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Daiichi-Sankyo

ESMO 2025 Highlights

DAIICHI SANKYO CO., LTD.

October 21st, 2025

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ESMO 2025 Highlights: Speakers

Ken Takeshita
Head of Global R&D

Abderrahmane Laadem
Head of Late-Stage Clinical Development

Agenda

1. Welcome message
2. Highlights from ESMO 2025
3. Q&A

Agenda

1. **Welcome message**
2. **Highlights from ESMO 2025**
3. **Q&A**

ESMO 2025 Major Data Disclosure

Over 30+ abstract have been accepted across multiple assets

5DXd ADCs

ENHERTU®

HER2+ BC
- **DESTINY-Breast05 Interim Analysis**
- DESTINY-Breast09 Subgroup
- **DESTINY-Breast11 Primary Analysis**

GASTRIC
- DESTINY-Gastric04 additional efficacy
- DESTINY-Gastric06 subgroup analysis

OTHER/Multiple Tumor Types
- DESTINY-CRC02 Final Analysis
- DESTINY-Endometrial01 TiP
- DESTINY-PanTumor02 Final Analysis
- DESTINY-PanTumor02 Oncogenic biomarkers Final Analysis

R-DXd

Ovarian Cancer
- **REJOICE-Ovarian01 Ph2 part Primary Analysis**

GASTRIC
- REJOICE-GI01 TiP

DATROWAY®

TNBC
- **TROPION-Breast02 Primary Analysis**
- **BEGONIA Final Analysis**

NSCLC
- ICARUS-Lung01 Carbon footprint

OTHER/Multiple Tumor Types
- TROPION-PanTumor03

I-DXd

SCLC
- IDeate-Lung01 Intracranial activity Primary Analysis
- MK-6070-001 (Gocatamig) updated results
- MK-6070-002 (Gocatamig +/- I-DXd) TiP

NSCLC
- KEYMAKER-U01 TiP

HER3-DXd

TNBC
- HERTHENA-Breast03 TiP

Next Wave

DS-3939

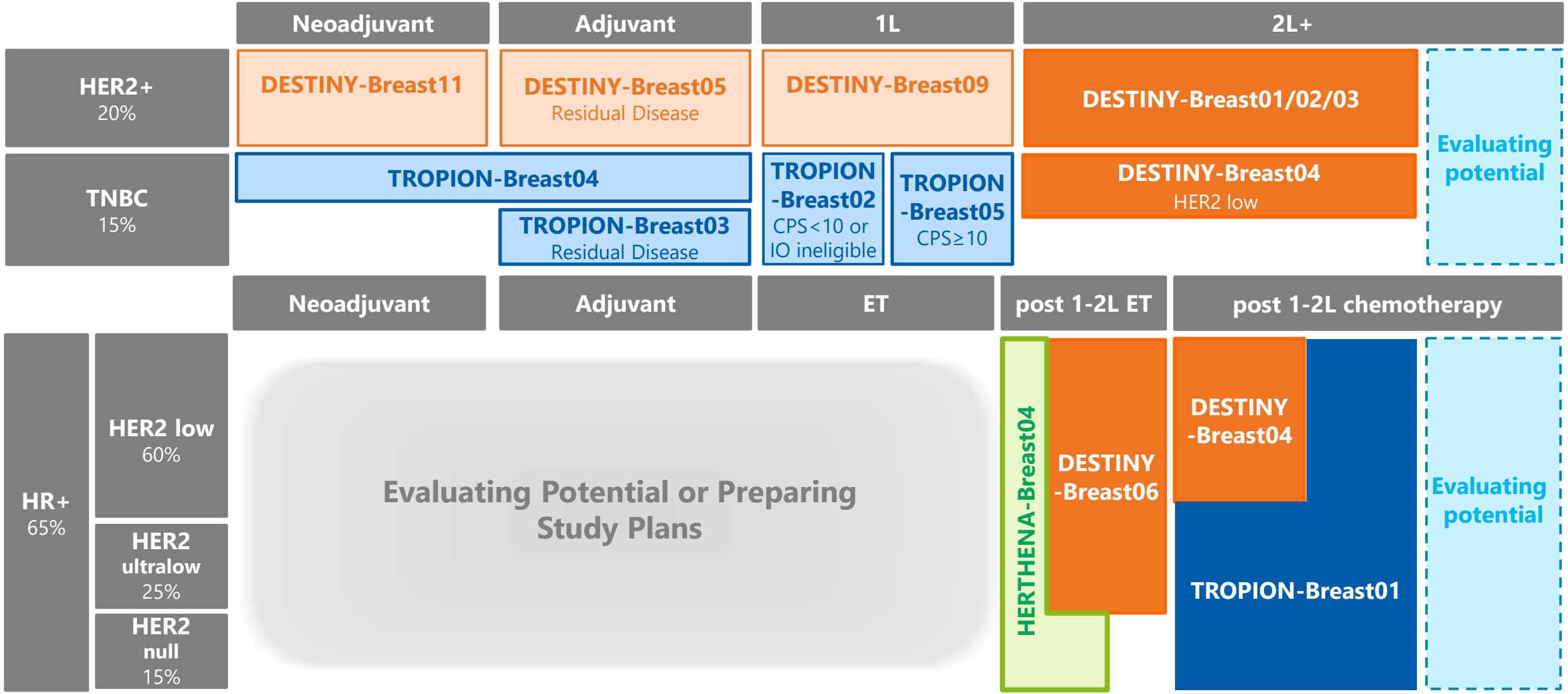
Multiple Tumor Types
- **DS3939-077 FIH study Initial results**

Cross-Asset

NSCLC
- Valemetostat combination with DATROWAY® in NSCLC - Initial Safety Results

Other /Multiple Tumor Types
- Valemetostat combination with Ipilimumab in GU tumors

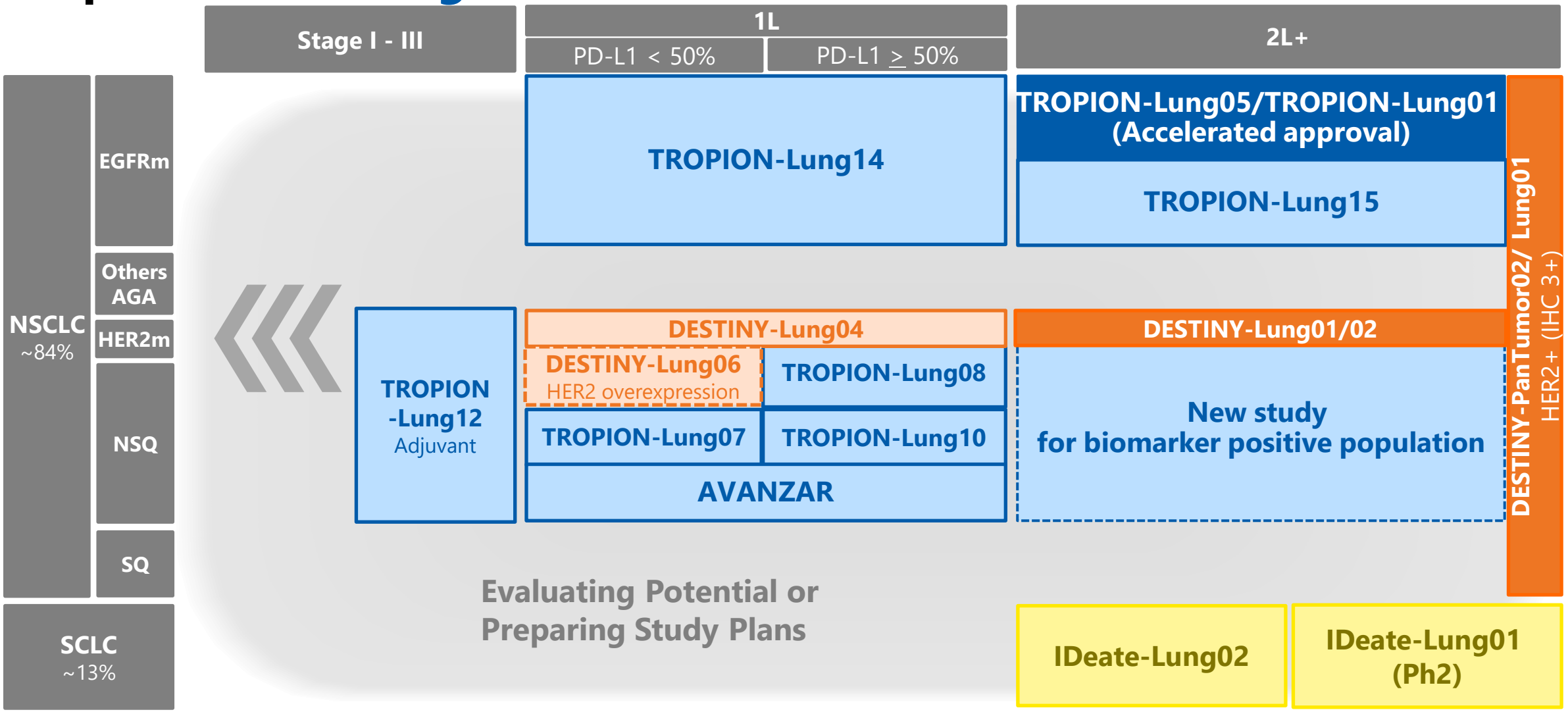
Establish and Expand DXd ADCs to Address the Broader Spectrum of Breast Cancer



- Pivotal studies only, not exhaustive
- Box size does not reflect the patient population
- Box indicates current potential target segment

CPS: combined positive score; ET: endocrine therapy; HR: hormone receptor; IHC: immunohistochemistry, IO: immune oncology, TNBC: triple-negative breast cancer

Establish and Expand DXd ADCs to Address the Broader Spectrum of Lung Cancer

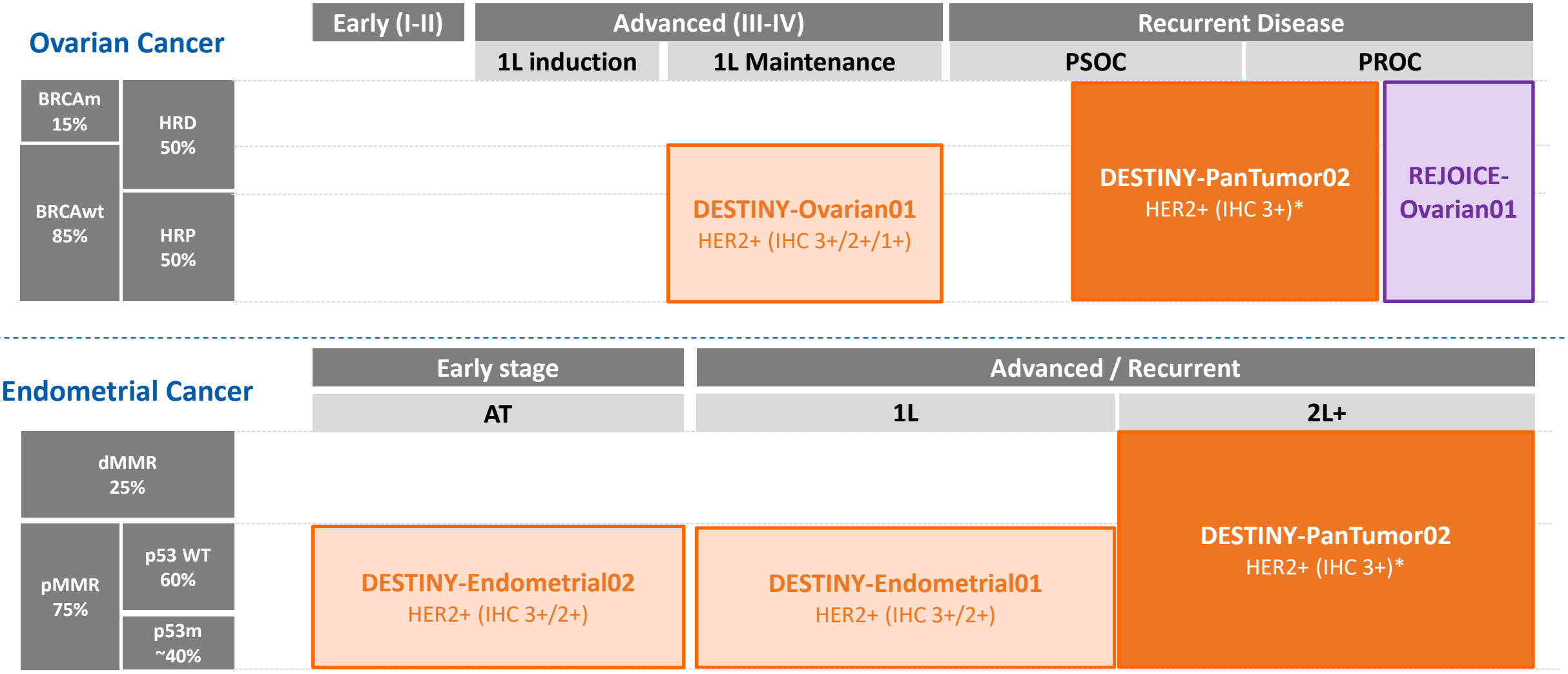


Launched | On-going | Planning | ENHERTU® | DATROWAY® | I-DXd

- Pivotal studies and major Ph2 only, not exhaustive
- Box size does not reflect the patient population
- Box indicates current potential target segment

AGA: actionable genomic alteration, IHC: immunohistochemistry, NSQ: non- squamous, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, SQ: squamous

Expand DXd ADCs within Women's Cancers to Address Broad Spectrum of Gynecological Cancers



Launched | Trial ongoing | ENHERTU® | Raludotatug deruxtecan (R-DXd)

- Pivotal studies only, not exhaustive.
- Box size does not reflect the patient population
- Box indicates current potential target segment

*T-DXd tumor agnostic approval (IHC 3+) in 2L+ setting. NCCN Ovarian Cancer Guidelines (Jan 2025) update Category 2B recommendation of T-DXd in HER2+ (IHC 3+) PSOC. NCCN Endometrial Cancer Guidelines (2025) includes a Category 2B recommendation for T-DXd in HER2+ (IHC 2+/3+) endometrial cancer in the 2L+ setting.

Agenda

1. Welcome message

2. **Highlights from ESMO 2025**
   - ✓ **DESTINY-Breast11**
   - ✓ **DESTINY-Breast05**
   - ✓ **TROPION-Breast02**
   - ✓ **BEGONIA**
   - ✓ **REJOICE-Ovarian01**
   - ✓ **DS-3939 Ph1**

3. Q&A

DESTINY-Breast11: neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel + trastuzumab + pertuzumab vs ddAC-THP for high-risk HER2+ early breast cancer

Nadia Harbeck

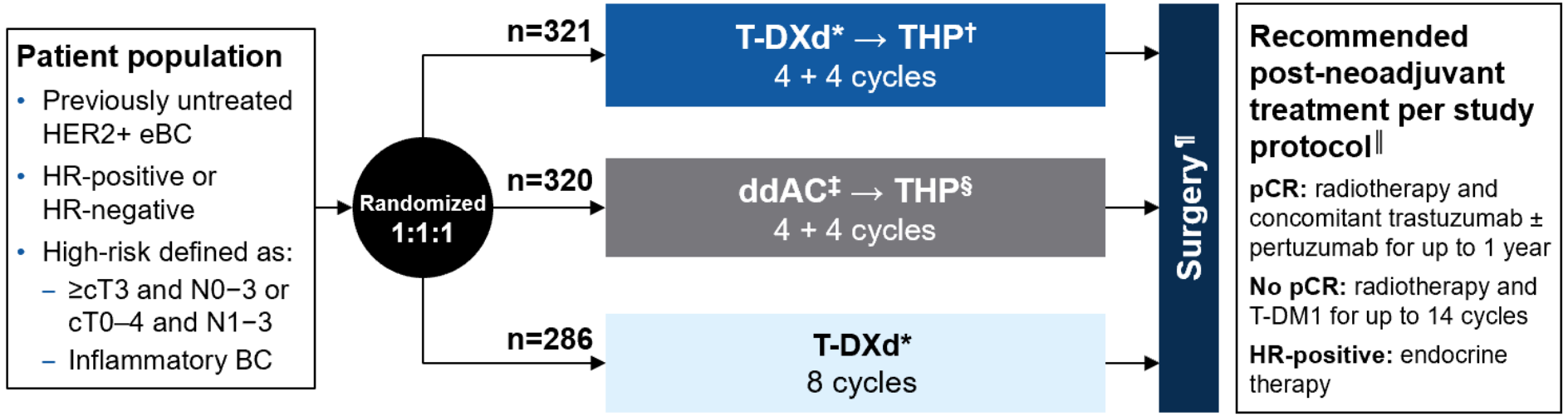
Breast Center, Department of OB&GYN and CCC Munich,
LMU University Hospital, Munich, Germany

Co-authors: Shanu Modi, Lajos Pusztai, Shinji Ohno, Jiong Wu, Sung-Bae Kim, Alessandra Fabi, Xuchen Cao, Rona Joseph, Rubi Li, Bogdan Żurawski, Santiago Escrivá-de-Romaní, Shin-Cheh Chen, Catherine Kelly, Giuseppe Curigliano, William Fraser Symmans, Shoubhik Mondal, Shahana Safdar, Pia Herbolsheimer, Jean-François Boileau

On behalf of the DESTINY-Breast11 investigators

DESTINY-Breast11 study design

A randomized, global, multicenter, open-label, Phase 3 study (NCT05113251)



Data cutoff: March 12, 2025

Primary endpoint

- pCR (ypT0/is ypN0) by blinded central review

Secondary endpoints

- pCR (ypT0 ypN0) by blinded central review
- EFS
- Safety
- Pharmacokinetics and immunogenicity
- Invasive disease-free survival
- Overall survival
- Health-related quality of life

Additional outcome measures

- Residual cancer burden (RCB)

Stratification factors

- HR status: ER and/or PR-positive or negative
- HER2 status: (IHC 3+ or ISH+ in the absence of IHC 3+ status)

The T-DXd alone arm closed on March 13 2024, following Independent Data Monitoring Committee recommendation
The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery

