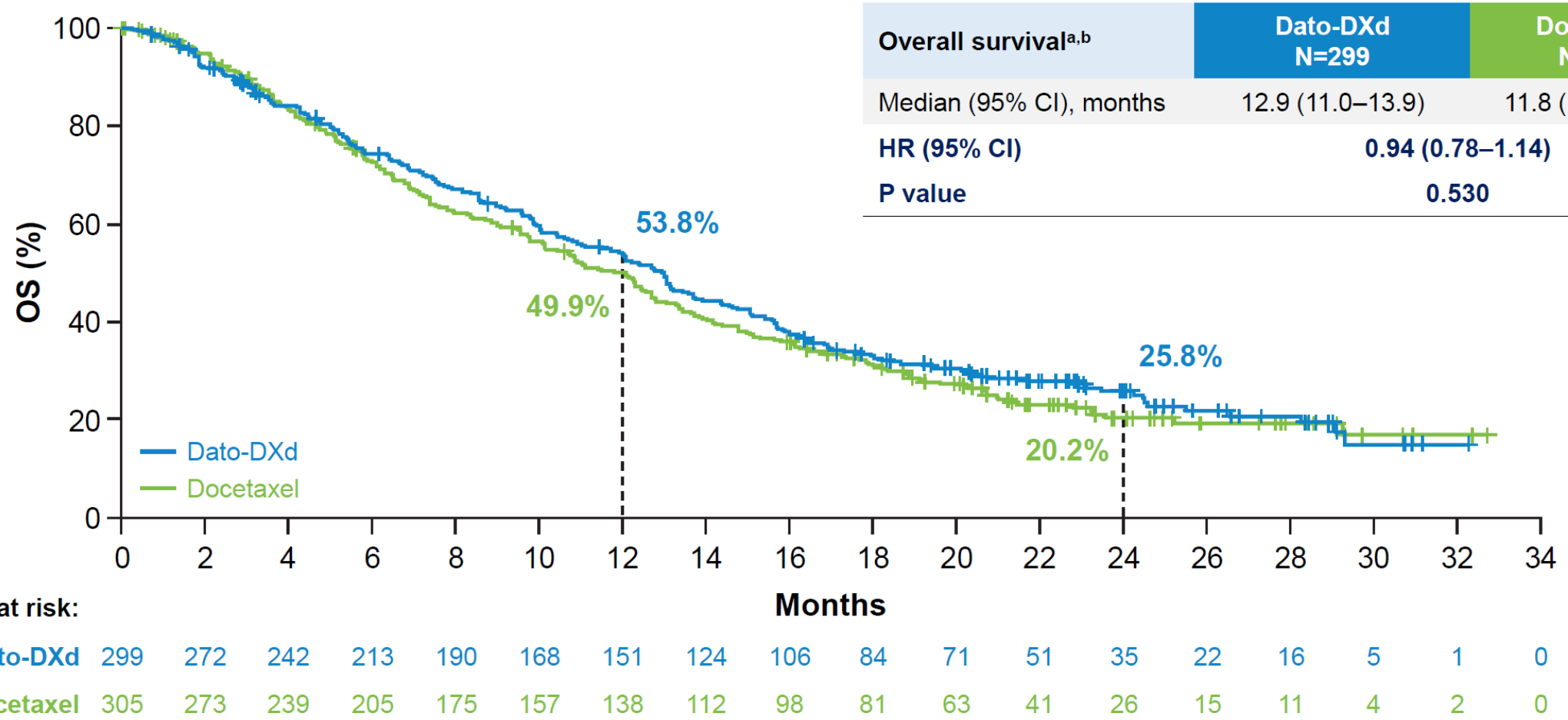
# TROPION-Lung01: Overall Survival: ITT

WCLC 2024

Daiichi-Sankyo




| Overall survival[a,b] | Dato-DXd N=299 | Docetaxel N=305 |
|---|---|---|
| Median (95% CI), months | 12.9 (11.0–13.9) | 11.8 (10.0–12.8) |
| **HR (95% CI)** | **0.94 (0.78–1.14)** | |
| **P value** | **0.530** | |

[a]Median (95% CI) OS follow-up was 23.1 (22.0, 24.8) months for Dato-DXd and 23.1 (21.7, 24.2) months for docetaxel. [b]At primary OS analysis (data cutoff: March 1, 2024), 433 OS events (IF) were observed.
IF, information fraction.

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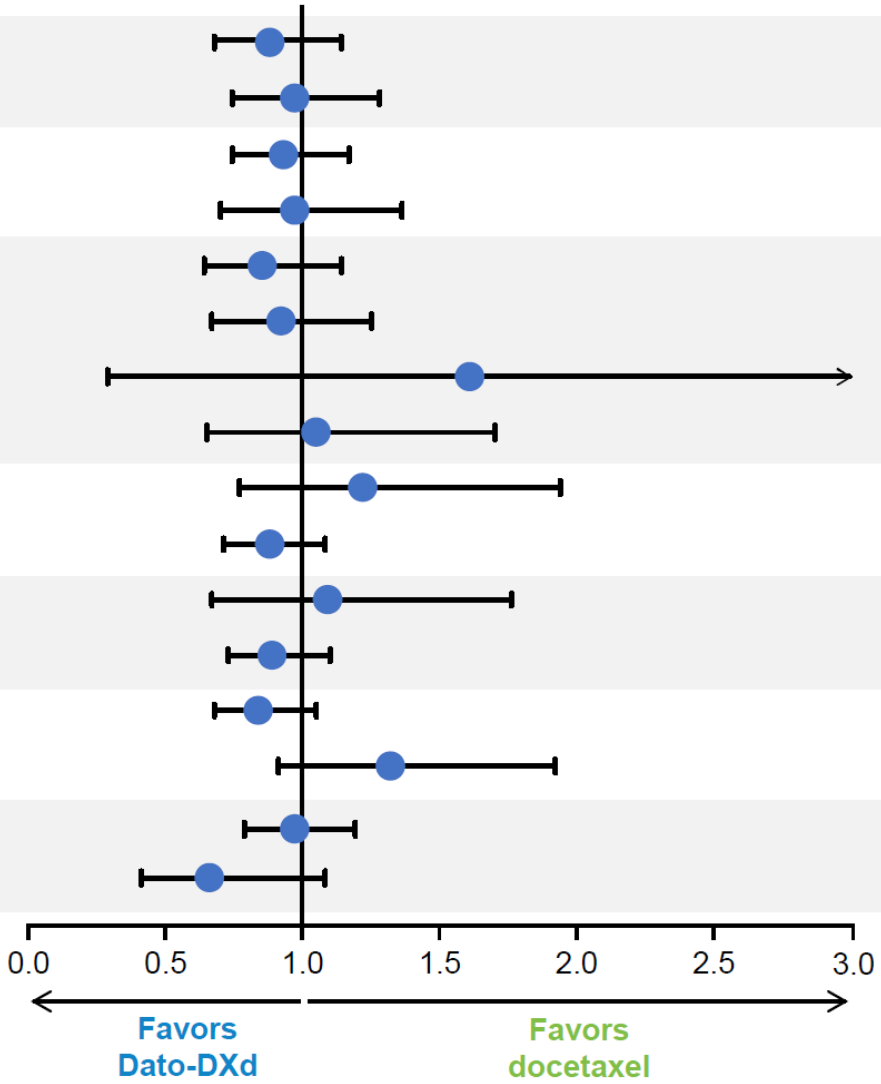
# TROPION-Lung01: Overall Survival: Subgroup Analyses