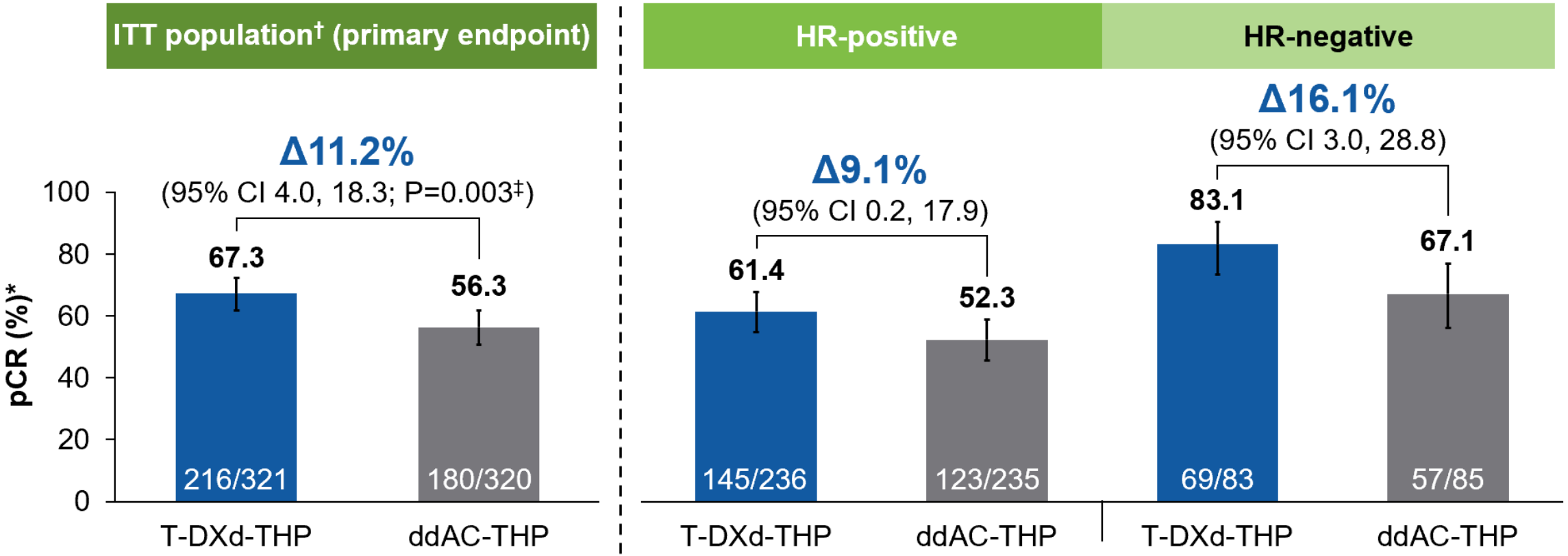
High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. *5.4 mg/kg Q3W; †paclitaxel (80 mg/m^2 QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m^2 Q2W) + cyclophosphamide (600 mg/m^2 Q2W); §paclitaxel (80 mg/m^2 QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; ‖administered as part of the patient's SOC at the investigator's discretion. cT, clinical tumor stage; ER, estrogen receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; N, nodal stage; PR, progesterone receptor; QXW, every X weeks; T-DM1, trastuzumab emtansine; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0, absence of invasive and in-situ cancer in the breast and axillary nodes

Patient demographics and key baseline characteristics

		T-DXd-THP (n=321)	ddAC-THP (n=320)	T-DXd (n=286)
Median (range) age, years		50 (25–82)	50 (23–79)	50 (23–79)
Female, n (%)		321 (100)	320 (100)	286 (100)
Geographical region, n (%)	Asia	152 (47.4)	152 (47.5)	124 (43.4)
	Western Europe	69 (21.5)	77 (24.1)	66 (23.1)
	North America	43 (13.4)	41 (12.8)	52 (18.2)
	Rest of world*	57 (17.8)	50 (15.6)	44 (15.4)
Race, n (%)†	Asian	160 (49.8)	157 (49.1)	127 (44.4)
	White	140 (43.6)	137 (42.8)	139 (48.6)
	Black or African American	5 (1.6)	7 (2.2)	7 (2.4)
	Other	12 (3.7)	10 (3.1)	8 (2.8)
Eastern Cooperative Oncology Group performance status score, n (%)	0	278 (86.6)	280 (87.5)	252 (88.1)
	1	43 (13.4)	40 (12.5)	34 (11.9)
HER2 status, n (%)‡	IHC 3+	280 (87.2)	283 (88.4)	254 (88.8)
	Other	40 (12.5)	36 (11.3)	32 (11.2)
HR status, n (%)§	Positive¶	236 (73.5)	235 (73.4)	205 (71.7)
Clinical tumor stage, n (%)	cT0–2	176 (54.8)	188 (58.8)	157 (54.9)
	cT3–4	145 (45.2)	132 (41.3)	129 (45.1)
Nodal status, n (%)‖	N0	26 (8.1)	35 (10.9)	20 (7.0)
	N+	287 (89.4)	281 (87.8)	254 (88.8)

*Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia; †not reported for four patients (1.2%), nine patients (2.8%) and five patients (1.7%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively; ‡centrally confirmed. Not categorized for one patient (0.3%) in the T-DXd-THP arm and missing for one patient (0.3%) in the ddAC-THP arm; §the proportion of patients with HR-negative disease was capped at 30% to reflect natural prevalence. Missing for two patients (0.6%) and one patient (0.3%) in the T-DXd-THP and T-DXd alone arms, respectively; ¶ER and/or PR-positive per electronic case report form data; ‖unknown in eight patients (2.5%), four patients (1.3%), and 12 patients (4.2%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively

pCR (ypT0/is ypN0): primary endpoint



Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP

Improvement was observed in both the HR-positive and HR-negative subgroups

For the ITT population, treatment effects were estimated by the difference in pCR with 95% CIs and P-values based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel–Haenszel weights)
Patients with no valid records regarding pCR status for any reason were considered to be non-responders (including but not limited to withdrawal from the study, progression of disease or death before surgery, lack of surgical specimen, or defined as not evaluable by the central pathologist). Subgroup analyses were unstratified. *By blinded central review; †pCR responders were defined as patients who only received randomized study treatment (at least one dose) and had pCR; ‡two-sided P-value crossed the 0.03 prespecified boundary. ITT, intent-to-treat

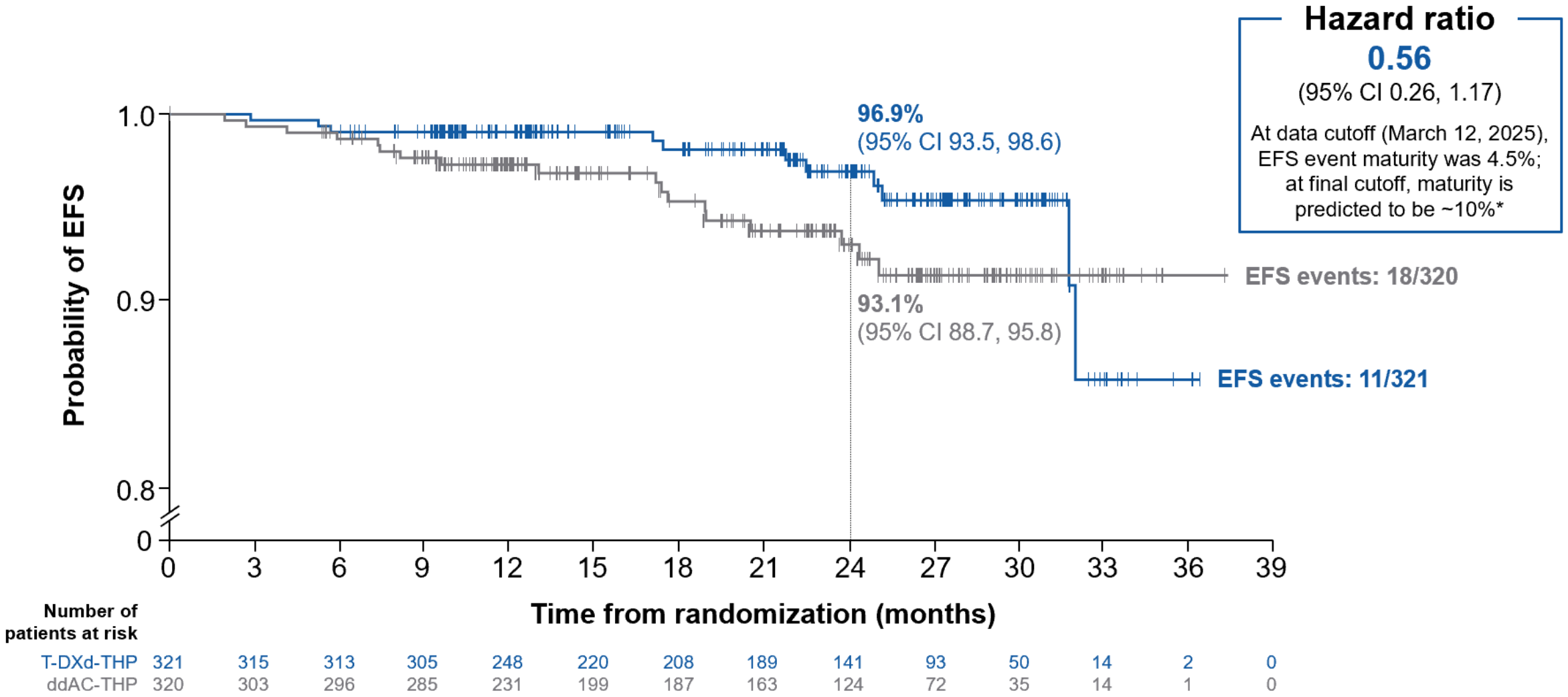
pCR (ypT0/is ypN0) by subgroups

		pCR rate, % (n/N) T-DXd-THP (n=321)	ddAC-THP (n=320)	ΔpCR, % (95% CI)
All patients		67.3 (216/321)	56.3 (180/320)	**11.2** (4.0, 18.3)
Age at baseline	<65 years	66.7 (188/282)	58.0 (167/288)	**8.7** (0.7, 16.5)
	≥65 years	71.8 (28/39)	40.6 (13/32)	**31.2** (8.0, 51.4)
Geographical region	Asia	66.5 (101/152)	56.6 (86/152)	**9.9** (−1.1, 20.6)
	Western Europe	75.4 (52/69)	62.3 (48/77)	**13.0** (−2.2, 27.5)
	North America	74.4 (32/43)	36.6 (15/41)	**37.8** (16.8, 55.7)
	Rest of world*	54.4 (31/57)	62.0 (31/50)	**−7.6** (−25.7, 11.2)
Eastern Cooperative Oncology Group performance status score	0	68.7 (191/278)	55.7 (156/280)	**13.0** (5.0, 20.9)
	1	58.1 (25/43)	60.0 (24/40)	**−1.9** (−22.6, 19.1)
Menopausal status	Post	68.8 (86/125)	56.9 (87/153)	**11.9** (0.5, 23.0)
	Pre	66.9 (123/184)	55.2 (90/163)	**11.6** (1.4, 21.7)
HER2 status	IHC 3+	71.1 (199/280)	61.5 (174/283)	**9.6** (1.8, 17.3)
	Other	42.5 (17/40)	16.7 (6/36)	**25.8** (5.2, 44.4)
HR status	Positive	61.4 (145/236)	52.3 (123/235)	**9.1** (0.2, 17.9)
	Negative	83.1 (69/83)	67.1 (57/85)	**16.1** (3.0, 28.8)
American Joint Committee on Cancer clinical stage	II–IIIA	65.7 (163/248)	56.4 (146/259)	**9.4** (0.9, 17.7)
	IIIB–IIIC	72.2 (52/72)	55.7 (34/61)	**16.5** (0.1, 32.3)
Nodal status	N0	57.7 (15/26)	57.1 (20/35)	**0.6** (−24.2, 24.8)
	N+	68.3 (196/287)	56.6 (159/281)	**11.7** (3.8, 19.5)

Improvement in pCR for T-DXd-THP vs ddAC-THP was observed across most pre-specified subgroups

Size of circle is proportional to the total sample size in a subgroup. *Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia

EFS



An early positive trend in EFS was observed, favoring T-DXd-THP vs ddAC-THP

The median duration of follow up was 24.3 months with T-DXd-THP and 23.6 months with ddAC-THP. *Predicted maturity assumes that the observed EFS hazard ratio continues after data cutoff (March 12, 2025)

Overall safety summary

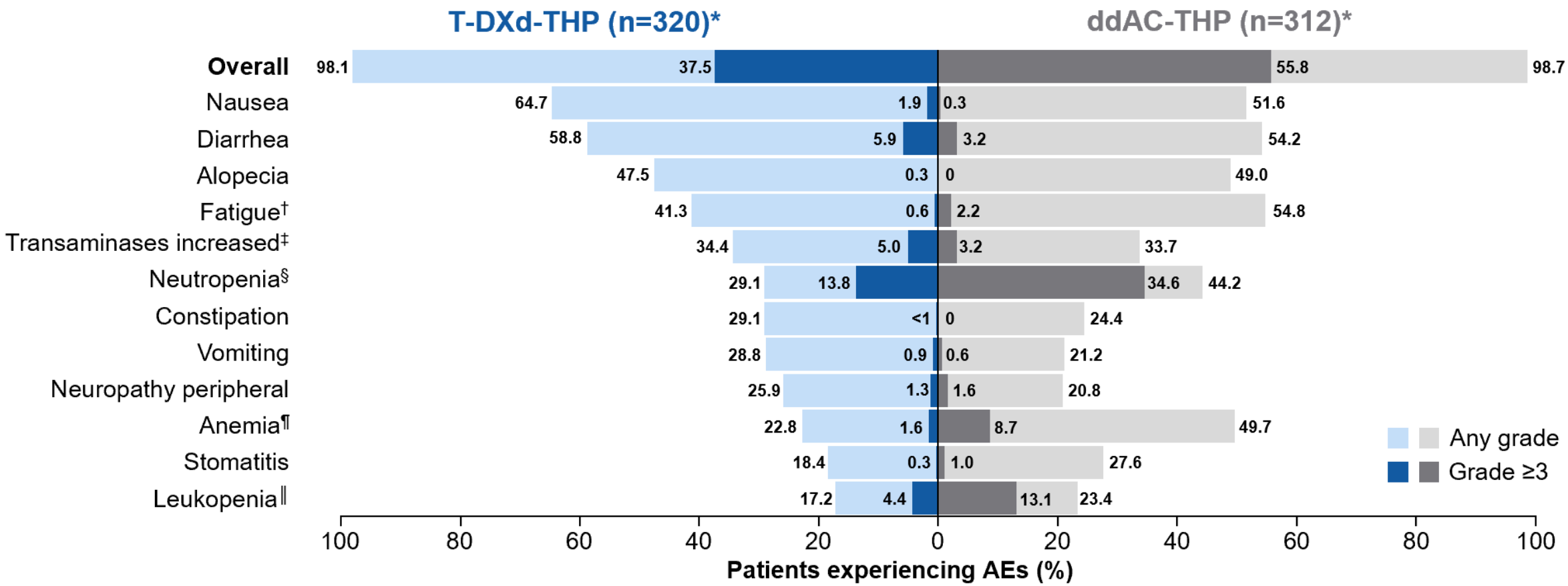
n (%)	T-DXd-THP (n=320)*	ddAC-THP (n=312)*
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any serious AE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death†	2 (0.6)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.4)	16 (5.1)
Grade ≥3	2 (0.6)	6 (1.9)
Grade 5	1 (0.3)	1 (0.3)
Left ventricular dysfunction	4 (1.3)	19 (6.1)
Grade ≥3	1 (0.3)	6 (1.9)
Grade 5	0	0
AE leading to surgical delay‡	11 (3.4)	8 (2.6)

The overall safety profile of T-DXd-THP was favorable vs ddAC-THP, with reduced rates of Grade ≥3 AEs, serious AEs, treatment interruptions, and left ventricular dysfunction

ILD incidence was low and similar in both arms

High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. Median total treatment duration of whole regimen was 24.1 months (T-DXd-THP), and 21.0 months (ddAC-THP). *Safety analyses included all patients who received at least one dose of any study treatment; †T-DXd-THP arm: death of unknown cause (n=1), drug-related pneumonitis adjudicated by the Independent ILD Adjudication Committee (n=1); ddAC-THP arm: investigator-determined drug-related bacterial encephalitis (n=1), drug-related pneumonitis adjudicated by the ILD Adjudication Committee (n=1); ‡defined as surgery not occurring within 3–6 weeks after the last cycle of neoadjuvant treatment

Treatment-emergent AEs in at least 20% of patients in either arm



T-DXd-THP had fewer any-grade and Grade ≥3 hematological and fatigue events than ddAC-THP
Aside from nausea, gastrointestinal toxicity was comparable between arms

*Safety analyses included all patients who received at least one dose of any study treatment; †grouped term: fatigue, asthenia, malaise, and lethargy; ‡grouped term: transaminases increased, aspartate transaminase increased, alanine transaminase increased, gamma-glutamyl transferase increased, liver function test abnormal, hypertransaminasemia, hepatic function abnormal, and liver function test increased; §grouped term: neutrophil count decreased and neutropenia; ¶grouped term: hemoglobin decreased, red blood cell count decreased, and anemia and hematocrit decreased; ‖grouped term: white blood cell count decreased and leukopenia. TEAE, treatment-emergent adverse event

Conclusions

- In DESTINY-Breast11, **T-DXd-THP showed the highest reported pCR rate in HER2+ eBC** for a registrational study in the neoadjuvant setting, despite a **high prevalence of HR-positive disease** and a **high-risk population**[1–3*]
- **T-DXd-THP showed a statistically significant and clinically meaningful improvement in pCR rate** vs ddAC-THP: Δ11.2% (95% CI 4.0, 18.3)
  - pCR benefit for T-DXd-THP vs ddAC-THP was independent of HR status and disease stage
- An **early positive trend in EFS** was observed, favoring T-DXd-THP vs ddAC-THP
  - Hazard ratio: 0.56 (95% CI 0.26, 1.17)
- The **safety profile of T-DXd-THP was favorable vs ddAC-THP**
  - Lower rates of Grade ≥3 AEs, serious AEs, and AEs leading to dose interruptions
  - Lower rates of hematological AEs, left-ventricular dysfunction, and fatigue
  - ILD rates were low and similar between arms

pCR rate

67.3%

More than two thirds of patients in the T-DXd-THP arm had a pCR

HR-positive: **61.4%**
HR-negative: **83.1%**

DESTINY-Breast11 results support T-DXd-THP as a more effective and less toxic neoadjuvant treatment compared with ddAC-THP, and it may become a preferred regimen for patients with high-risk HER2+ eBC

*Historical pCR rates (defined by ypT0/is ypN0) from other registrational studies for neoadjuvant SOC treatments in HER2+ eBC ranged from 39.3% to 62.7%, and HR-positive prevalence ranged from 46.7% to 62.4%[1–3]

1. Huober J, et al. *J Clin Oncol*. 2022;40:2946–2956; 2. Hurvitz SA, et al. *Lancet Oncol*. 2018;19:115–126; 3. Gianni L, et al. *Lancet Oncol*. 2012;13:25–32

Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with high-risk human epidermal growth factor receptor 2–positive (HER2+) primary breast cancer with residual invasive disease after neoadjuvant therapy: Interim analysis of DESTINY-Breast05

Charles E Geyer Jr,[a,b] Yeon Hee Park, Zhiming Shao, Chiun-Sheng Huang, Carlos Barrios, Jame Abraham, Aleix Prat, Naoki Niikura, Michael Untch,
Seock-Ah Im, Wei Li, Huiping Li, Yongsheng Wang, Herui Yao, Sung-Bae Kim, Elton Mathias, Yuta Sato, Wenjing Lu, Hanan Abdel-Monem, Sibylle Loibl

On behalf of the DESTINY-Breast05 investigators

[a]NSABP Foundation, Pittsburgh, PA, USA
[b]University of Pittsburgh Hillman Cancer Center, Pittsburgh, PA, USA

DESTINY-Breast05 study design

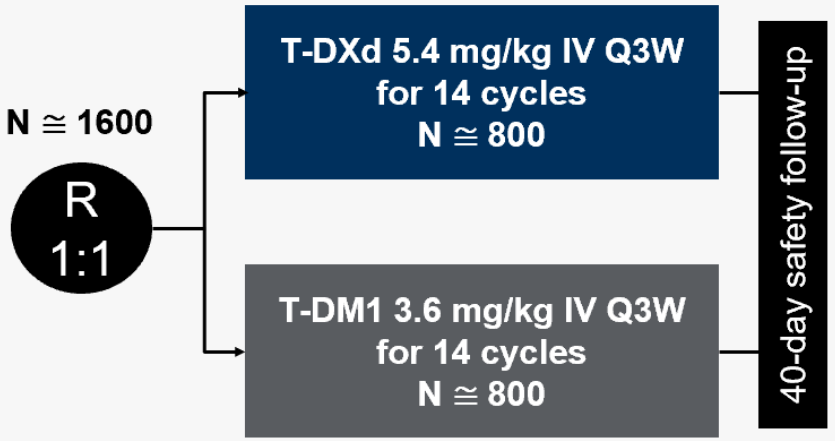
A global, multicenter, randomized, open-label phase 3 trial (NCT04622319)

Key Eligibility Criteria

- **Residual invasive disease in the breast and/or axillary lymph nodes** after neoadjuvant chemotherapy with HER2-directed therapy (NAT)[a]
- **High-risk defined as presentation prior to NAT with:**
  - **Inoperable eBC (cT4,N0-3,M0 or cT1-3,N2-3,M0) OR**
  - **Operable eBC (cT1-3,N0-1,M0) with axillary node–positive disease (ypN1-3) after NAT**
- **Centrally confirmed HER2+** (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1

Stratification factors

- Extent of disease at presentation (inoperable, operable)
- HER2-targeted NAT (single, dual)
- Hormone receptor status (positive, negative)
- Post-NAT pathologic nodal status (positive, negative)



Primary endpoint

- IDFS

Key secondary endpoint

- DFS

Other secondary endpoints

- OS
- DRFI
- BMFI
- Safety

- **Concomitant adjuvant ET was allowed per local practices**
- **If administered, RT could be initiated concurrent with study therapy or completed prior to initiation of study therapy (sequential) per investigator**
- **ILD monitoring program for patients treated with RT**
  - All patients had baseline non-contrast, low dose (LD) chest CT during screening
  - All RT patients (concurrent and sequential) had LD chest CT 6 weeks after start of study therapy, then every 12 weeks while on therapy, and at 40-day follow-up
  - Sequential RT patients had additional LD chest CT after completion of RT prior to start of study therapy

BMFI, brain metastasis–free interval; CT, computed tomography; eBC, early breast cancer; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence–free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]NAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy.

Baseline demographics and clinical characteristics

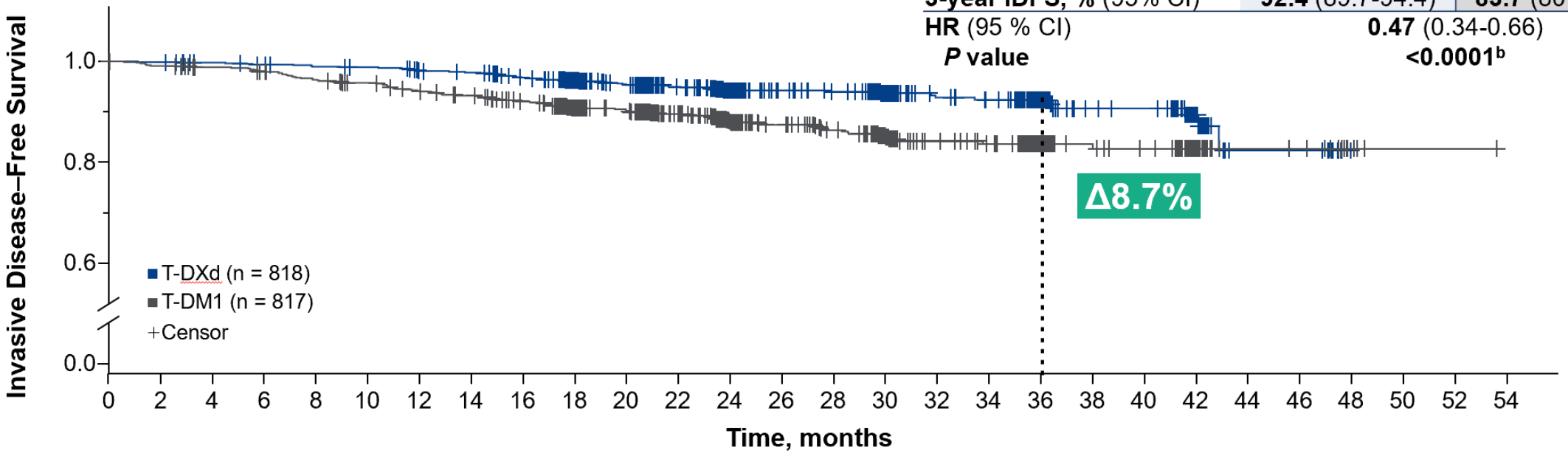
	T-DXd n = 818	T-DM1 n = 817
Age, median (range), years	50.3 (24-78)	50.6 (21-83)
<65	735 (89.9)	736 (90.1)
≥65	83 (10.1)	81 (9.9)
Female sex, n (%)	814 (99.5)	814 (99.6)
Race		
White	301 (36.8)	333 (40.8)
Black or African American	22 (2.7)	13 (1.6)
Asian	**399 (48.8)**	**386 (47.2)**
Other	96 (11.7)	85 (10.4)
Region, n (%)		
Asia	**392 (47.9)**	**380 (46.5)**
Europe	222 (27.1)	223 (27.3)
North America + Australia	57 (7.0)	72 (8.8)
Rest of world[a]	147 (18.0)	142 (17.4)
ECOG PS score, n (%)		
0	656 (80.2)	652 (79.8)
1	162 (19.8)	165 (20.2)
HER2 expression,[b] n (%)		
IHC 3+	**676 (82.6)**	**670 (82.0)**
IHC 2+ and ISH+	129 (15.8)	133 (16.3)
IHC 2+ and ISH−	2 (0.2)	0
IHC 1+ and ISH+	11 (1.3)	14 (1.7)
Hormone receptor status,[c] n (%)		
Positive	**581 (71.0)**	**583 (71.4)**
Negative	237 (29.0)	234 (28.6)

	T-DXd n = 818	T-DM1 n = 817
Operative status at disease presentation,[c] n (%)		
Operable (cT1-3, N0-1, M0)	387 (47.3)	393 (48.1)
Inoperable (cT4, N0-3, M0 or cT1-3, N2-3, M0)	**431 (52.7)**	**424 (51.9)**
Post-NAT pathologic nodal status,[c] n (%)		
Positive	**660 (80.7)**	**658 (80.5)**
Negative	158 (19.3)	159 (19.5)
Neoadjuvant HER2-targeted therapy, n (%)		
Trastuzumab alone	176 (21.5)	171 (20.9)
Trastuzumab + pertuzumab	**637 (77.9)**	**641 (78.5)**
Trastuzumab + other HER2-targeted therapy	3 (0.4)	3 (0.4)
Trastuzumab + pertuzumab + other HER2-targeted therapy	2 (0.2)	2 (0.2)
Neoadjuvant chemotherapy, n (%)		
Taxanes	818 (100)	817 (100)
Platinum compounds	386 (47.2)	392 (48.0)
Anthracycline	**423 (51.7)**	**399 (48.8)**
Radiotherapy treatment, n (%)		
Adjuvant radiotherapy	**764 (93.4)**	**759 (92.9)**
Concurrent	438 (53.5)	480 (58.8)
Sequential	326 (39.9)	279 (34.1)
No radiotherapy	54 (6.6)	58 (7.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NAT, neoadjuvant therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Included regions: Argentina, Brazil, Chile, Czech Republic, Israel, Mexico, Peru, Poland, Romania, Russian Federation. [b]Centrally confirmed. [c]As reported in electronic data capture.

Primary endpoint: IDFS[a]

	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:

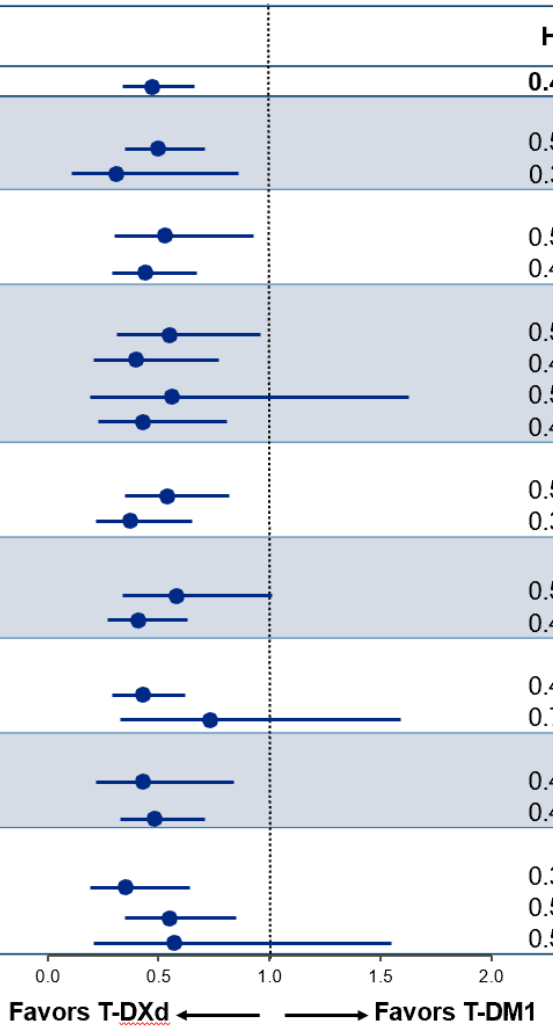
T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0

53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1

HR, hazard ratio; IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, *P* = 0.0183.
[a]IDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. [b]Two-sided *P* value from stratified log-rank test. Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

Primary endpoint subgroup analysis: IDFS

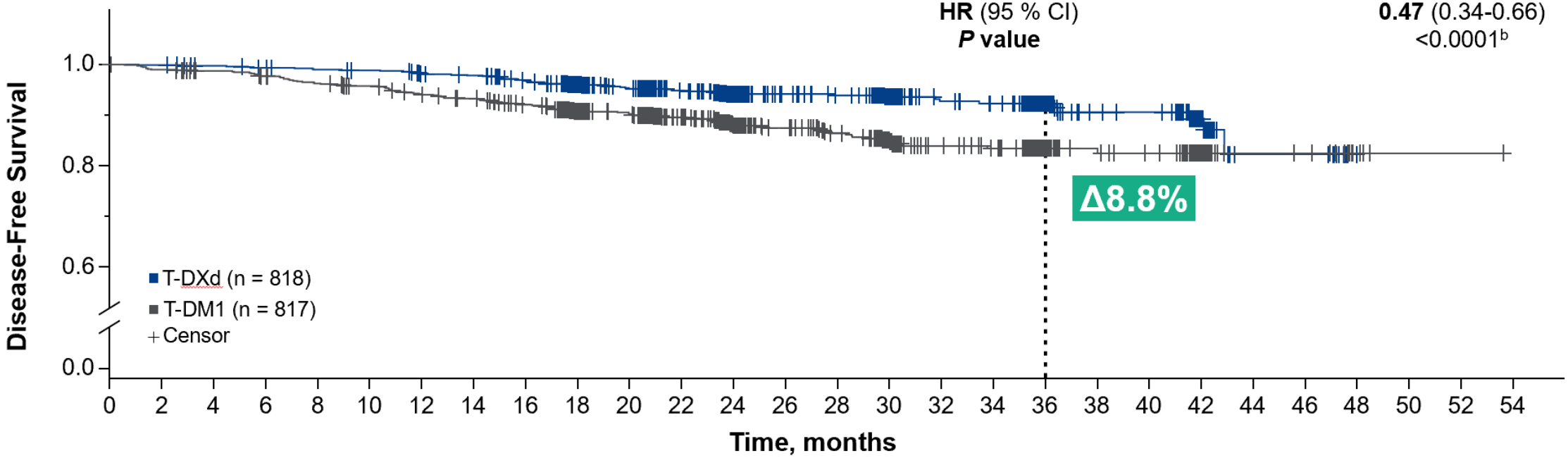
	No. events/patients		3-year IDFS, % (95% CI)		
	T-DXd	T-DM1	T-DXd n = 818	T-DM1 n = 817	HR (95% CI)[b]
All patients	**51/818**	**102/817**	**92.4 (89.7-94.4)**	**83.7 (80.2-86.7)**	**0.47 (0.34-0.66)**
Age					
<65 years	46/735	87/736	92.1 (89.2-94.3)	84.1 (80.2-87.2)	0.50 (0.35-0.71)
≥65 years	5/83	15/81	94.9 (87.0-98.1)	79.2 (67.9-87.0)	0.31 (0.11-0.86)
Race					
Asian	19/399	34/386	95.1 (91.9-97.0)	89.5 (85.3-92.6)	0.53 (0.30-0.93)
Non-Asian	32/419	68/431	89.5 (84.5-93.0)	77.9 (72.1-82.7)	0.44 (0.29-0.67)
Region					
Asia	19/392	33/380	95.0 (91.9-97.0)	89.7 (85.4-92.7)	0.55 (0.31-0.96)
Europe	13/222	30/223	93.1 (86.9-96.4)	82.9 (75.8-88.1)	0.40 (0.21-0.77)
North America + Australia	5/57	10/72	85.8 (63.9-94.9)	80.7 (65.3-89.7)	0.56 (0.19-1.63)
Rest of world	14/147	29/142	85.1 (73.6-91.8)	69.2 (56.3-79.0)	0.43 (0.23-0.81)
Hormone receptor status					
Postive	33/581	59/583	93.5 (90.6-95.6)	86.8 (82.9-89.9)	0.54 (0.35-0.82)
Negative	18/237	43/234	89.4 (82.0-93.9)	75.6 (67.6-81.9)	0.37 (0.22-0.65)
Disease status at presentation before NAT					
Operable (cT1-3, N0-1, M0)	21/387	34/393	92.8 (88.0-95.7)	88.4 (83.8-91.8)	0.58 (0.34-1.01)
Inoperable (cT4, N0-3, M0 or cT1-3, N2-3, M0)	30/431	68/424	92.0 (88.5-94.5)	79.4 (73.9-83.8)	0.41 (0.27-0.63)
Post-NAT pathologic nodal status					
Positive[a]	40/660	87/658	92.5 (89.3-94.8)	82.5 (78.4-85.9)	0.43 (0.29-0.62)
Negative[a]	11/158	15/159	91.6 (85.3-95.3)	88.3 (80.6-93.0)	0.73 (0.33-1.59)
HER2-targeted NAT					
Single	13/176	27/171	87.5 (77.6-93.3)	77.9 (67.7-85.2)	0.43 (0.22-0.84)
Dual	38/642	75/646	93.6 (90.9-95.5)	85.2 (81.4-88.2)	0.48 (0.33-0.71)
Radiotherapy treatment					
Sequential radiotherapy	15/326	34/279	93.8 (88.4-96.7)	83.2 (76.4-88.2)	0.35 (0.19-0.64)
Concurrent radiotherapy	30/438	57/480	92.8 (89.7-95.0)	85.1 (80.6-88.6)	0.55 (0.35-0.85)
No radiotherapy	6/54	11/58	81.0 (61.0-91.4)	73.4 (56.4-84.6)	0.57 (0.21-1.55)



HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDFS, invasive disease–free survival; NAT, neoadjuvant therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Positive pathologic nodal status defined as ypN1-3 and negative pathologic nodal status defined as ypN0. [b]From unstratified Cox proportional hazards model.