WCLC 2024

Daiichi-Sankyo

| | | No. of events/No. of patients | | HR |
|---|---|---|---|---|
| | | Dato-DXd | Docetaxel | |
| **Age at randomization** | <65 years | 117/162 | 112/155 | 0.88 |
| | ≥65 years | 98/137 | 106/150 | 0.97 |
| **Sex** | Male | 136/183 | 156/210 | 0.93 |
| | Female | 79/116 | 62/95 | 0.97 |
| **Race** | White | 90/123 | 95/126 | 0.85 |
| | Asian | 83/121 | 79/120 | 0.92 |
| | Black/African American | 4/6 | 2/4 | 1.61 |
| | Other | 33/43 | 35/47 | 1.05 |
| **Smoking status** | Never | 43/60 | 31/52 | 1.22 |
| | Former/current | 172/239 | 186/251 | 0.88 |
| **Brain metastases at baseline** | With | 37/50 | 31/47 | 1.09 |
| | Without | 178/249 | 187/258 | 0.89 |
| **Histology** | Nonsquamous | 160/234 | 163/234 | 0.84 |
| | Squamous | 55/65 | 55/71 | 1.32 |
| **Actionable genomic alterations[a]** | Absent | 182/249 | 185/254 | 0.97 |
| | Present | 33/50 | 33/51 | 0.66 |




Data cutoff: March 1, 2024.

[a]Regardless of histology.

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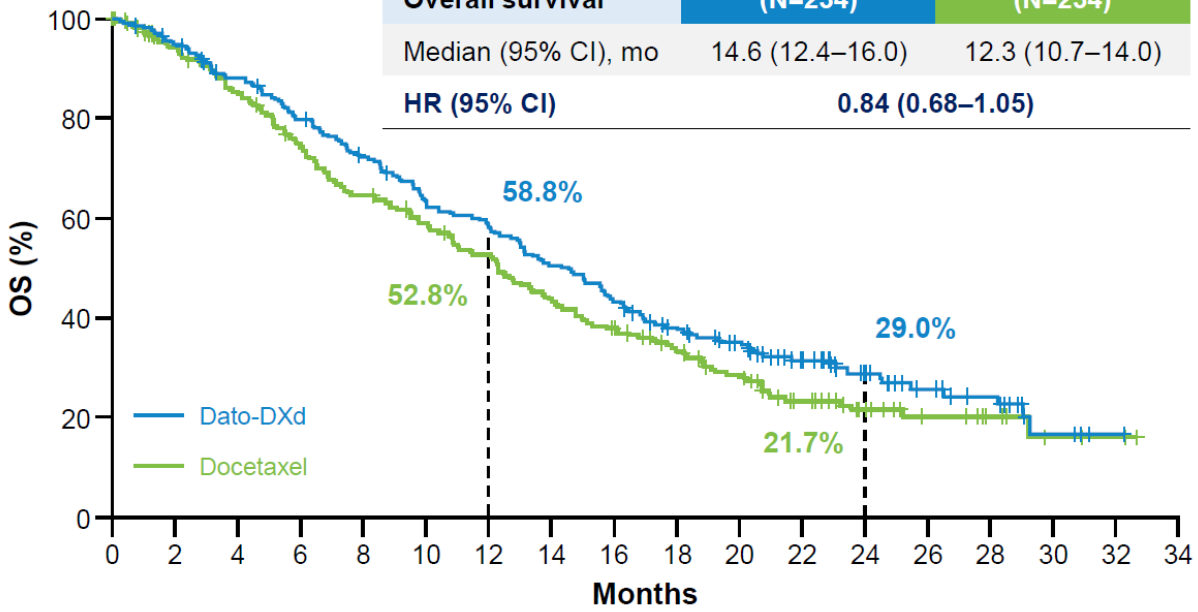
# TROPION-Lung01: Overall Survival by Histology

WCLC 2024

Daiichi-Sankyo

## Nonsquamous

| Overall survival | Dato-DXd (N=234) | Docetaxel (N=234) |
|---|---|---|
| Median (95% CI), mo | 14.6 (12.4–16.0) | 12.3 (10.7–14.0) |
| HR (95% CI) | 0.84 (0.68–1.05) | |

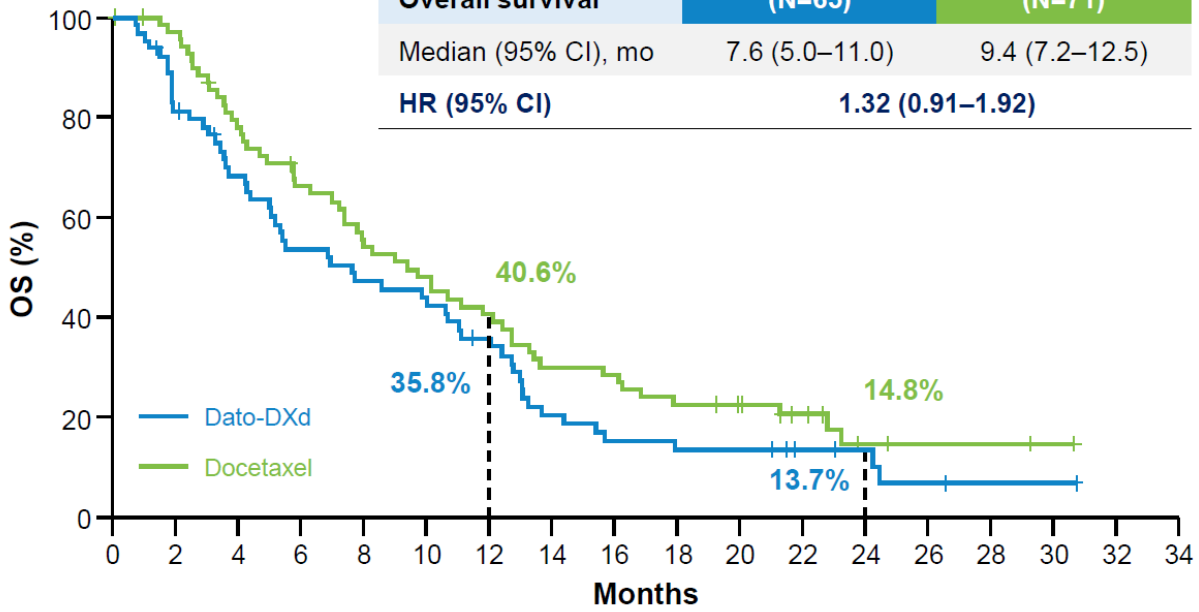



No. at risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 234 | 220 | 200 | 180 | 161 | 141 | 130 | 112 | 97 | 76 | 63 | 46 | 31 | 20 | 15 | 4 | 1 | 0 |
| Docetaxel | 234 | 206 | 186 | 161 | 139 | 125 | 111 | 92 | 79 | 66 | 50 | 32 | 22 | 12 | 8 | 3 | 2 | 0 |