Key secondary endpoint: DFS[a]

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	**52** (6.4)	**103** (12.6)
3-year DFS, % (95% CI)	**92.3** (89.5-94.3)	**83.5** (79.9-86.4)
HR (95 % CI)	**0.47** (0.34-0.66)	
***P* value**	<0.0001[b]	



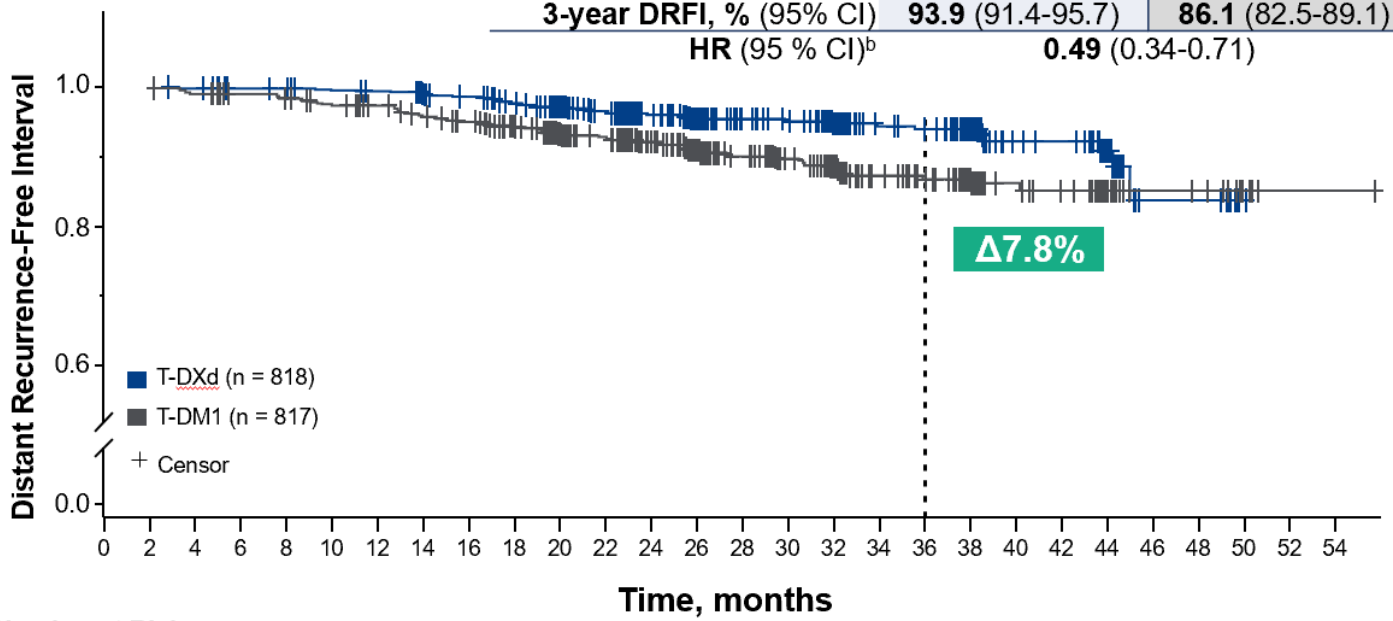
Number at Risk:

T-DXd	818	788	781	776	771	768	758	753	731	683	633	543	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	779	767	757	743	733	718	707	686	631	598	526	416	354	336	233	186	177	120	84	79	38	14	13	4	1	1	0

DFS, disease-free survival; HR, hazard ratio; INV, investigator assessment; STEEP, Standardized Definitions for Efficacy End Points in adjuvant breast cancer trials; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, *P* = 0.0144.
[a]DFS defined as the time between randomization and the date of the first occurrence of an IDFS event per STEEP criteria, including second primary non-breast cancer event or contralateral or ipsilateral ductal carcinoma in situ. [b]Two-sided *P* value from stratified log-rank test. Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

Secondary endpoints: DRFI[a], BMFI, and OS

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	**42** (5.1)	**81** (9.9)
3-year DRFI, % (95% CI)	**93.9** (91.4-95.7)	**86.1** (82.5-89.1)
HR (95 % CI)[b]	**0.49** (0.34-0.71)	



Number at Risk:

T-DXd	818	786	778	774	770	767	757	753	731	684	635	545	442	382	372	276	219	213	129	92	90	46	14	14	0	0	0	0
T-DM1	817	780	769	761	746	739	724	713	694	639	606	533	424	362	345	240	192	182	121	84	79	38	14	13	4	1	1	0

	T-DXd n = 818	T-DM1 n = 817
BMFI		
Patients with recurrence in CNS, n (%)	**17** (2.1)	**26** (3.2)
3-year BMFI rate, % (95% CI)	**97.6** (96.2-98.5)	**95.8** (93.6-97.2)
HR (95% CI)[b]	**0.64** (0.35-1.17)	
OS (2.9% maturity)		
Patient deaths, n (%)	**18** (2.2)	**29** (3.5)
Survival at 3 years % (95% CI)	**97.4** (95.8-98.4)	**95.7** (93.5-97.2)
HR (95% CI)[b]	**0.61** (0.34-1.10)	

BMFI, brain metastasis–free interval; DRFI, distant recurrence–free interval; HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]DRFI is defined as the time between randomization and the date of distant breast cancer recurrence. [b]HR and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

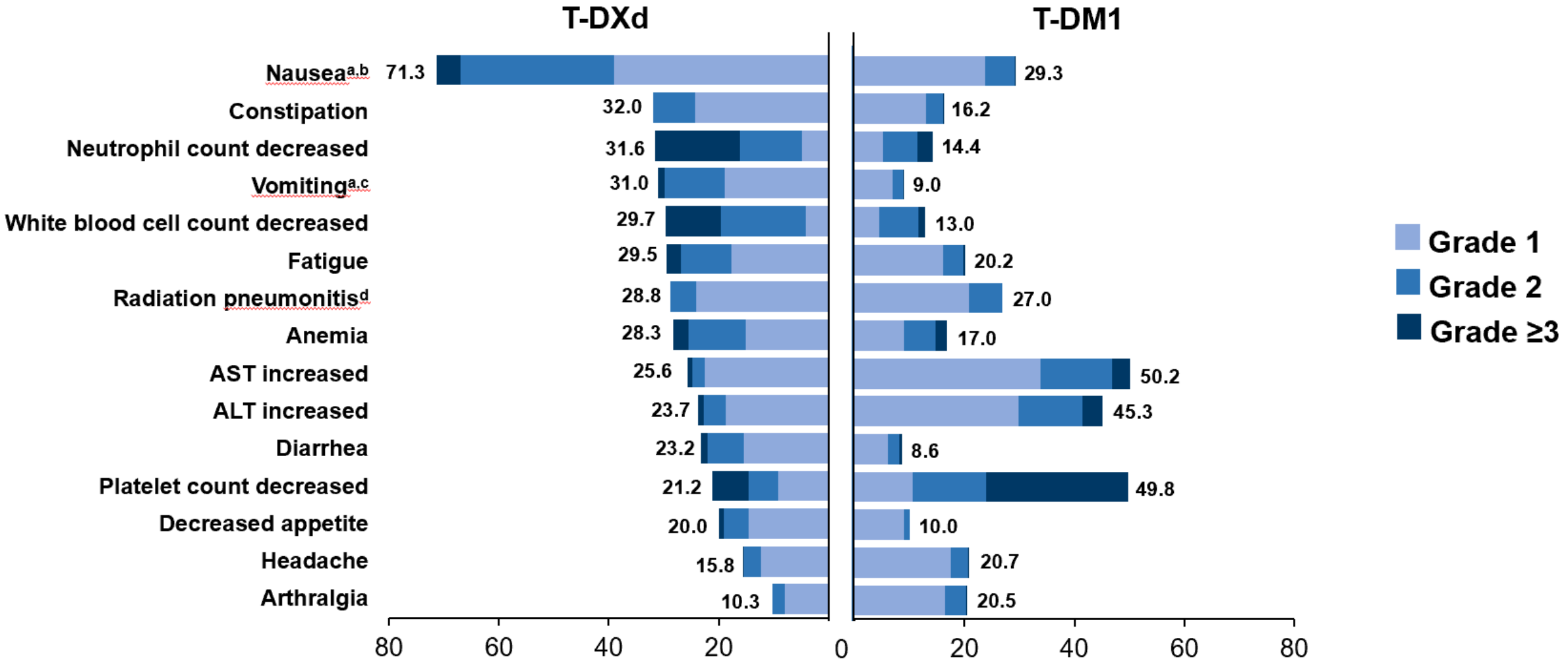
Overall safety summary

TEAEs, n (%)	T-DXd n = 806[a]	T-DM1 n = 801[a]
Any grade	802 (99.5)	788 (98.4)
Grade ≥3	**408 (50.6)**	**416 (51.9)**
Serious	**140 (17.4)**	**109 (13.6)**
Associated with drug discontinuation	**144 (17.9)**	**103 (12.9)**
Drug-related ILD/pneumonitis[b]	**87 (10.8)**	**20 (2.5)**
Associated with drug interruptions	400 (49.6)	329 (41.1)
Associated with dose reductions	**213 (26.4)**	**213 (26.6)**
Associated with deaths	**3 (0.4)**	**5 (0.6)**

- **In the T-DXd arm, causes of death (n = 3) were 2 ILD/pneumonitis[c] and respiratory tract infection (adjudicated as not ILD)**
- **In the T-DM1 arm, causes of death (n = 5) were leiomyosarcoma of the uterus, aneurysm, non-neutropenic sepsis, ovarian cancer, and traumatic pneumothorax**

ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-related adverse event.
[a]All patients who received at least 1 dose of study treatment. [b]Investigator-assessed as drug-related ILD and pneumonitis per preferred term. [c]Investigator assessed and adjudication committee confirmed.

TEAEs in ≥20% of patients (either arm)



ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Prophylactic antiemetics were recommended but not mandatory. [b]In the T-DXd and T-DM1 arms: 39.1% and 23.7% grade 1, 27.8% and 5.5% grade 2, and 4.5% and 0.1% grade 3 events, respectively. [c]In the T-DXd and T-DM1 arms: 19.0% and 6.9% grade 1, 10.9% and 2.0% grade 2, and 1.1% and 0.1% grade 3 events. [d]In the T-DXd and T-DM1 arms: 24.2% and 20.8% grade 1, 4.6% and 6.1% grade 2 events.

Adverse events of special interest: ILD/pneumonitis and LV dysfunction

n (%)	Adjudicated Drug-related ILD					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806)[a]	77 (9.6)	16 (2.0)	52 (6.5)	7 (0.9)	0	2 (0.2)
T-DM1 (n = 801)[a]	13 (1.6)	8 (1.0)	5 (0.6)	0	0	0

Adjuvant radiotherapy timing (sequential or concurrent) showed no differences in adjudicated drug-related ILD

Similar distributions of any grade adjudicated drug-related ILD events were observed with sequential and concurrent radiotherapy in both treatment arms (T-DXd: 10.7% and 9.6.% vs T-DM1: 2.6% and 1.0%, respectively)

n (%)	LV dysfunction					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806)[a]	23 (2.9)	1 (0.1)	20 (2.5)	2 (0.2)	0	0
T-DM1 (n = 801)[a]	14 (1.7)	0	11 (1.4)	3 (0.4)	0	0

CT, computed tomography; ILD, interstitial lung disease; LV, left ventricular; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All patients who received at least 1 dose of study treatment.

Conclusions

- DESTINY-Breast05 demonstrated **a statistically significant and clinically meaningful improvement in IDFS and DFS with T-DXd vs T-DM1 in high-risk[a] patients with HER2+ eBC and residual invasive disease after NAT**
- **IDFS benefit was consistent across all prespecified subgroups**
- **Benefit in DRFI with T-DXd was also observed**
- **CNS metastases and deaths were numerically fewer with T-DXd vs T-DM1**
- The overall **safety profile** of T-DXd was **manageable with no new signals**
  - >72% of patients completed treatment and was comparable in both arms
  - **Adjudicated drug-related ILD was reported in 9.6% of patients receiving T-DXd, with the majority being grade 1 or 2 and reversible**, suggesting that the risk is manageable with appropriate monitoring and timely intervention

IDFS Benefit T-DXd versus T-DM1

53% reduction in the risk of invasive disease recurrence or death

3-year IDFS rate
92.4% versus 83.7%
HR 0.47
***P* value <0.0001**

Adjuvant T-DXd demonstrated superior efficacy with manageable safety in patients with high-risk HER2+ eBC and residual invasive disease after NAT, representing a potential new standard of care in this post-neoadjuvant setting

DFS, disease-free survival; eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDFS, invasive disease–free survival; ILD, interstitial lung disease; NAT, neoadjuvant therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Defined as cT4, N0-3, M0 or cT1-3, N2-3, M0 at presentation (before NAT) or cT1-3, N0-1, M0, with axillary node–positive disease (ypN1-3) following NAT.

First-line datopotamab deruxtecan (Dato-DXd) vs chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) for whom immunotherapy was not an option: Primary results from the randomised, phase 3 TROPION-Breast02 trial

Rebecca A. Dent[1], Zhimin Shao[2], Peter Schmid[3], Javier Cortés[4], David W. Cescon[5], Shigehira Saji[6], Kyung Hae Jung[7], Thomas Bachelot[8], Shouman Wang[9], Gul Basaran[10], Yee Soo Chae[11], Rofhiwa Mathiba[12], Shin-Cheh Chen[13], Agostina Stradella[14], Nicola Battelli[15], Naoki Niikura[16], Kechen Zhao[17], Petra Vuković[18], Micah J. Maxwell[19], Tiffany A. Traina[20]

[1]National Cancer Center Singapore, Singapore; [2]Fudan University Shanghai Cancer Center, Fudan, China; [3]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK; [4]International Breast Cancer Center (IBCC), Pangaea Oncology, Barcelona, Spain; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Fukushima Medical University, Fukushima, Japan; [7]Asan Medical Center – University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Centre Léon Bérard, Lyon, France; [9]Xiangya Hospital of Central South University, Changsha, China; [10]MAA Acibadem University, School of Medicine, Medical Oncology Department, Istanbul, Türkiye; [11]Kyungpook National University Chilgok Hospital, Kyungpook National University School of Medicine, Kyungpook, Republic of Korea; [12]Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [13]Chang Gung Medical Foundation – Taipei Chang Gung Memorial Hospital, Taipei City, Taiwan; [14]Institut Catala d'Oncologia - Hospital Duran i Reynals (ICO L'Hospitalet), Barcelona, Spain; [15]Ospedale Generale Provinciale Macerata, Macerata, Italy; [16]Tokai University School of Medicine, Kanagawa, Japan; [17]Biometrics, Late-Stage Development, Oncology R&D, AstraZeneca, Wilmington, DE, USA; [18]Clinical Development, Late-Stage Development, Oncology R&D, AstraZeneca, Cambridge, UK; [19]Clinical Development, Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, MD, USA; [20]Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY, USA

TROPION-Breast02: Study Design

Randomised, phase 3, open-label, global study (NCT05374512)

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.

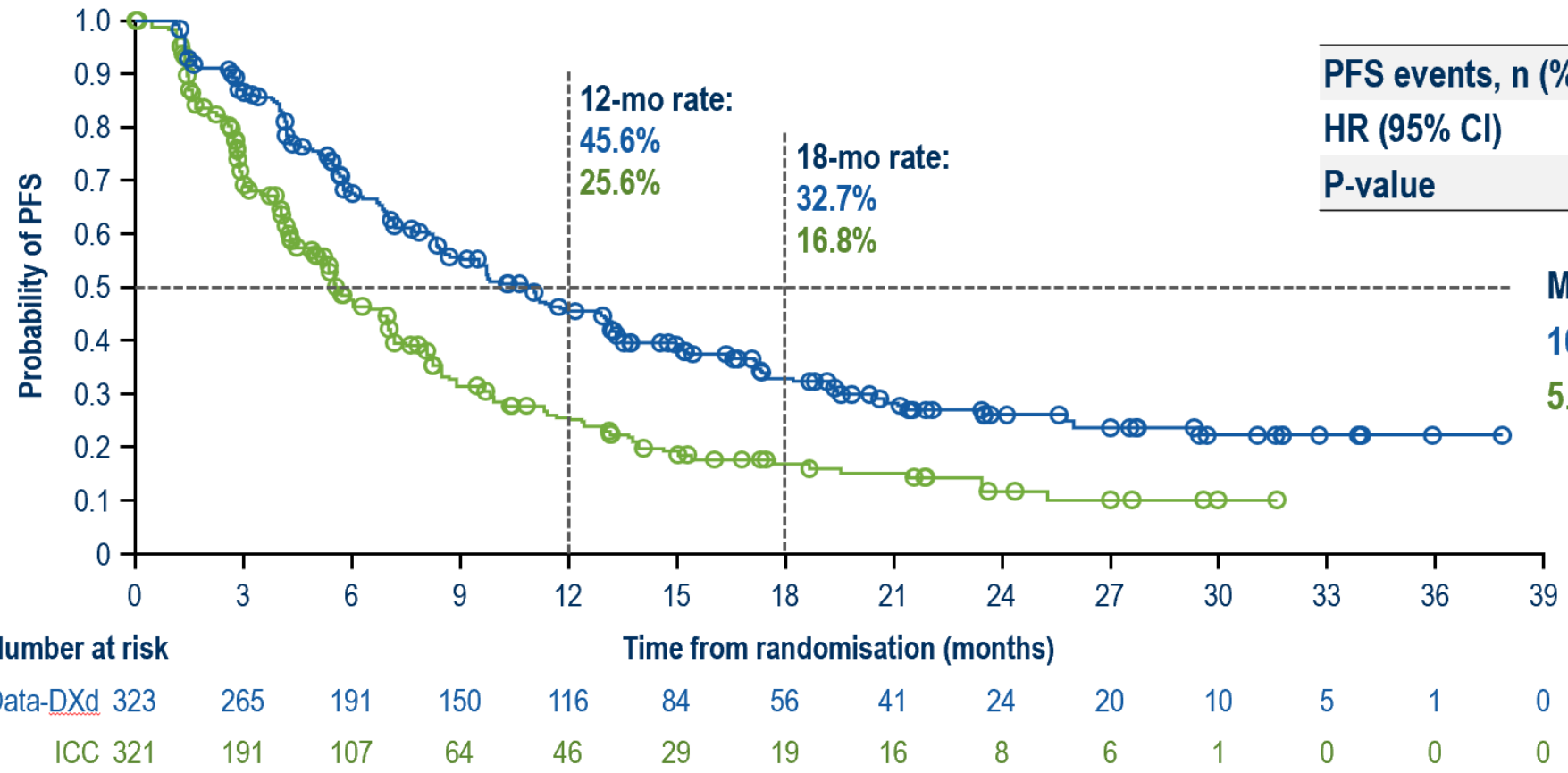
Demographics and Baseline Characteristics

		Dato-DXd (n=323)	ICC (n=321)
Median age (range), years		56 (27–85)	57 (23–83)
Female, n (%)		323 (100)	319 (99)
Race, n (%)	Black or African American	13 (4)	14 (4)
	Asian	151 (47)	131 (41)
	White	131 (41)	153 (48)
	Other*	28 (9)	23 (7)
Geographic region, n (%)	US, Canada, Europe	120 (37)	120 (37)
	Other geographic regions	203 (63)	201 (63)
ECOG PS, n (%)	0	195 (60)	182 (57)
	1	128 (40)	139 (43)
DFI history, n (%)	*De novo*	109 (34)	110 (34)
	Prior DFI 0–12 months‡	67 (21)	66 (21)
	Prior DFI 0–6 months	***47 (15)***	***51 (16)***
	Prior DFI >12 months‡	147 (46)	145 (45)

		Dato-DXd (n=323)	ICC (n=321)
PD-L1 status,† n (%)	Low (CPS <10)	287 (89)	291 (91)
	High (CPS ≥10)	34 (11)	29 (9)
Metastases, n (%)	Visceral	253 (78)	233 (73)
	Liver	93 (29)	98 (31)
	Brain§	36 (11)	28 (9)
Number of metastatic sites, n (%)	<3	207 (64)	215 (67)
	≥3	116 (36)	106 (33)
Pre-selected choice of chemotherapy, n (%)	Nab-paclitaxel	180 (56)	172 (54)
	Paclitaxel	82 (25)	92 (29)
	Eribulin mesylate/eribulin	43 (13)	35 (11)
	Carboplatin	11 (3)	14 (4)
	Capecitabine	7 (2)	8 (2)

*Including not reported. †Based on central laboratory testing, using Agilent PD-L1 IHC 22C3 pharmDx Assay (Agilent Technologies, Santa Clara, CA); PD-L1 status missing/not applicable in 2 patients in the Dato-DXd arm and 1 patient in the ICC arm. ‡Prior (neo)adjuvant cancer therapy was received by 66% of patients, including nitrogen mustards (57%), taxanes (57%), anthracyclines (56%), pyrimidine analogues (27%), platinum compounds (16%), and PD-(L)1 inhibitors (5%). §Patients with asymptomatic, stable brain metastases were permitted in the study.