## Squamous

| Overall survival | Dato-DXd (N=65) | Docetaxel (N=71) |
|---|---|---|
| Median (95% CI), mo | 7.6 (5.0–11.0) | 9.4 (7.2–12.5) |
| HR (95% CI) | 1.32 (0.91–1.92) | |




| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 65 | 52 | 42 | 33 | 29 | 27 | 21 | 12 | 9 | 8 | 8 | 5 | 4 | 2 | 1 | 1 | 0 | 0 |
| | 71 | 67 | 53 | 44 | 36 | 32 | 27 | 20 | 19 | 15 | 13 | 9 | 4 | 3 | 3 | 1 | 0 | 0 |

- In patients with NSQ histology, 16% risk reduction for death and 2.3-month improvement in median OS with Dato-DXd
- OS improvements in the NSQ subset were seen regardless of actionable genomic alteration status[a]:
  - **Present**: 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]); **Absent:** 13.6 vs 12.3 months (HR [95% CI], 0.89 [0.70–1.13])

Data cutoff: March 1, 2024.

[a]Based on the number of patients in the respective actionable genomic alteration subsets. Values were calculated based on patient data in the electronic case report forms.

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# TROPION-Lung01: TRAEs ≥15% and Adjudicated Drug-Related ILD

WCLC 2024

Daiichi-Sankyo

| TRAEs,[a] n (%) | Dato-DXd (N=297) | | Docetaxel (N=290) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| **Stomatitis** | 141 (47)[b] | 20 (7) | 45 (16) | 3 (1) |
| **Nausea** | 101 (34) | 7 (2) | 48 (17) | 3 (1) |
| **Alopecia** | 95 (32) | 0 | 101 (35) | 1 (<1)[c] |
| **Decreased appetite** | 68 (23) | 1 (<1) | 46 (16) | 1 (<1) |
| **Asthenia** | 56 (19) | 8 (3) | 56 (19) | 5 (2) |
| **Anemia**[d] | 44 (15) | 12 (4) | 60 (21) | 12 (4) |
| **Diarrhea** | 30 (10) | 1 (<1) | 55 (19) | 4 (1) |
| **Neutropenia**[e] | 14 (5) | 2 (1) | 76 (26) | 68 (23) |
| **Leukopenia**[f] | 9 (3) | 0 | 45 (16) | 38 (13) |
| **Adjudicated drug-related ILD or pneumonitis** | 26 (9)[g] | 11 (4) | 12 (4) | 4 (1) |

- Stomatitis events, the most common TRAE with Dato-DXd, were primarily grade 1 (23%) or grade 2 (18%)
- Hematologic toxicities, including neutropenia and febrile neutropenia[h], were more common with docetaxel
- No new adjudicated drug-related ILD events or deaths occurred since the PFS database lock
- Similar safety profiles were seen for the full safety analysis set and the NSQ subgroup

Data cutoff: March 1, 2024.

[a]Occurring in ≥15% of patients in either treatment group, plus all events of adjudicated drug-related ILD or pneumonitis. [b]Due to rounding, summed rates may not reflect total percentage of TRAEs. [c]Includes an event incorrectly reported as grade 3. [d]Grouped preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased. [e]Grouped preferred terms of neutropenia and neutrophil count decreased. [f]Grouped preferred terms of leukopenia and white blood cell count decreased. [g]Includes one patient in the Dato-DXd group who experienced a grade 2 event that was adjudicated to be drug-related ILD by the adjudication committee. The investigator attributed the event to disease progression and removed the patient from the clinical database. [h]0.3% vs 6.9% for Dato-DXd and docetaxel, respectively.

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# Study design

TROPION-Lung05

- **Dato-DXd** is a TROP2-directed ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- In the **phase 1 TROPION-PanTumor01** study, Dato-DXd showed promising efficacy in patients with actionable genomic alterations[2]
- **TROPION-Lung05** (NCT04484142) is a **phase 2**, single-arm study evaluating Dato-DXd in patients with **advanced or metastatic NSCLC with actionable genomic alterations** that progressed on or after targeted therapy and platinum-based chemotherapy

**Screening**

**Key inclusion criteria**

- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies in the metastatic setting
- Radiographic disease progression after targeted therapy

**Treatment**

Dato-DXd
6 mg/kg
Q3W

**Endpoints[a]**

**Primary:** ORR by BICR

**Secondary:**

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

ADC, antibody-drug conjugate; BICR, blinded independent central review; CBR, clinical benefit rate; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG1, immunoglobulin G1; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; TROP2, trophoblast cell-surface antigen 2; TTR, time to response.

[a]The primary completion date will occur when all patients have had either a minimum of 9 months of follow-up after the start of study treatment or have discontinued from the study.

**1.** Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329-2340. **2.** Shimizu T, et al. *J Clin Oncol*. Published online June 16, 2023.

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# TROPION-Lung05

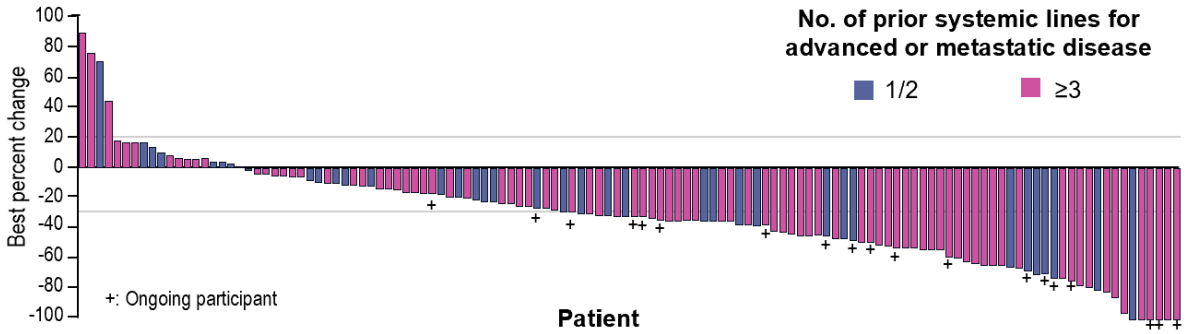
ESMO 2023

Daiichi-Sankyo

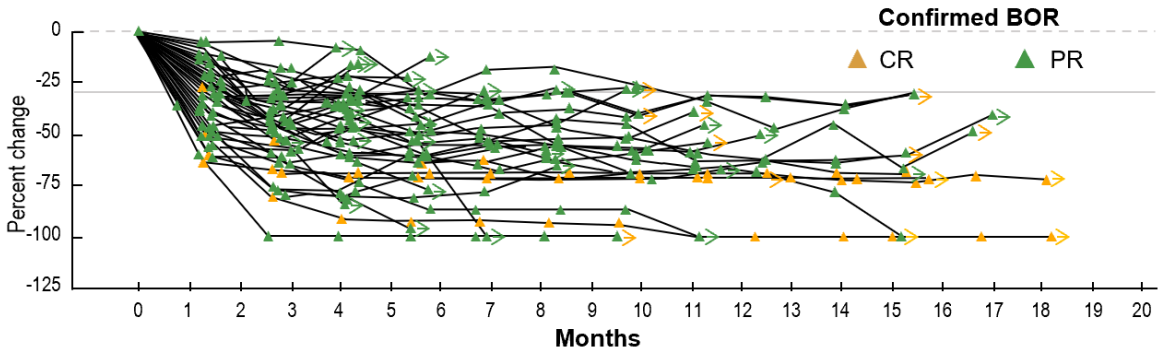
## Encouraging antitumor activity was observed with Dato-DXd treatment in a heavily pretreated NSCLC population with AGAs

### Efficacy

**Best Percent Change From Baseline in Sum of Diameters of Target Lesions**




**Percent Change From Baseline in Sum of Diameters of Target Lesions in Patients With Confirmed CR/PR[c]**




### TROPION-Lung05 Study

Ph2, single-arm study evaluating Dato-DXd in patients with advanced or metastatic NSCLC with AGAs that progressed on or after targeted therapy and platinum-based chemotherapy

| Response per BICR | All treated patients (N=137) | Patients with *EGFR* mutations (N=78) | Patients with *ALK* rearrangement (N=34) |
|---|---|---|---|
| **ORR confirmed,** n (%) [95% CI][a] | 49 (35.8) [27.8-44.4] | 34 (43.6) [32.4-55.3] | 8 (23.5) [10.7-41.2] |
| **Median DOR** (95% CI), months | 7.0 (4.2-9.8) | 7.0 (4.2-10.2) | 7.0 (2.8-8.4) |
| **DCR confirmed,** n (%) [95% CI][a] | 108 (78.8) [71.0-85.3] | 64 (82.1) [71.7-89.8] | 25 (73.5) [55.6-87.1] |
| **Median PFS,** (95% CI), months[b] | 5.4 (4.7-7.0) | 5.8 (5.4-8.3) | 4.3 (2.6-6.9) |

Data cutoff: Dec 2022

- Confirmed ORR and median PFS in all treated patients were **35.8% and 5.4 months**, respectively
- Dato-DXd had a manageable safety profile, characterized by a low incidence of hematologic or drug-related grade ≥3 toxicities
- Adjudicated drug related ILD was 5 (4%) in total and 1 (1%) for grade ≥3 (as a grade 5 event)

a The 2-sided 95% Cis are based on the Clopper-Pearson exact binomial method. b Median PFS and PFS probabilities are based on the Kaplan-Meier method. c Per BICR

AGA: actionable genomic alterations, BICR: blinded independent central review, BOR: best overall response, CI: confidence interval, CR: complete response, DCR: disease control rate, DOR: duration of response, ILD: interstitial lung disease, NSCLC: non-small cell lung cancer, ORR: objective response rate, PFS: progression-free survival, PR: partial response

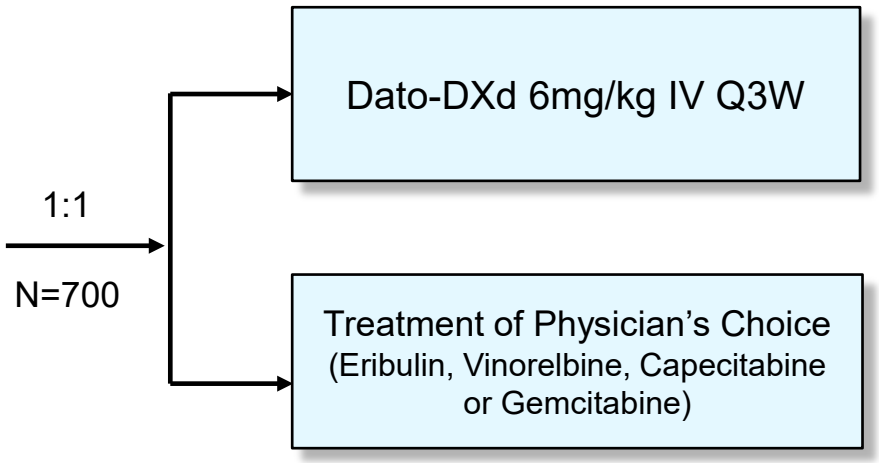
# TROPION-Breast01

Ph3 Study of Dato-DXd vs treatment of physician's choice in 2nd/3rd Line HR+ HER2- mBC

Key Eligibility Criteria:

- HR+ HER2- BC patients previously treated with one or two^ lines of chemotherapy in advanced/metastatic setting:
  - Progressed or not suitable for endocrine therapy
  - Progressed following most recent antineoplastic therapy
- Targeted agents (such as mTOR inhibitors, PD-1/PD-L1 inhibitors), endocrine therapies and CDK4/6 inhibitors on their own do not contribute to the count of prior lines of chemotherapy, although regimens with such agents in combination with chemotherapy would still count as one line of chemotherapy*.

^3L population capped at 50%
*Prior PARP inhibitors will be regarded as a line of chemotherapy




Stratification factors:
- 1 vs 2 lines of chemo in adv./met. setting
- Geographic location
- Previous CDK 4/6 inhibitor

Dual primary endpoint
PFS (BICR) and OS

Secondary endpoints
PFS (inv), ORR, DoR, TTR, DCR, PRO, TEAE, PK, immunogenicity

Exploratory endpoints
PFS-2, Trop2 IHC expression, other biomarkers, exposure/efficacy relationship, additional PRO

Response assessment: Scan q6w (based on 6 mo. mPFS in control arm)