Progression-Free Survival by BICR



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

Median PFS (95% CI)

10.8 mo (8.6–13.0)

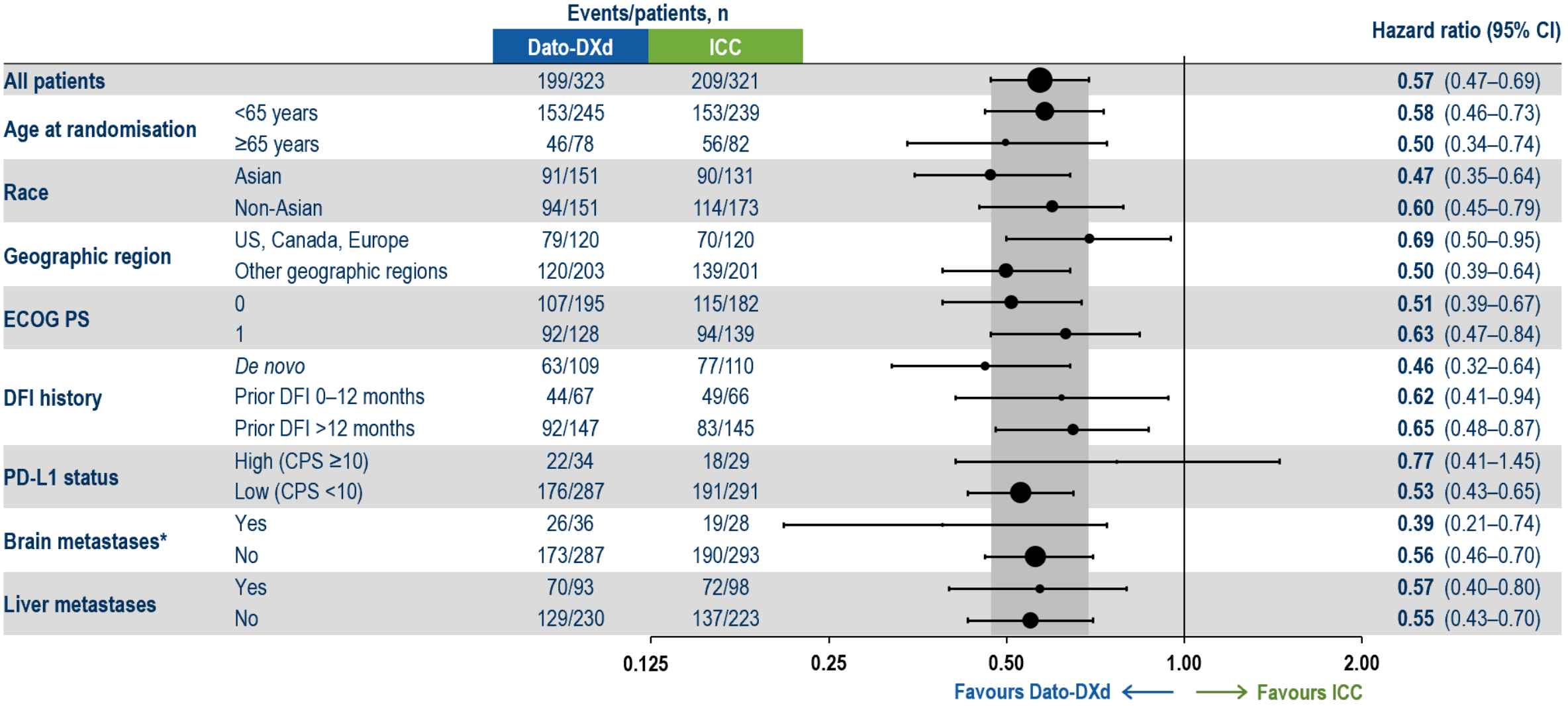
5.6 mo (5.0–7.0)

Δ 5.3 mo*

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with ICC, reducing the risk of progression or death by 43%

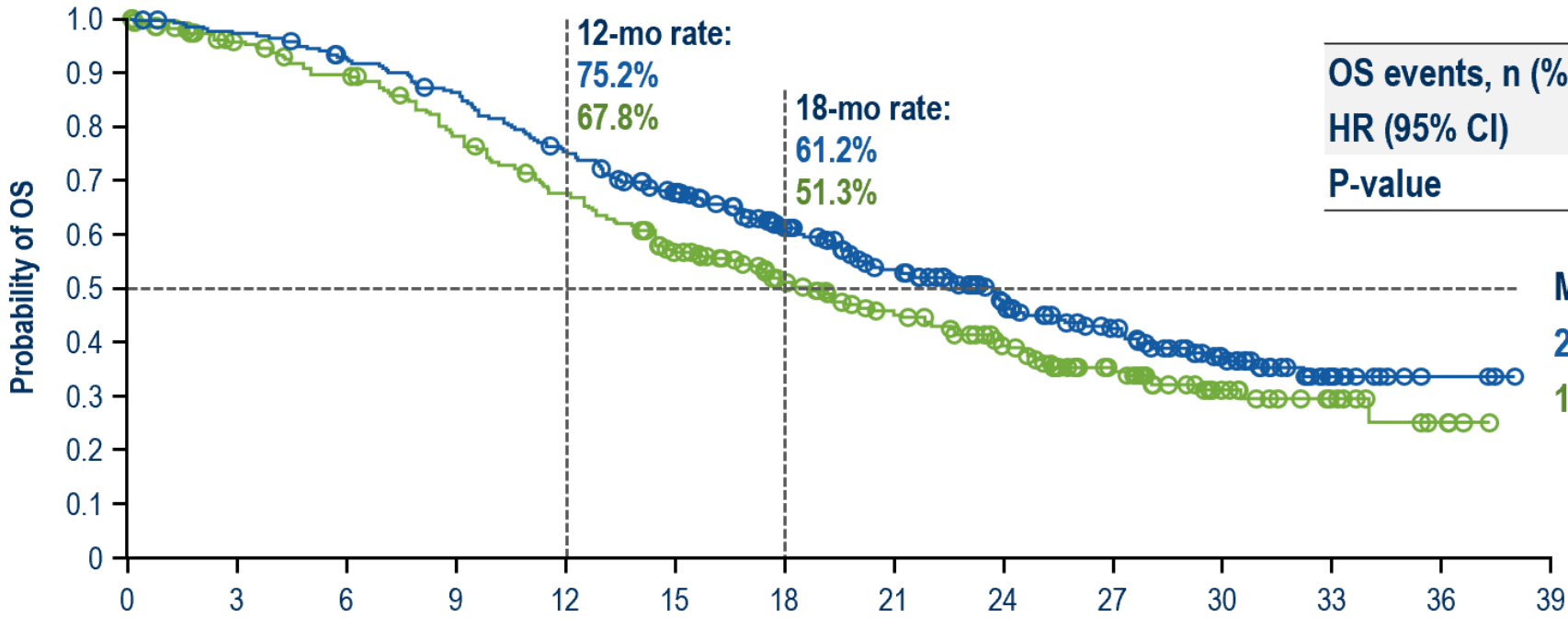
*Numbers are rounded. To two decimal points: median PFS 10.84 (95% CI 8.57–12.98) with Dato-DXd, 5.55 (95% CI 4.96–6.97) with ICC; Δ 5.29 months.
CI, confidence interval; HR, hazard ratio; mo, months.

PFS by BICR Subgroup Analysis



*Patients with asymptomatic, stable brain metastases were permitted in the study.

Overall Survival



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

Median OS (95% CI)

23.7 mo (19.8–25.6)

18.7 mo (16.0–21.8)

Δ 5.0 mo

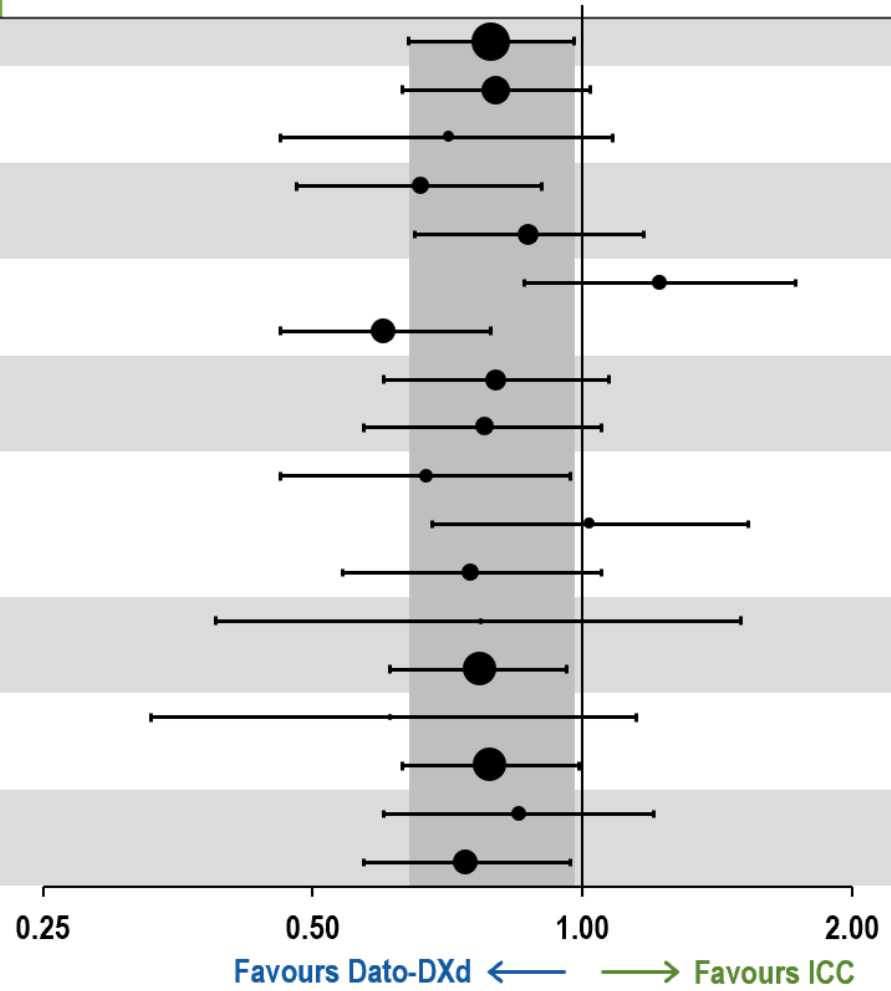
Number at risk

Data-DXd	323	311	291	272	235	201	157	122	86	64	37	14	3	0
ICC	321	290	268	231	199	158	122	93	70	48	27	12	4	0

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with ICC, reducing the risk of death by 21%

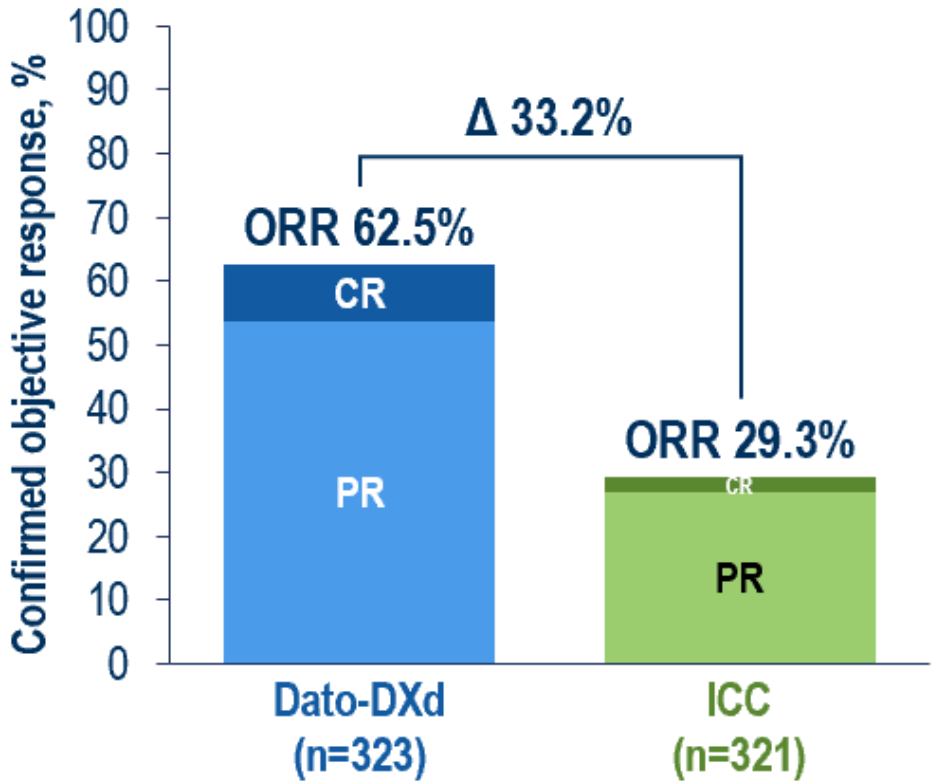
OS Subgroup Analysis

		Events/patients, n		Hazard ratio (95% CI)
		Dato-DXd	ICC	
All patients		168/323	181/321	**0.79** (0.64–0.98)
Age at randomisation	<65 years	128/245	132/239	**0.80** (0.63–1.02)
	≥65 years	40/78	49/82	**0.71** (0.46–1.08)
Race	Asian	76/151	78/131	**0.66** (0.48–0.90)
	Non-Asian	82/151	98/173	**0.87** (0.65–1.17)
Geographic region	US, Canada, Europe†	72/120	59/120	**1.22** (0.86–1.73)
	Other geographic regions	96/203	122/201	**0.60** (0.46–0.79)
ECOG PS	0	93/195	92/182	**0.80** (0.60–1.07)
	1	75/128	89/139	**0.78** (0.57–1.05)
DFI history	*De novo*	51/109	63/110	**0.67** (0.46–0.97)
	Prior DFI 0–12 months	51/67	45/66	**1.02** (0.68–1.53)
	Prior DFI >12 months	66/147	73/145	**0.75** (0.54–1.05)
PD-L1 status	High (CPS ≥10)	17/34	18/29	**0.77** (0.39–1.50)
	Low (CPS <10)	149/287	163/291	**0.77** (0.61–0.96)
Brain metastases*	Yes	21/36	19/28	**0.61** (0.33–1.15)
	No	147/287	162/293	**0.79** (0.63–0.99)
Liver metastases	Yes	64/93	66/98	**0.85** (0.60–1.20)
	No	104/230	115/223	**0.74** (0.57–0.97)



*Patients with asymptomatic, stable brain metastases were permitted in the study.
†Ad hoc analysis of the US cohort showed comparable OS HR to the ITT population.