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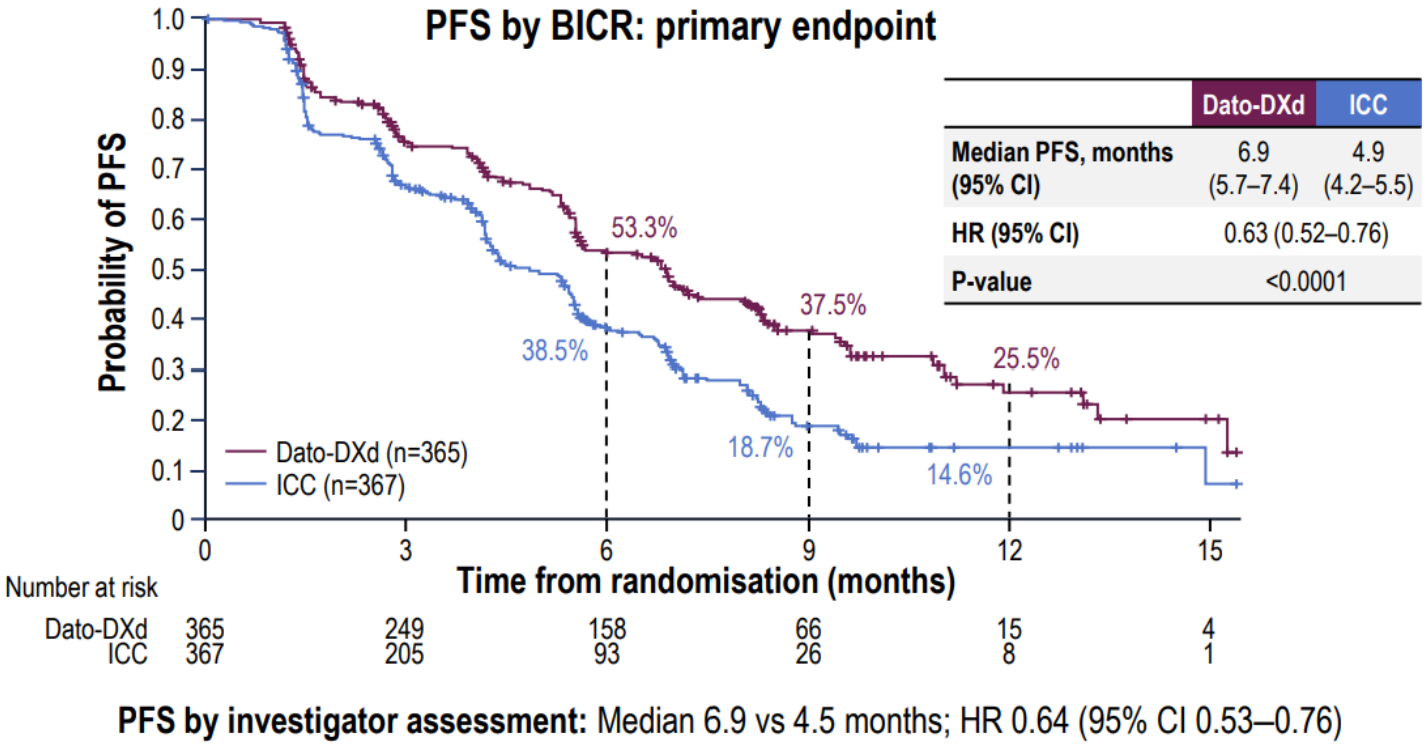
# TROPION-Breast01

ESMO 2023

Daiichi-Sankyo

## TROPION-Breast01 enables Dato-DXd to aim to set a new standard for TROP2 ADCs in HR+/HER2 low or negative BC

**PFS**




| | Dato-DXd | ICC |
|---|---|---|
| Median PFS, months (95% CI) | 6.9 (5.7–7.4) | 4.9 (4.2–5.5) |
| HR (95% CI) | 0.63 (0.52–0.76) | |
| P-value | <0.0001 | |

**PFS by investigator assessment:** Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

Data cutoff: Jul 2023

### TROPION-Breast01 Study

- The dual primary endpoints are PFS and OS
- TLR was obtained in Sep 2023

- 63% of the patients received 1L and 37% received 2L chemotherapy prior to Dato-DXd
- **Median PFS by BICR: 6.9 months** for Dato-DXd (n=365) and 4.9 months for ICC (n=367). OS data was not mature at the point of analysis
- **Confirmed ORR: 36.4%** for Dato-DXd and 22.9% for ICC.
- Rate of grade≥3 TRAEs in the Dato-DXd group (21%) was **less than half** that in the ICC group (45%)
- **ILD rate was low; mainly grade 1/2 events**. There were one grade 3 and one grade 5 adjudicated ILD event

ADC: antibody-drug conjugate, BC: breast cancer, BICR: blinded independent central revie, CI: confidence interval, HR: hazard ratio, HR: hormone receptor, ICC: investigator's choice of chemotherapy, ILD: interstitial lung disease, ORR: objective response rate, PFS: progression-free survival, OS: overall survival, TLR: top line results, TRAE: treatment related adverse events

DATROWAY®

# Study Design

TROPION-Breast02 Randomised, phase 3, open-label, global study

Daiichi-Sankyo

## Key inclusion criteria:

- Patients with histologically or cytologically documented locally recurrent inoperable or metastatic TNBC*
- No prior chemotherapy or targeted systemic therapy in the locally recurrent inoperable or metastatic setting
- Immunotherapy not an option†
- ECOG PS 0 or 1
- No minimum DFI‡

1:1

**Dato-DXd**
6 mg/kg IV Day 1 Q3W
**(n=323)**

**Investigator's choice of chemotherapy (ICC)#**
Paclitaxel, nab-paclitaxel, capecitabine, eribulin mesylate/eribulin, carboplatin
**(n=321)**

## Endpoints

**Dual primary:**

- OS
- PFS by BICR per RECIST v1.1

**Secondary included:**

- PFS (investigator-assessed)
- ORR, DoR
- Safety

**Randomisation stratified by:**

- Geographic region (US/Canada/Europe vs other geographic regions)
- PD-L1 status (high [CPS ≥10] vs low [CPS <10])§
- DFI history (*de novo* vs prior DFI 0–12 months vs prior DFI >12 months)¶

- Treatment continued until investigator-assessed RECIST v1.1 progressive disease, unacceptable toxicity, or another discontinuation criterion was met
- Following progression or discontinuation of study treatment, patients could receive subsequent therapies, including approved ADCs or chemotherapy, at the investigator's discretion‖

*According to ASCO/CAP criteria. †Including patients with PD-L1-low tumours, or patients with PD-L1-high tumours with (a) disease relapse after prior PD-(L)1 inhibitor therapy for early-stage breast cancer, (b) comorbidities precluding PD-(L)1 inhibitor therapy, or (c) no regulatory access to PD-(L)1 inhibitor therapy. ‡DFI defined as time between date of completion of treatment with curative intent and date of first documented local or distant disease recurrence. §Recruitment of patients with PD-L1-high tumours who would otherwise be eligible for pembrolizumab if regulatory access was available was capped at ~10% of randomised patients. ¶Recruitment of patients with DFI 0–12 months was capped at ~20% of randomised patients. #If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI >12 months: paclitaxel 80 mg/m$^2$ IV, D1, 8, 15, Q3W, or nab-paclitaxel 100 mg/m$^2$ IV, D1, 8, 15, Q4W; if prior taxane and DFI 0–12 months: capecitabine 1000 or 1250 mg/m$^2$ orally twice daily, D1–14, Q3W (dose determined by standard institutional practice), or eribulin mesylate 1.4 mg/m$^2$ / eribulin 1.23 mg/m$^2$ IV, Day 1, 8, Q3W, or carboplatin AUC6 IV, D1, Q3W. ‖In the Dato-DXd vs ICC arm, 65% vs 72% of patients received any subsequent therapy in any treatment line; 14% vs 30% received a subsequent ADC (sacituzumab govitecan, sacituzumab tirumotecan, trastuzumab deruxtecan).

ADC, antibody-drug conjugate; BICR, blinded independent central review; CPS, combined positive score; D, day; DFI, disease-free interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; ORR, objective response rate; PD-(L)1, programmed cell death (ligand) 1; PFS, progression-free survival; QXW, every X weeks.

DATROWAY®

# Paving the way for the new 1L SOC in mTNBC

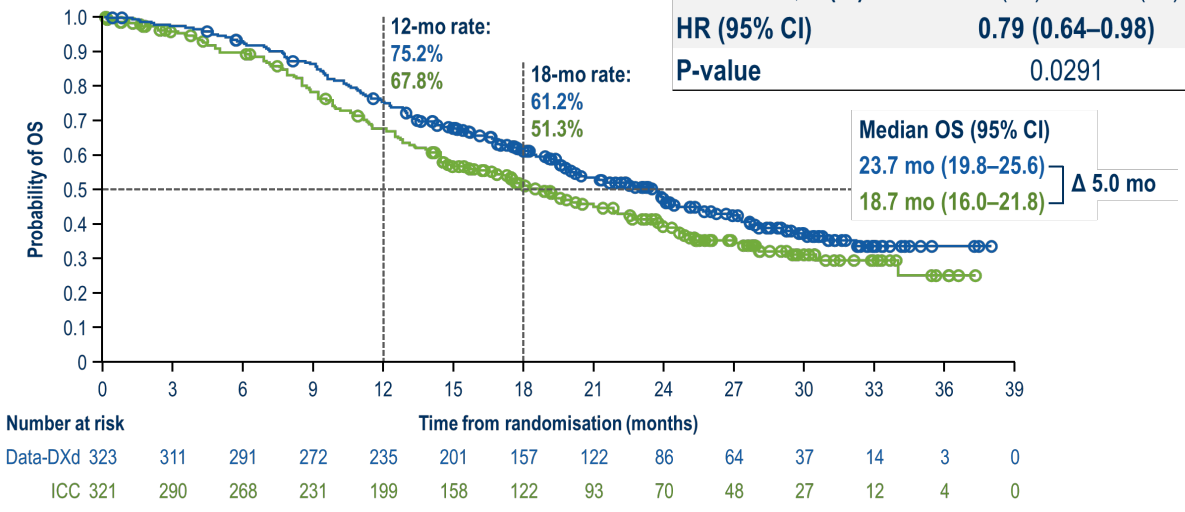
TROPION-Breast02 Ph3 (ESMO 2025)

Daiichi-Sankyo

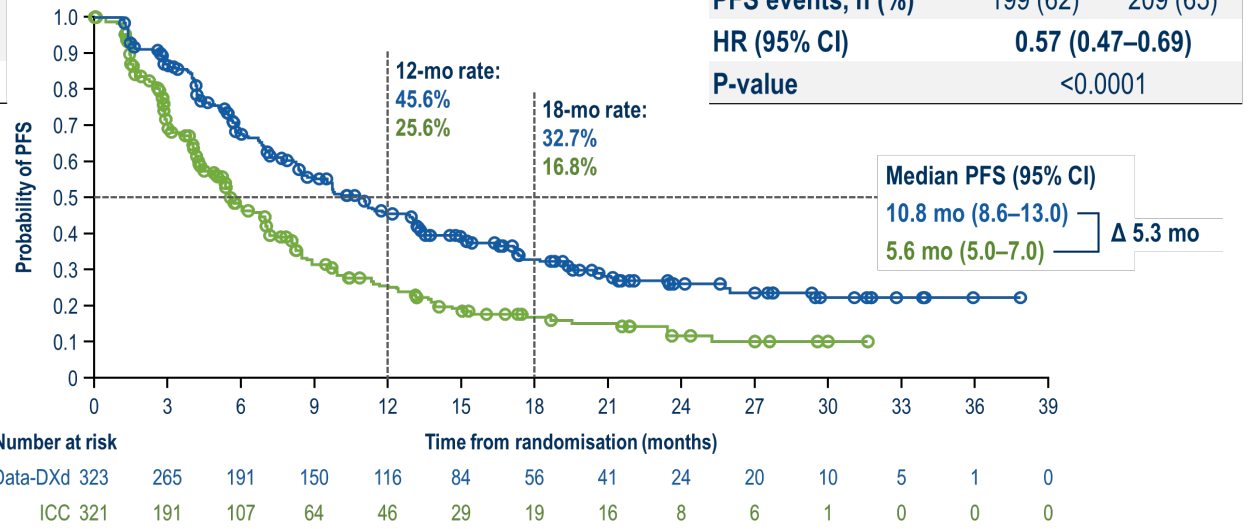
## TROPION-Breast02 met both dual primary endpoints OS and PFS in patients with mTNBC for whom immunotherapy is not an option

### Efficacy: OS (left) and PFS (right)

| | Dato-DXd | ICC |
|---|---|---|
| OS events, n (%) | 168 (52) | 181 (56) |
| HR (95% CI) | 0.79 (0.64–0.98) | |
| P-value | 0.0291 | |




| | Dato-DXd | ICC |
|---|---|---|
| PFS events, n (%) | 199 (62) | 209 (65) |
| HR (95% CI) | 0.57 (0.47–0.69) | |
| P-value | <0.0001 | |




Data cutoff: August 25, 2025

- DATROWAY® demonstrated a statistically significant and clinically meaningful improvement in OS and PFS with a 5.0-month improvement in median OS and 5.3-month improvement in median PFS
- ORR with DATROWAY® was more than double that with chemotherapy (62.5% vs. 29.3%)
- The safety profile of DATROWAY® was manageable and generally consistent with the known profile

CI: confidence interval, ESMO: European Society for Medical Oncology, HR: hazard ratio, ICC: investigator's choice of chemotherapy, mo: month, mTNBC: metastatic triple-negative breast cancer, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, SOC: standard of care