Response by BICR

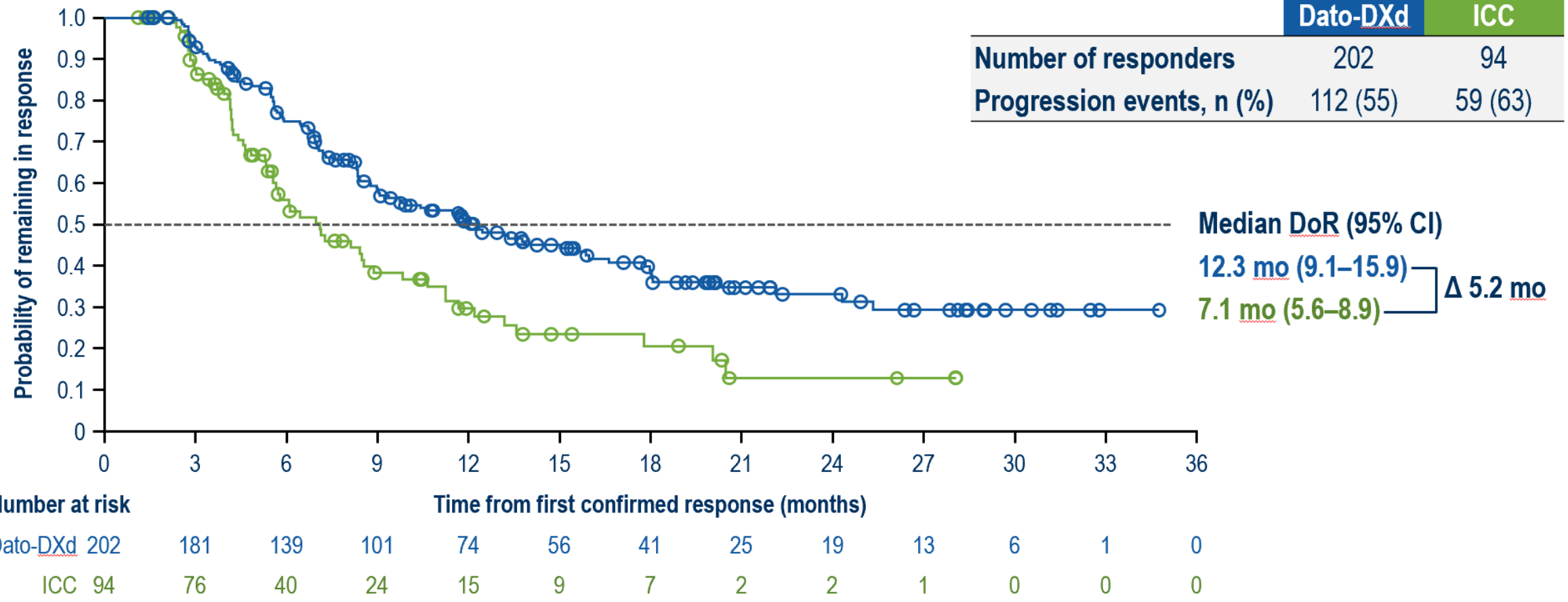


	Dato-DXd (n=323)	ICC (n=321)
Confirmed objective response, n (%)	202 (62.5)	94 (29.3)
Odds ratio (95% CI)	4.24 (3.03–5.95)	
Best confirmed objective response, n (%)		
Complete response	29 (9.0)	8 (2.5)
Partial response	173 (53.6)	86 (26.8)
Stable disease	87 (26.9)	151 (47.0)
Progressive disease	27 (8.4)	52 (16.2)
Not evaluable	7 (2.2)	24 (7.5)

With Dato-DXd, confirmed ORR was more than double that with ICC, and confirmed complete response rate was more than three times that with ICC

Duration of Response

	Dato-DXd	ICC
Number of responders	202	94
Progression events, n (%)	112 (55)	59 (63)



With Dato-DXd, median duration of response was >1 year

Overall Safety Summary

- **Median total treatment duration:**
  - **Dato-DXd: 8.5 months** (range 0.7–38.0)
  - **ICC: 4.1 months** (range 0.1–32.0)
- **Patients with total exposure >12 months:**
  - **Dato-DXd: 35.1%**
  - **ICC: 9.4%**

Treatment-related AEs, n (%)	Dato-DXd (n=319)	ICC (n=309)
Any grade	296 (93)	257 (83)
Grade ≥3	105 (33)	89 (29)
Serious TRAEs	29 (9)	26 (8)
Associated with dose interruption	76 (24)	60 (19)
Associated with dose reduction	85 (27)	56 (18)
Associated with discontinuation	14 (4)	23 (7)
Associated with death	0	0

Despite more than double the median duration of treatment in the Dato-DXd arm, rates of grade ≥3 and serious treatment-related AEs were similar, and discontinuations were lower, with Dato-DXd vs ICC

TRAEs, treatment-related adverse events.

Most Common Treatment-Related AEs (≥15% of Patients)

Treatment-related AEs, n (%)	Dato-DXd (n=319)		ICC (n=309)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Dry eye*	76 (24)	4 (1)	9 (3)	0
Stomatitis	182 (57)	27 (8)	27 (9)	0
Nausea	142 (45)	2 (<1)	53 (17)	2 (<1)
Constipation	72 (23)	1 (<1)	31 (10)	0
Vomiting	65 (20)	4 (1)	23 (7)	1 (<1)
Decreased appetite	49 (15)	1 (<1)	20 (6)	1 (<1)
Neutropenia†	39 (12)	10 (3)	90 (29)	40 (13)
Anaemia‡	48 (15)	6 (2)	64 (21)	10 (3)
Leukopenia§	27 (8)	3 (<1)	55 (18)	13 (4)
Peripheral neuropathy¶	14 (4)	0	75 (24)	5 (2)
Alopecia	130 (41)	0	96 (31)	1 (<1)‖
Fatigue#	101 (32)	8 (3)	86 (28)	9 (3)

*In the Dato-DXd arm only, ophthalmologic assessments were required every 3 cycles while on therapy; this was not required in the ICC arm. For all patients in both arms, ophthalmologic assessments were required at baseline, as clinically indicated, and at end of therapy.
†Grouped term comprising preferred terms of neutropenia and neutrophil count decreased. ‡Grouped term comprising preferred terms of haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased. §Grouped term comprising preferred terms of white blood cell count decreased and leukopenia. ¶Grouped term comprising preferred terms of neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, paraesthesia, and peripheral sensory neuropathy. #Grouped term comprising preferred terms of fatigue, asthenia, and malaise. ‖Per Common Terminology Criteria for Adverse Events version 5.0, the maximum grade for alopecia is grade 2.

Treatment-Related AESIs for Dato-DXd

AESI category, n (%) Preferred term*	Dato-DXd (n=319)			ICC (n=309)		
	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis†	78 (24)	87 (27)	27 (8)	22 (7)	8 (3)	0
Stomatitis	72 (23)	83 (26)	27 (8)	19 (6)	8 (3)	0
Ocular surface events‡§	76 (24)	50 (16)	23 (7)	9 (3)	5 (2)	1 (<1)
Dry eye	51 (16)	21 (7)	4 (1)	6 (2)	3 (1)	0
Keratitis	21 (7)	14 (4)	7 (2)	1 (<1)	0	0
Conjunctivitis	7 (2)	13 (4)	1 (<1)	0	0	0
Adjudicated drug-related ILD/pneumonitis¶	1 (<1)	7 (2)	1 (<1)#	1 (<1)	1 (<1)	0

Treatment-related oral mucositis/stomatitis:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 11 (3%), 36 (11%), and 0 patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 103/114 patients (90%) at data cutoff

Treatment-related ocular surface events:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 18 (6%), 14 (4%), and 3 (<1%) patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 49/73 patients (67%) at data cutoff

*Details for preferred terms included if reported in ≥20 patients in either arm. †Comprising the preferred terms of aphthous ulcer, mouth ulceration, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis. ‡Comprising the preferred terms of acquired corneal dystrophy, blepharitis, conjunctivitis, corneal disorder, corneal epithelium defect, corneal erosion, corneal exfoliation, corneal lesion, corneal toxicity, dellen, dry eye, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, meibomian gland dysfunction, photophobia, punctate keratitis, ulcerative keratitis, vision blurred, visual acuity reduced, visual impairment, and xerophthalmia. §In the Dato-DXd arm only, ophthalmologic assessments were required every 3 cycles while on therapy; this was not required in the ICC arm. For all patients in both arms, ophthalmologic assessments were required at baseline, as clinically indicated, and at end of therapy. ¶Comprising the preferred terms of interstitial lung disease and pneumonitis. #Grade 5 – this event was characterised by the investigator as grade 3 pneumonitis, with death assessed as related to breast cancer.

Conclusions

- TROPION-Breast02 **met both dual primary endpoints**: first-line Dato-DXd demonstrated statistically significant and clinically meaningful improvement in **OS and PFS** over ICC
  - OS HR 0.79 (95% CI 0.64–0.98); P=0.0291
  - PFS by BICR HR 0.57 (95% CI 0.47–0.69); P<0.0001
  - ≥5-month improvement in both median OS and PFS

TROPION-Breast02 enrolled patients who are **representative of the real-world** TNBC population, including those **often excluded from clinical trials** (e.g. 15% had DFI 0–6 months)

- The Dato-DXd **safety profile was manageable** and generally **consistent** with the known profile
  - Despite more than double the median duration of treatment, rates of grade ≥3 and serious TRAEs were similar, and discontinuations were lower, with Dato-DXd vs ICC

TROPION-Breast02 results support Dato-DXd as the new first-line standard of care for patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy is not an option

Datopotamab deruxtecan (Dato-DXd) in combination with durvalumab as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer: Results from arms 7 and 8 of the phase 1b/2 BEGONIA study

Peter Schmid,[1] Hwei-Chung Wang,[2] Filipa Lynce,[3] Yeon Hee Park,[4] Cynthia X. Ma,[5] Kyung Hae Jung,[6] Shin-Cheh Chen,[7] Ming-Feng Hou,[8] Catherine Prady,[9] Ling-Ming Tseng,[10] Jamil Asselah,[11] Piotr J. Wysocki,[12] Simon Lord,[13] Purnima Rao-Melacini,[14] Karola Warzyszyńska,[15] Petra Vuković,[16] Seock-Ah Im[17]

[1]Centre for Experimental Cancer Care Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK; [2]Department of Surgery, China Medical University Hospital, Taichung, Taiwan; [3]Department of Medical Oncology, Breast Oncology Program, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [4]Division of Hematology Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA; [6]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [7]Division of Breast Surgery, Department of General Surgery, Chang Gung Memorial Hospital, Taoyuan, Taiwan; [8]Division of Breast Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [9]Oncology, Sherbrooke University, Centre Intégré de Cancérologie de la Montérégie, CISSS Montérégie Centre, Greenfield Park, QC, Canada; [10]Comprehensive Breast Health Center, Taipei Veterans General Hospital, Taipei, Taiwan; [11]Medical Oncology, McGill University Health Centre, Montreal, QC, Canada; [12]Department of Oncology, Jagiellonian University Medical College, Krakow, Poland; [13]Department of Oncology, Medical Sciences Division, University of Oxford, Oxford, UK; [14]Statistics, Oncology R&D, AstraZeneca, Mississauga, ON, Canada; [15]Clinical Development, Oncology R&D, AstraZeneca, Warsaw, Poland; [16]Clinical Development, Oncology R&D, AstraZeneca, Cambridge, UK; [17]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul National University, Seoul, Republic of Korea.

BEGONIA Study

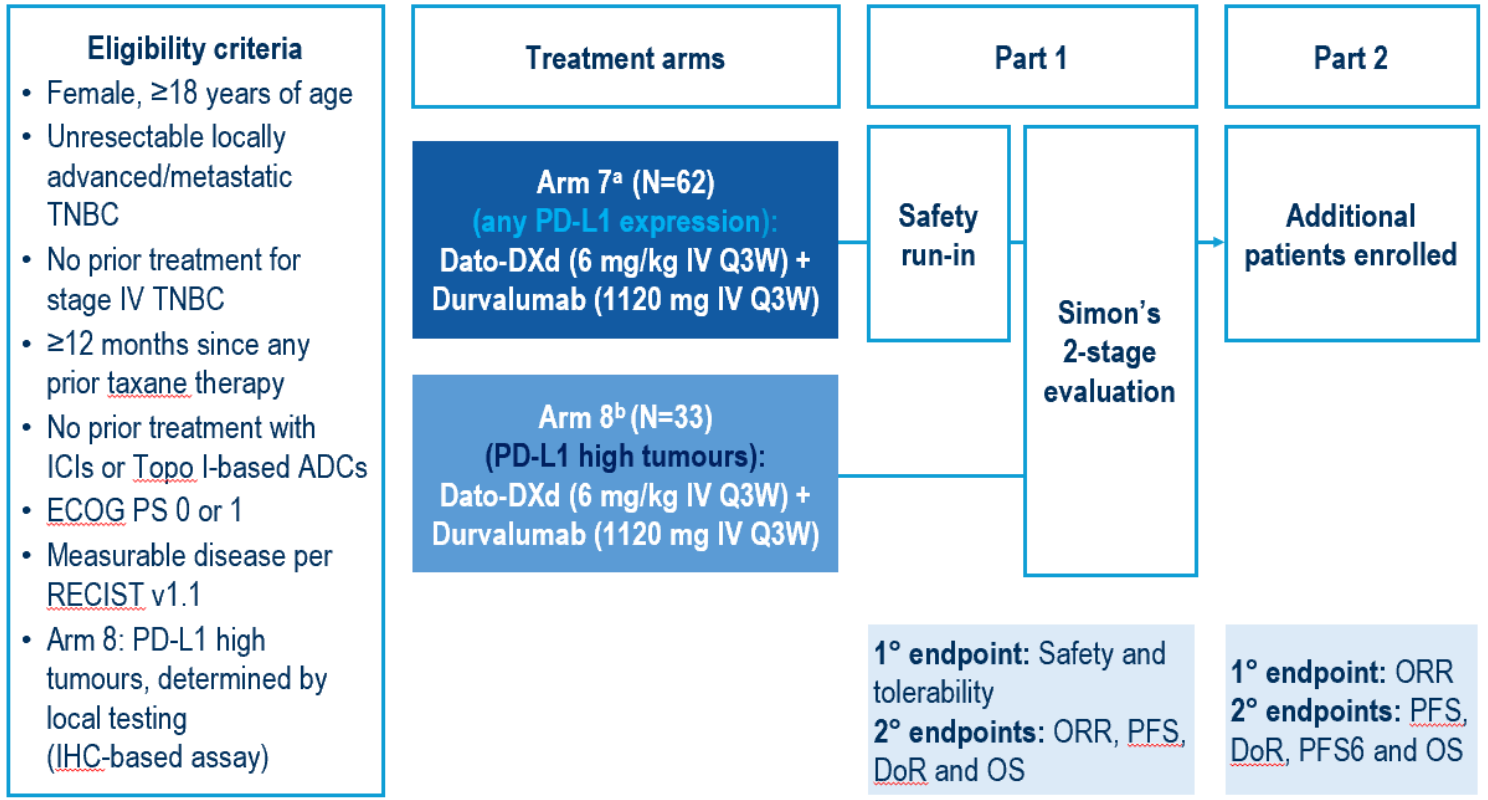
Rationale

- PD-(L)1 inhibition + chemotherapy is SoC for patients with PD-L1 high advanced/metastatic TNBC[1,2]
  - Outcomes remain poor; most patients progress within one year (PFS ~10 months)[3]
  - Treatment options are limited, particularly for patients with PD-L1 low tumours[1,4]
- Dato-DXd, a TROP2-directed ADC,[5] is approved for the treatment of adults with unresectable or metastatic HR+/HER2− breast cancer who have received prior ET and chemotherapy for unresectable or metastatic disease, based on the results of the phase 3 TROPION-Breast01 study[6,7]
- BEGONIA (NCT03742102) is a phase 1b/2, multicentre, multi-arm, 2-stage, 2-part, open-label platform study evaluating the safety and efficacy of durvalumab + other novel therapies as 1L treatment for advanced/metastatic TNBC[8]

Here we report updated data in patients regardless of PD-L1 status (Arm 7) and with PD-L1 high tumours per local testing (Arm 8)

Eligibility criteria

- Female, ≥18 years of age
- Unresectable locally advanced/metastatic TNBC
- No prior treatment for stage IV TNBC
- ≥12 months since any prior taxane therapy
- No prior treatment with ICIs or Topo I-based ADCs
- ECOG PS 0 or 1
- Measurable disease per RECIST v1.1
- Arm 8: PD-L1 high tumours, determined by local testing (IHC-based assay)



NCT03742102, DCO: 29 November 2024

[a]Patients were enrolled into Arm 7 regardless of PD-L1 expression, which was retrospectively assessed using the VENTANA® PD-L1 (IHC antibody for PD-L1, SP263 [Roche Diagnostics]) Assay (off-label use); PD-L1 high: TAP ≥10%; PD-L1 low: TAP <10%.
[b]Patients were enrolled with PD-L1 high tumours determined via local testing methods.

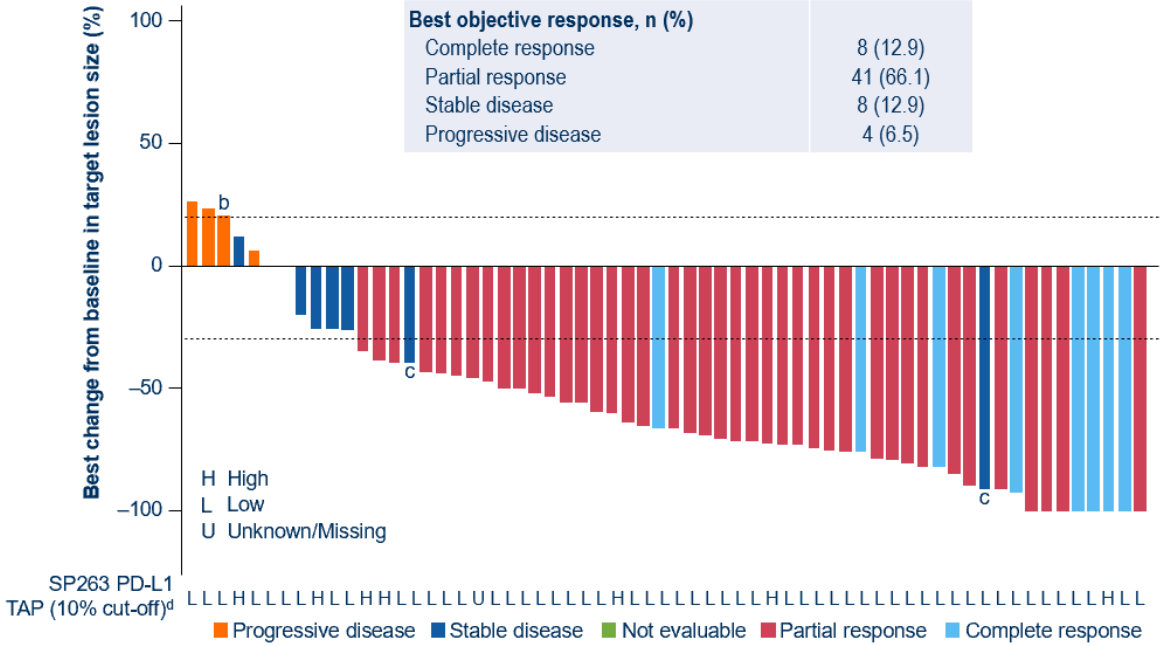
1L; first-line; ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death (ligand)-1; PFS, progression-free survival; PFS6, progression-free survival 6 months following date of first dose; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SoC, standard of care; TAP, tumour area positivity; Topo-I, topoisomerase I; TNBC, triple-negative breast cancer.

1. Gennari A, et al. Ann Oncol 2021;32:1475–95; 2. European Medicines Agency, KEYTRUDA® Summary of Product Characteristics 2025; 3. Cortes J, et al. Lancet. 2020;396:1817–28; 4. European Medicines Agency, TRODELVY® Summary of Product Characteristics 2025; 5. Okajima D, et al. Cancer Res 2023;83(7_Suppl):A2932; 6. Bardia, A et al. J Clin Oncol 2025;43:285–96; 7. European Medicines Agency, DATROWAY® Summary of Product Characteristics 2025; 8. Schmid P, et al. Ann Oncol 2023;34:S337.