I-DXd

# Addressing Unmet Needs in ES-SCLC

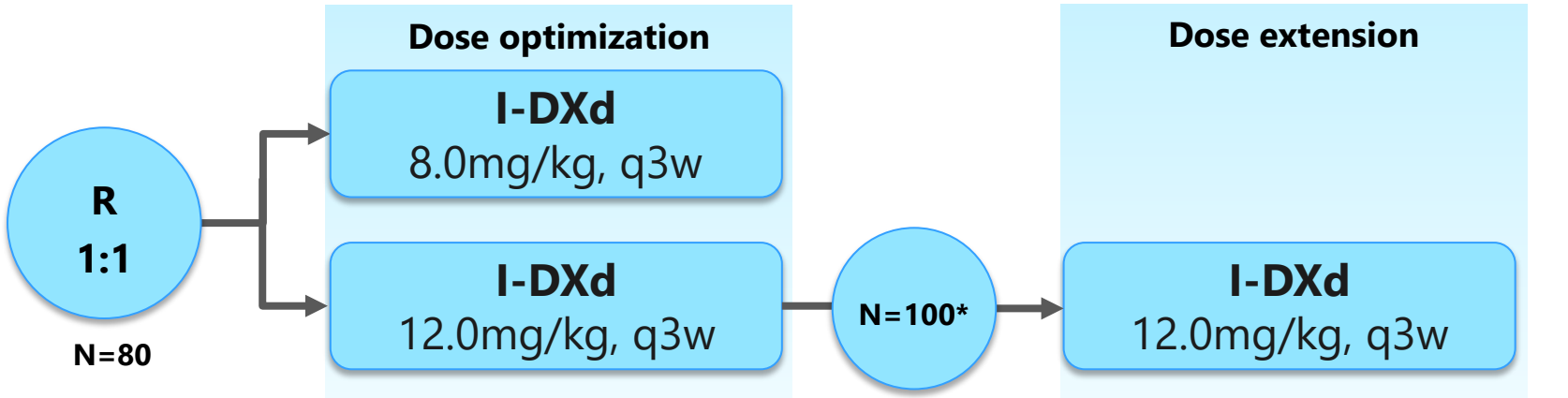
IDeate-Lung01 Ph2 (WCLC 2025)

## Promising data from dose extension part in ES-SCLC in Apr 2025

### IDeate-Lung01 Study Design

**Eligible Patients**

- ES-SCLC
- Prior therapy with at least one platinum-based line
- Minimum of two previous lines of systemic therapy (current protocol)




Primary endpoint: ORR
Secondary endpoint: PFS, DOR, OS etc.

- IDeate-Lung01 compared 8.0mg/kg and 12mg/kg and choose 12mg/kg as an optimal dose in dose optimization part
- The data will be presented at a future medical conference
- As for ES-SCLC, IDeate-Lung02 (Ph3) for 2L treatment and combination study with MK-6070 (gocatamig) are ongoing

* Extended enrollment at the selected dose

DOR: duration of response, ES-SCLC: extensive-stage small cell lung cancer, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, q3w: every 3 weeks

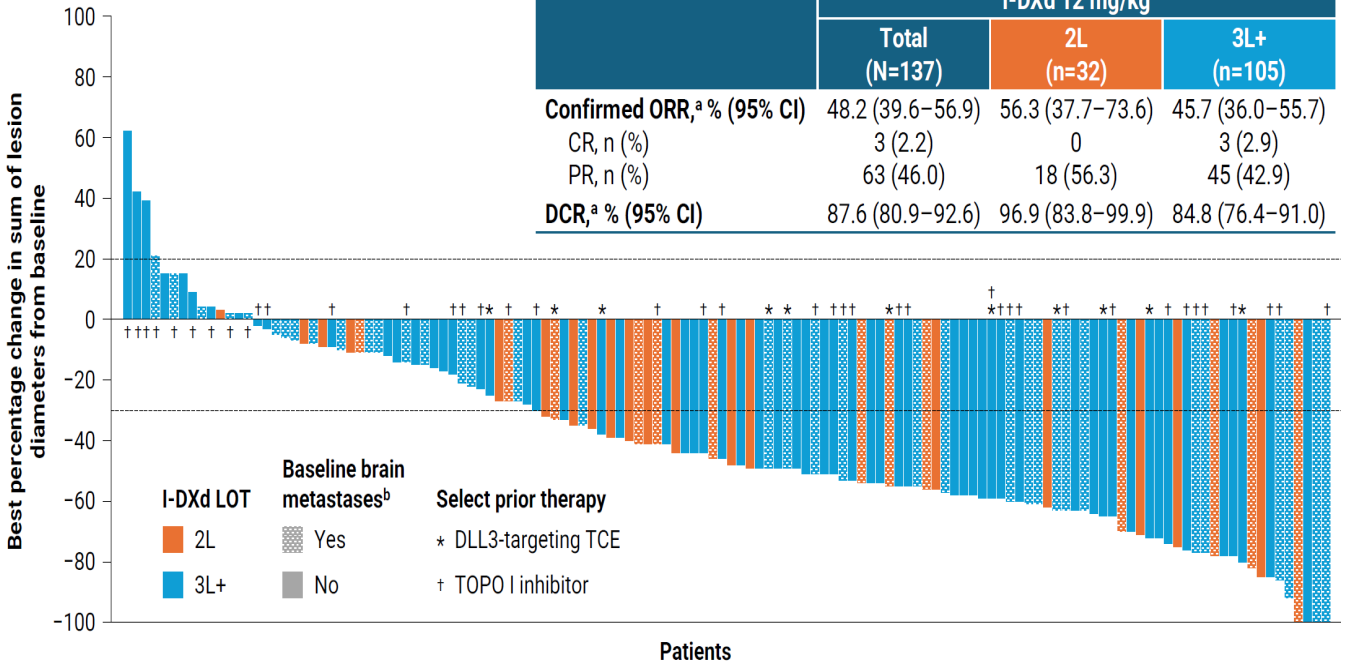
I-DXd

# Striving to Fill the Unmet Need in SCLC

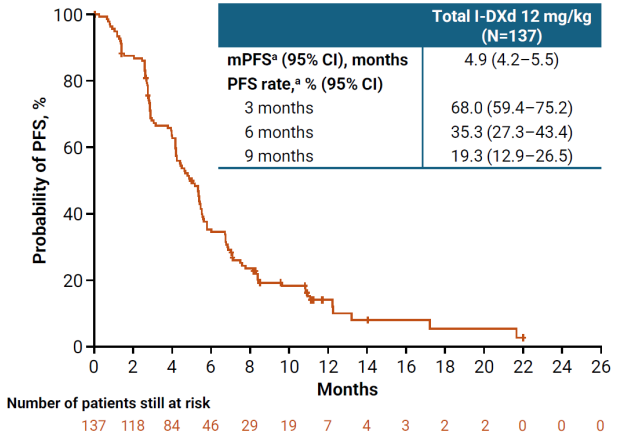
IDeate-Lung01 Ph2 (WCLC 2025)

## I-DXd demonstrated remarkable efficacy in previously treated ES-SCLC

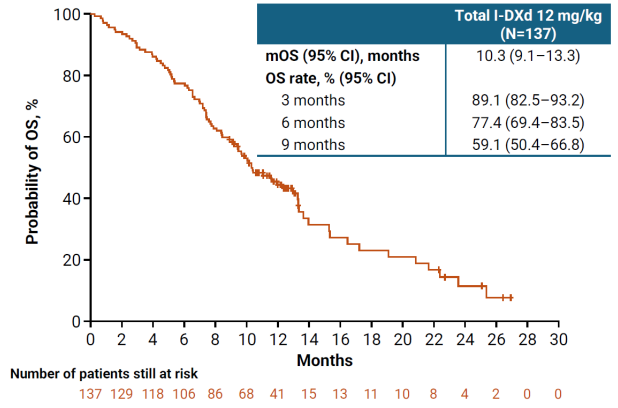
### Efficacy: ORR (left), PFS (upper right), OS (lower right)




| | I-DXd 12 mg/kg | | |
|---|---|---|---|
| | Total (N=137) | 2L (n=32) | 3L+ (n=105) |
| Confirmed ORR,[a] % (95% CI) | 48.2 (39.6–56.9) | 56.3 (37.7–73.6) | 45.7 (36.0–55.7) |
| CR, n (%) | 3 (2.2) | 0 | 3 (2.9) |
| PR, n (%) | 63 (46.0) | 18 (56.3) | 45 (42.9) |
| DCR,[a] % (95% CI) | 87.6 (80.9–92.6) | 96.9 (83.8–99.9) | 84.8 (76.4–91.0) |




| | Total I-DXd 12 mg/kg (N=137) |
|---|---|
| mPFS[a] (95% CI), months | 4.9 (4.2–5.5) |
| PFS rate,[a] % (95% CI) | |
| 3 months | 68.0 (59.4–75.2) |
| 6 months | 35.3 (27.3–43.4) |
| 9 months | 19.3 (12.9–26.5) |




| | Total I-DXd 12 mg/kg (N=137) |
|---|---|
| mOS (95% CI), months | 10.3 (9.1–13.3) |
| OS rate, % (95% CI) | |
| 3 months | 89.1 (82.5–93.2) |
| 6 months | 77.4 (69.4–83.5) |
| 9 months | 59.1 (50.4–66.8) |

- The overall confirmed ORR was 48.2%.
  - ✓ The ORR for 2L was 56.3%, and for 3L and beyond was 45.7%
- I-DXd 12 mg/kg showed mPFS 4.9 mo, and mOS 10.3 mo

**IDeate-Lung01**

- ✓ Evaluating the efficacy and safety of I-DXd monotherapy in ES-SCLC
- ✓ Comparing 8 mg/kg and 12 mg/kg in the dose-optimization phase
- ✓ 12 mg/kg selected for the expansion phase
- ✓ Primary endpoint: ORR

Data cutoff: March 3, 2025

CI: confidence interval, CR: complete response, DCR: disease control rate, ES-SCLC: extensive-stage small cell lung cancer, LOT: line of treatment, mo: month, mOS: median overall survival, mPFS: median progression-free survival, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, PR: partial response, SCLC: small cell lung cancer, TCE: T-call engager, WCLC: World Conference on Lung Cancer

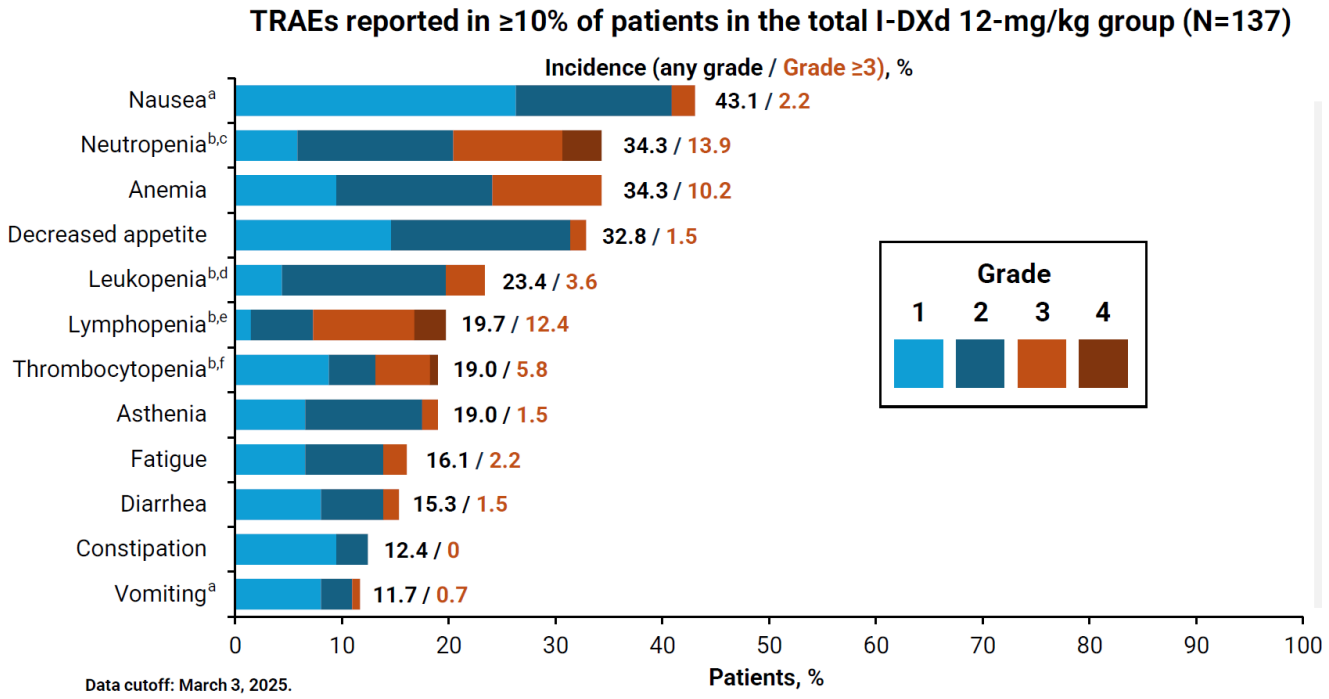
I-DXd

# Striving to Fill the Unmet Need in SCLC

IDeate-Lung01 Ph2 (WCLC 2025)

## Safety profile of I-DXd 12 mg/kg was manageable and consistent with previous studies

### Safety




- Among the most common TRAEs, the majority were Grade 1 or 2
- Adjudicated treatment-related ILD reported in 17 patients (12.4%):
  - ✓ Grade 1 or 2, n=11 (8.0%)
  - ✓ Grade 3, n=4 (2.9%)
  - ✓ Grade 5, n=2 (1.5%)

Data cutoff: March 3, 2025

- The FDA granted Breakthrough Therapy Designation to I-DXd for ES-SCLC progressed after platinum-based chemotherapy in Aug 2025

ES-SCLC: extensive-stage small cell lung cancer, ILD: interstitial lung disease, SCLC: small cell lung cancer, TRAE: treatment-related adverse event, WCLC: World Conference on Lung Cancer