Overall Response and Duration of Response (Arm 7)

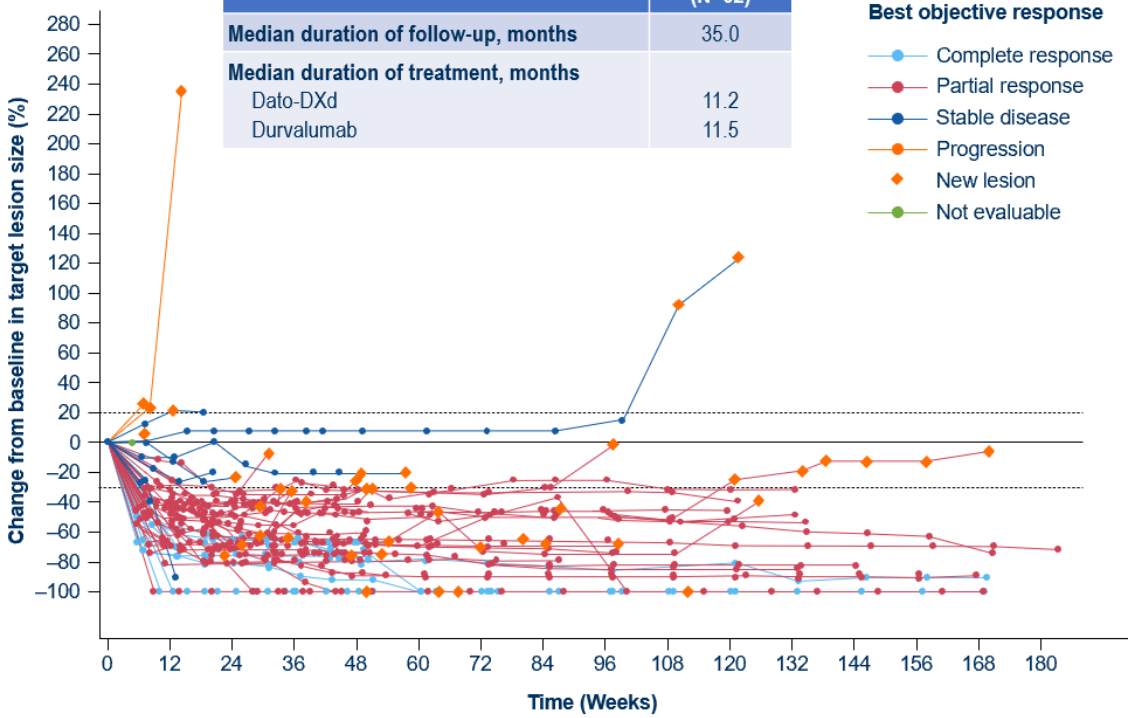
Overall, 11.3% patients had PD-L1 high tumours and 87.1% had PD-L1 low tumours

	Arm 7 (N=62)
Confirmed ORR,[a] % (95% CI)	49 (79.0) (66.8–88.3)
Best objective response, n (%)	
Complete response	8 (12.9)
Partial response	41 (66.1)
Stable disease	8 (12.9)
Progressive disease	4 (6.5)



Responses were observed in patients with PD-L1 high and PD-L1 low tumours

	Arm 7 (N=62)
Median duration of follow-up, months	35.0
Median duration of treatment, months	
Dato-DXd	11.2
Durvalumab	11.5



Median **DoR** was 17.6 months (95% CI 10.5–27.3)
Median **PFS** was 14.0 months (95% CI 11.0–21.1)

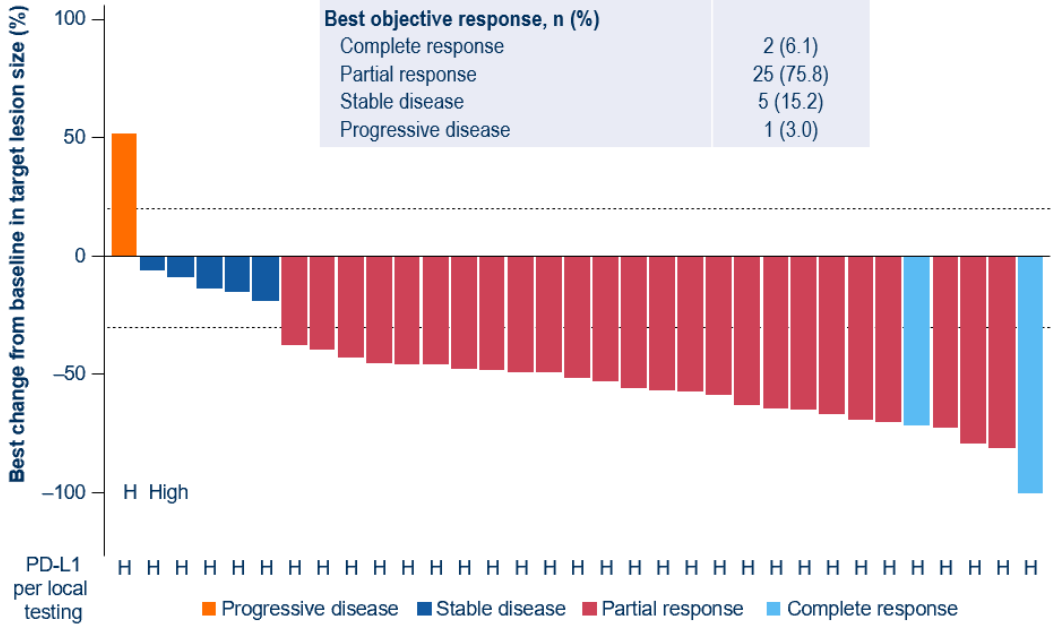
[a]Investigator-assessed, per RECIST v1.1. [b]Patient with imputed values. [c]Unconfirmed response. [d]PD-L1 status determined by central testing using the SP263 TAP 10% cut-off.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ORR, objective response rate; PD-L1, programmed death ligand-1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TAP, tumour area positivity.

Overall Response and Duration of Response (Arm 8)

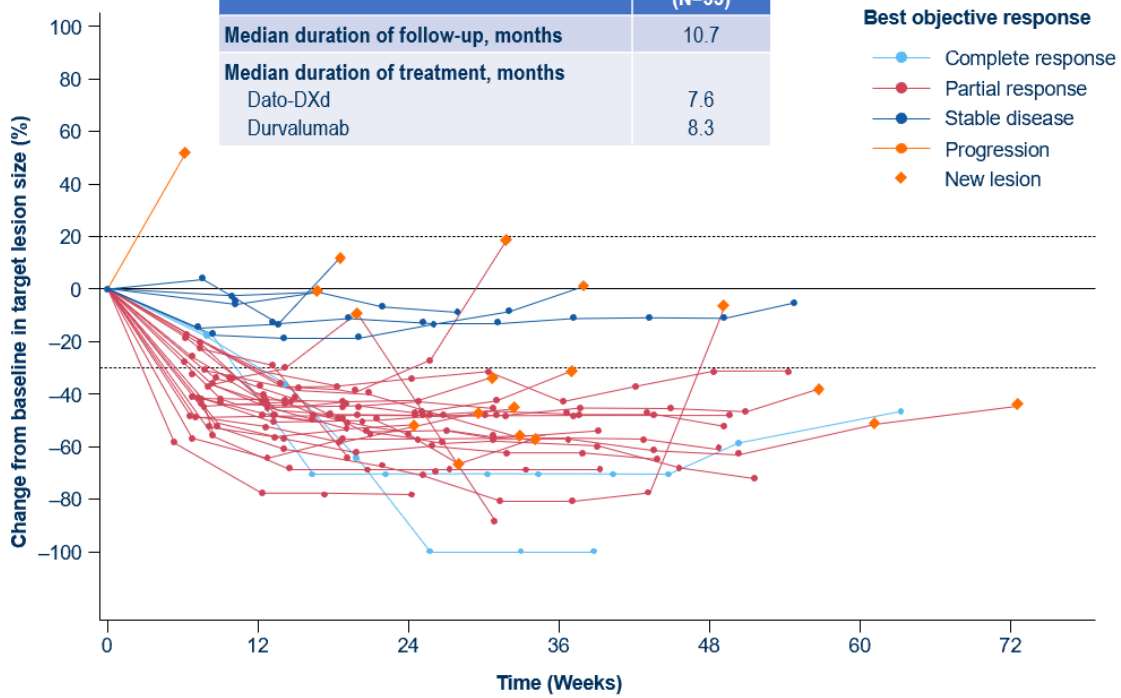
PD-L1 high tumours

	Arm 8 (N=33)
Confirmed ORR,[a] % (95% CI)	27 (81.8) (64.5–93.0)
Best objective response, n (%)	
Complete response	2 (6.1)
Partial response	25 (75.8)
Stable disease	5 (15.2)
Progressive disease	1 (3.0)



Confirmed ORR was 81.8% (95% CI 64.5–93.0)

	Arm 8 (N=33)
Median duration of follow-up, months	10.7
Median duration of treatment, months	
Dato-DXd	7.6
Durvalumab	8.3



Median **DoR** and median **PFS** were immature given the short duration of median follow-up of 8.3 months in censored patients

[a]Investigator-assessed, per RECIST v1.1.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ORR, objective response rate; PD-L1, programmed death ligand-1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

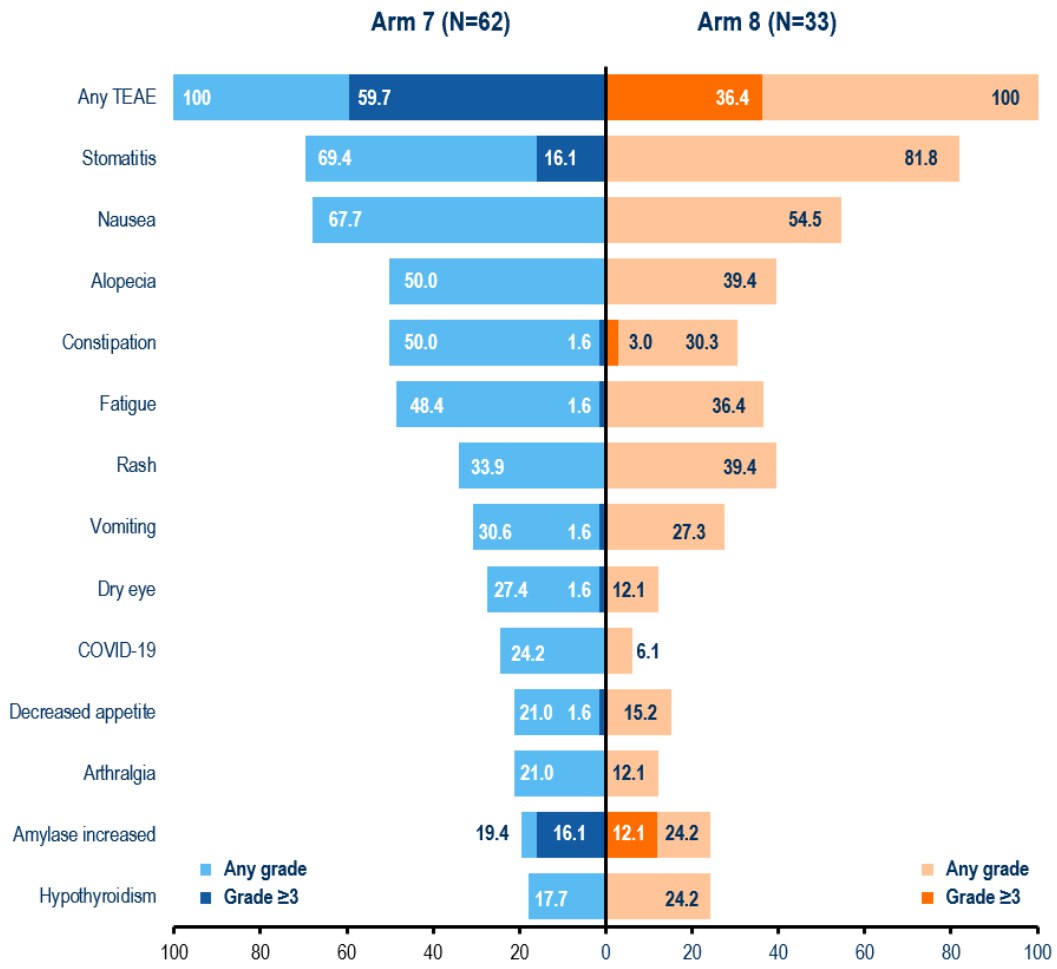
Overall Safety Summary[a]

	Arm 7 (N=62)	Arm 8 (N=33)
Median duration of treatment, months		
Dato-DXd	11.2	7.6
Durvalumab	11.5	8.3
Any TEAE, n (%)	62 (100)	33 (100)
Maximum CTCAE grade 3/4	37 (59.7)	12 (36.4)
Any treatment-related AE, n (%)	62 (100)	33 (100)
Maximum CTCAE grade 3/4	30 (48.4)	8 (24.2)
Any SAE, n (%)	18 (29.0)	5 (15.2)
Any TEAE leading to death, n (%)	1 (1.6)[b]	0
Any TEAE leading to discontinuation of either treatment, n (%)	12 (19.4)	3 (9.1)
Discontinuation of Dato-DXd	12 (19.4)	2 (6.1)
Discontinuation of durvalumab	3 (4.8)	2 (6.1)
Any TEAE leading to dose reduction of Dato-DXd[c], n (%)	24 (38.7)	7 (21.2)
Any TEAE leading to dose interruption (either treatment), n (%)	44 (71.0)	23 (69.7)
Any imAE, n (%)	20 (32.3)	11 (33.3)
Maximum CTCAE grade 3/4	1 (1.6)	0

[a]CTCAE grading was reported per CTCAE v4.03. [b]Due to dehydration, considered to be not related to study treatment. [c]Dose reductions were not permitted for durvalumab.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; imAE, immune-mediated adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Most common TEAEs(≥20% of patients in either arm)[a,b]



- Across both arms, rates of adjudicated drug-related ILD were low, with no grade ≥3 events:
  - Arm 7: two grade 2 events, one grade 1 event
  - Arm 8: one grade 2 event
- The most frequently reported AESI preferred terms (≥15%) for Dato-DXd were stomatitis (Arm 7: 69.4%; Arm 8: 81.8%), dry eye (Arm 7: 27.4%; Arm 8: 12.1%), keratitis (Arm 7: 16.1%; Arm 8: 3.0%), vision blurred (Arm 7: 8.1%; Arm 8: 15.2%) and oropharyngeal pain (Arm 7: 11.3%; Arm 8: 15.2%)
- The most frequently reported imAEs for durvalumab were thyroid events (hypothyroid events [Arm 7: 22.6%; Arm 8: 24.2%]; hyperthyroid events [Arm 7: 8.1%; Arm 8: 0%])
- Rates of diarrhoea and neutropenia were limited in both arms:

  Arm 7:
  - Diarrhoea: 16.1% any grade, one grade 3 event
  - Neutropenia: 4.8% any grade, one grade 3 event

  Arm 8:
  - Diarrhoea: 6.1% any grade, no grade 3 events
  - Neutropenia: 0% any grade

[a]CTCAE grading was reported per CTCAE v4.03; [b]TEAEs (by MedDRA preferred term) of any grade reported in ≥20% of patients.

AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; ILD, interstitial lung disease; imAE, immune-mediated adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Conclusions

- **The combination of Dato-DXd + durvalumab demonstrated robust antitumour activity in patients with advanced/metastatic TNBC with any PD-L1 expression (Arm 7) and in those with high PD-L1 expression (Arm 8)**

  Arm 7
  - Median duration of follow-up was 35.0 months
  - Confirmed ORR was 79.0% (95% CI 66.8–88.3); consistent response rates were observed regardless of PD-L1 status
  - Median DoR was 17.6 months (95% CI 10.5–27.3)
  - Median PFS was 14.0 months (95% CI 11.0–21.1)

  Arm 8
  - Median duration of follow-up was 10.7 months
  - Confirmed ORR was 81.8% (95% CI 64.5–93.0)
  - Median DoR and median PFS were immature given the short duration of median follow-up of 8.3 months in censored patients

- **The safety profile of the combination of Dato-DXd + durvalumab was manageable, with no new safety signals**

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TNBC, triple-negative breast cancer.

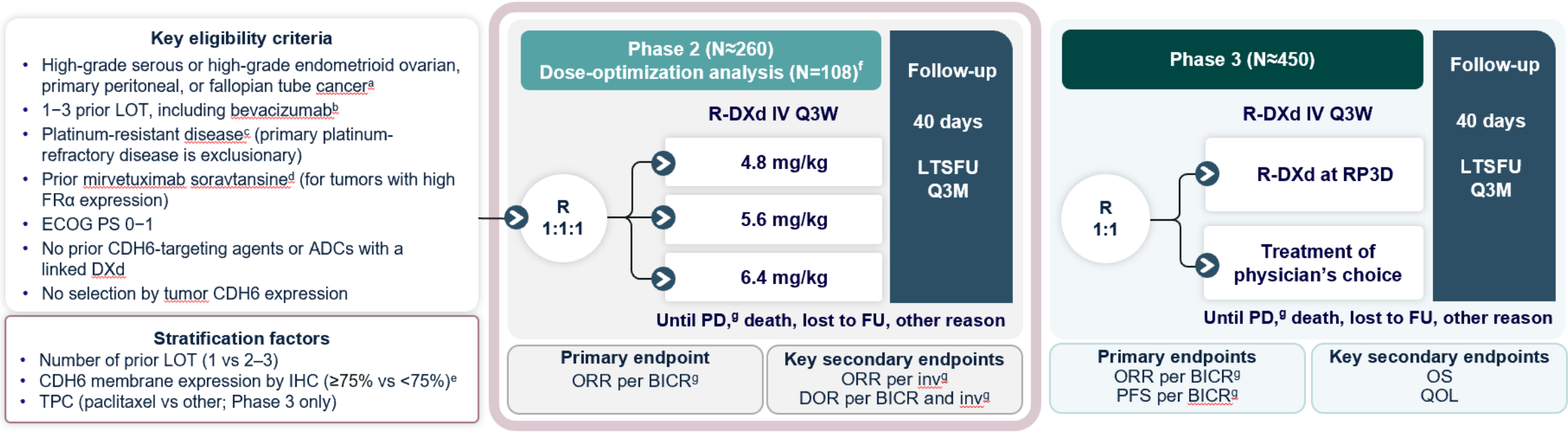
Raludotatug deruxtecan (R-DXd) in patients with platinum-resistant ovarian cancer: Primary analysis of the Phase 2, dose-optimization part of the REJOICE-Ovarian01 study

Isabelle Ray-Coquard,[1] Kosei Hasegawa,[2] Nicoletta Colombo,[3] Jung-Yun Lee,[4] David Cibula,[5] Yunong Gao,[6] Sabrina Chiara Cecere,[7] Peng-Hui Wang,[8] Lubomir Bodnar,[9] Sally Baron-Hay,[10] Diana Bello Roufai,[11] Mayu Yunokawa,[12] David Garcia-Illescas,[13] Sook-hee Hong,[14] Maria Cristina Petrella,[15] Sandra Re,[16] Madan Gopal Kundu,[16] Karin Yamada,[17] Veronique D'Hondt,[19] Lydia Gaba[19]

[1]Centre Léon Bérard, University Claude Bernard, and GINECO, Lyon, France; [2]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [3]European Institute of Oncology, IRCCS, Milan, Italy; [4]Yonsei Cancer Center and Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]Charles University and General University Hospital, Prague, Czech Republic; [6]Beijing Cancer Hospital, Beijing Institute for Cancer Research, Beijing, China; [7]IRCCS Fondazione G. Pascale, Naples, Italy; [8]Taipei Veterans General Hospital, Taipei, Taiwan; [9]University of Siedlce, Siedlce, Poland; [10]GenesisCare North Shore, St Leonards, NSW, Australia; [11]Institut Curie, Saint-Cloud, France; [12]The Cancer Institute Hospital of Japanese Foundation for Cancer, Tokyo, Japan; [13]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [14]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [15]Azienda Ospedaliera Universitaria Careggi, Florence, Italy; [16]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]Institut du Cancer de Montpellier Val d'Aurelle, Parc Euromedecine, GINECO, Montpellier, France; [19]Hospital Clinic Barcelona and GEICO, Barcelona, Spain.

REJOICE-Ovarian01 (NCT06161025): Study design

A Phase 2/3 multicenter, randomized study of R-DXd in patients with platinum-resistant, high-grade serous or endometroid ovarian, primary peritoneal, or fallopian tube cancer[1,2]



We present the primary analysis from the dose-optimization part of the Phase 2/3 REJOICE-Ovarian01 study, in 107 patients with platinum-resistant OC who had a follow-up of ≥18 weeks or discontinued treatment

[a]Patients must have ≥1 lesion not previously irradiated and amenable to biopsy; must consent to provide a pretreatment biopsy and, in Phase 2 only, an on-treatment biopsy tissue sample and have ≥1 measurable lesion per RECIST 1.1. [b]Unless ineligible. [c]Defined as 1 line of prior platinum therapy (≥4 cycles with best response of not PD) with radiologically documented progression >90 and ≤180 days following last dose of platinum therapy, or 2–3 lines of prior platinum therapy (≥2 cycles) with radiologically documented progression ≤180 days following the last dose of platinum. [d]Unless ineligible, not approved, or not available locally. [e]A stratification cutoff of 75% tumor cell membrane staining at any intensity was selected based on the median observed percentage tumor cell membrane staining (at any intensity) in the Phase 1 study population.[3] [f]Overall, 108 patients were randomized to receive R-DXd. One patient did not receive treatment, so 107 patients were treated and were included in the safety analysis set. [g]Per RECIST 1.1.
ADC, antibody–drug conjugate; BICR, blinded independent central review; CDH6, cadherin 6; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; FU, follow-up; IHC, immunohistochemistry; IV, intravenous; inv, investigator; LOT, lines of therapy; LTSFU, long-term survival follow up; ORR, objective response rate; OS, overall survival; RP3D, recommended phase 3 dose; PD, progressive disease; Q3M, every 3 months; Q3W, every 3 weeks; QOL, quality of life; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TPC, treatment of physician's choice.

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06161025. Accessed October 7, 2025. 2. Ray-Coquard I, et al. Poster presentation at American Society of Clinical Oncology 2024; May 31–June 4; Chicago, IL, USA. Poster TPS5625. 3. Moore KN, et al. Oral presentation at the Society of Gynecologic Oncology 2024 Annual Meeting on Women's Cancer. March 16–18, 2024; San Diego, CA, USA.

Baseline characteristics and prior systemic therapies

Patient and tumor characteristics	R-DXd 4.8–6.4 mg/kg[a] N=107
Age, median (range), years	60 (34–81)
Age >70 years, n (%)	17 (15.9)
Region, n (%)	
Asia	45 (42.1)
Europe	61 (57.0)
Australia	1 (0.9)
ECOG PS, n (%)	
0	61 (57.0)
1	46 (43.0)
Cancer type, n (%)	
Ovarian	91 (85.0)
Peritoneal	4 (3.7)
Fallopian tube	12 (11.2)
Tumor FIGO stage at initial diagnosis, n (%)	
I–II	11 (10.3)
III	53 (49.5)
IV	39 (36.4)
Unknown	4 (3.7)

Tumor characteristics and prior therapies	R-DXd 4.8–6.4 mg/kg[a] N=107
Number of prior lines of systemic therapy, n (%)	
1	10 (9.3)
2	42 (39.3)
3	55 (51.4)
Received prior therapy, n (%)	
Bevacizumab	89 (83.2)
PARP inhibitor	75 (70.1)
Mirvetuximab soravtansine	3 (2.8)
Last platinum-free interval, n (%)	
<3 months	47 (43.9)
3–6 months	60 (56.1)
Tumor CDH6 membrane positivity at any intensity at baseline,[b] n (%)	n=101[c]
Any positivity	**95 (94.1)**
<75% positive	41 (40.6)
≥75% positive[d]	60 (59.4)

Data cutoff: February 26, 2025. Study was initiated on February 27, 2024.

[a]Only patients treated with ≥1 dose were included in this analysis and made up the safety analysis cohort. [b]Tumor CDH6 positivity was defined as the percentage of viable tumor cells positive for CDH6 membrane staining at any intensity (1+/2+/3+) determined by CDH6 clinical trial assay (SP450; Roche Diagnostics). [c]Six tumor samples were of insufficient quality to determine CDH6 membrane positivity. [d]A stratification cutoff of 75% tumor cell membrane staining at any intensity was selected based on the median observed percentage tumor cell membrane staining (at any intensity) in the Phase 1 study population.[1]

CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; PARP, poly (adenosine diphosphate [ADP]-ribose) polymerase; PD, progressive disease.

1. Moore KN, et al. Oral presentation at the Society of Gynecologic Oncology 2024 Annual Meeting on Women's Cancer. March 16–18, 2024; San Diego, CA, USA.

R-DXd monotherapy demonstrated promising antitumor activity at all doses in patients with platinum-resistant OC

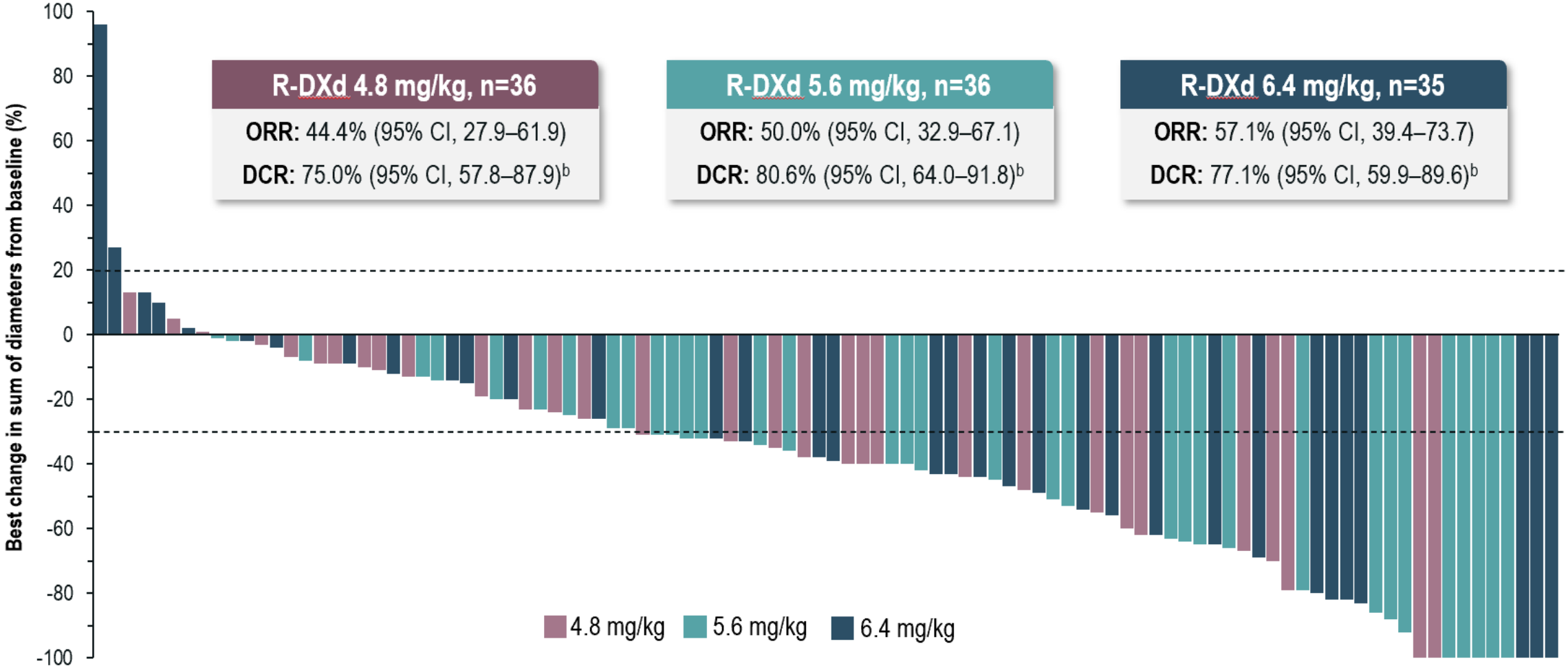
Confirmed response by BICR[a]	R-DXd 4.8 mg/kg n=36	R-DXd 5.6 mg/kg n=36	R-DXd 6.4 mg/kg n=35	R-DXd 4.8–6.4 mg/kg N=107
ORR, % (95% CI)	44.4 (27.9–61.9)	50.0 (32.9–67.1)	57.1 (39.4–73.7)	50.5 (40.6–60.3)
BOR,[b] n (%)				
CR	1 (2.8)	2 (5.6)	0	3 (2.8)
PR	15 (41.7)	16 (44.4)	20 (57.1)	51 (47.7)
SD	17 (47.2)	15 (41.7)	10 (28.6)	42 (39.3)
PD	2 (5.6)	2 (5.6)	4 (11.4)	8 (7.5)
Not evaluable	1 (2.8)[c]	1 (2.8)[d]	1 (2.9)[c]	3 (2.8)
DCR,[e] % (95% CI)	75.0 (57.8–87.9)	80.6 (64.0–91.8)	77.1 (59.9–89.6)	77.6 (68.5–85.1)
TTR, median (range), weeks	7.1 (5.4–18.7)	6.6 (5.1–18.3)	7.2 (5.3–19.1)	7.1 (5.1–19.1)

Data cutoff: February 26, 2025. The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.

[a]Per RECIST 1.1. [b]BOR was defined as the best response across all timepoints; CR, ≥2 assessments of CR ≥4 weeks apart, prior to progression; PR, ≥2 assessments of PR (or CR) ≥4 weeks apart, prior to progression (not meeting criteria for CR); SD, ≥1 assessment of SD (or better) ≥5 weeks following treatment initiation, and before progression (not meeting criteria for CR or PR); PD, progression ≥12 weeks following treatment initiation (not meeting criteria for CR, PR, or SD); [c]Patient had no baseline tumor assessment by BICR. [d]Patient had no adequate post-baseline tumor assessment by BICR. [e]DCR was defined as percentage of patients with BOR of CR, PR, or SD (per RECIST 1.1).

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; OC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; TTR, time to response.

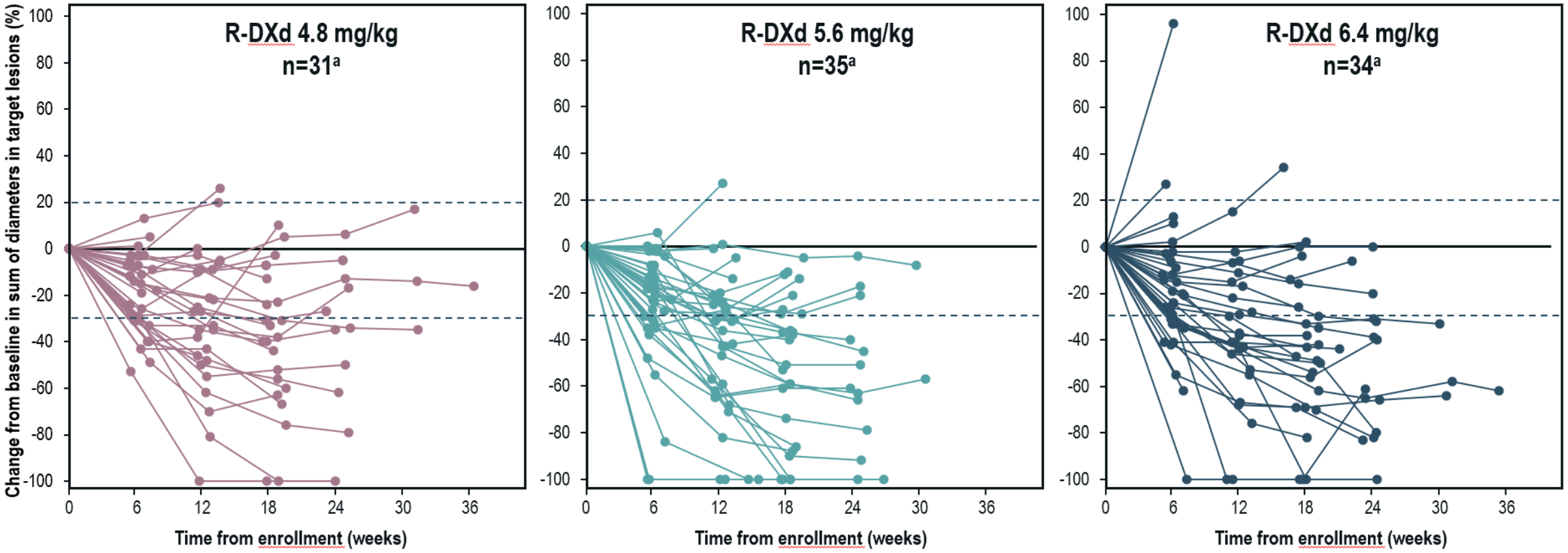
Clinically meaningful tumor responses were seen irrespective of dose[a]



Data cutoff: February 26, 2025. The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.

[a]Antitumor response assessed by BICR per RECIST 1.1. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan, both by BICR, were included in the waterfall plot (n=100). Six patients (R-DXd 4.8 mg/kg [n=5]; 6.4 mg/kg [n=1]) did not have measurable disease at baseline and one patient (R-DXd 5.6 mg/kg) had no adequate post-baseline tumor assessment. [b]DCR was defined as percentage of patients with BOR of CR, PR, or SD (per RECIST 1.1).
BICR, blinded independent central review; CI, confidence interval; DCR, disease control rate; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1.

R-DXd treatment was associated with rapid responses at all doses



Median TTR:[b] 7.1 weeks (range, 5.4–18.7)

Median TTR:[b] 6.6 weeks (range, 5.1–18.3)

Median TTR:[b] 7.2 weeks (range, 5.3–19.1)

Data cutoff: February 26, 2025. The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.

[a]Antitumor response assessed by BICR per RECIST 1.1. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan, both by BICR, were included in the spider plots (n=100). Six patients (R-DXd 4.8 mg/kg [n=5]; 6.4 mg/kg [n=1]) did not have measurable disease at baseline and one patient (R-DXd 5.6 mg/kg) had no adequate post-baseline tumor assessment. [b]By BICR per RECIST 1.1. Overall median TTR was 7.1 weeks (range, 5.1–19.1).

BICR, blinded independent central review; CI, confidence interval; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TTR, time to response.

The 5.6-mg/kg dose provided the optimal benefit–risk profile

	R-DXd 4.8 mg/kg n=36	R-DXd 5.6 mg/kg n=36	R-DXd 6.4 mg/kg n=35	R-DXd 4.8–6.4 mg/kg N=107
Any TEAE, n (%)	35 (97.2)	36 (100)	35 (100)	106 (99.1)
Grade ≥3	16 (44.4)	20 (55.6)	20 (57.1)	56 (52.3)
Any treatment-related TEAE, n (%)	32 (88.9)	34 (94.4)	34 (97.1)	100 (93.5)
Grade ≥3	10 (27.8)	11 (30.6)	17 (48.6)	38 (35.5)
Grade 5	0	0	0	0
Any SAE, n (%)	14 (38.9)	12 (33.3)	14 (40.0)	40 (37.4)
Grade ≥3	13 (36.1)	10 (27.8)	11 (31.4)	34 (31.8)
Grade 5	3 (8.3)[a]	2 (5.6)[b]	1 (2.9)[c]	6 (5.6)
Any treatment-related SAE, n (%)	3 (8.3)	3 (8.3)	7 (20.0)	13 (12.1)
Grade ≥3	3 (8.3)	3 (8.3)	5 (14.3)	11 (10.3)
Grade 5	0	0	0	0
Dose modifications associated with treatment-related TEAEs,[d] n (%)				
Drug discontinuation	3 (8.3)	0	3 (8.6)	6 (5.6)
Dose reduction	5 (13.9)	4 (11.1)	11 (31.4)	20 (18.7)
Dose delay	8 (22.2)	7 (19.4)	10 (28.6)	25 (23.4)
ILD/pneumonitis adjudicated as treatment related,[e] n (%)				
Any grade	1 (2.8)	1 (2.8)	2 (5.7)	4 (3.7)
Grade ≥3	1 (2.8)[f]	0	0	1 (0.9)
Grade 5	0	0	0	0

The safety profile of the 4.8 and 5.6 mg/kg cohorts were similar.

Treatment-related TEAEs occurred more frequently in the 6.4 mg/kg cohort (vs 4.8 and 5.6 mg/kg cohorts)

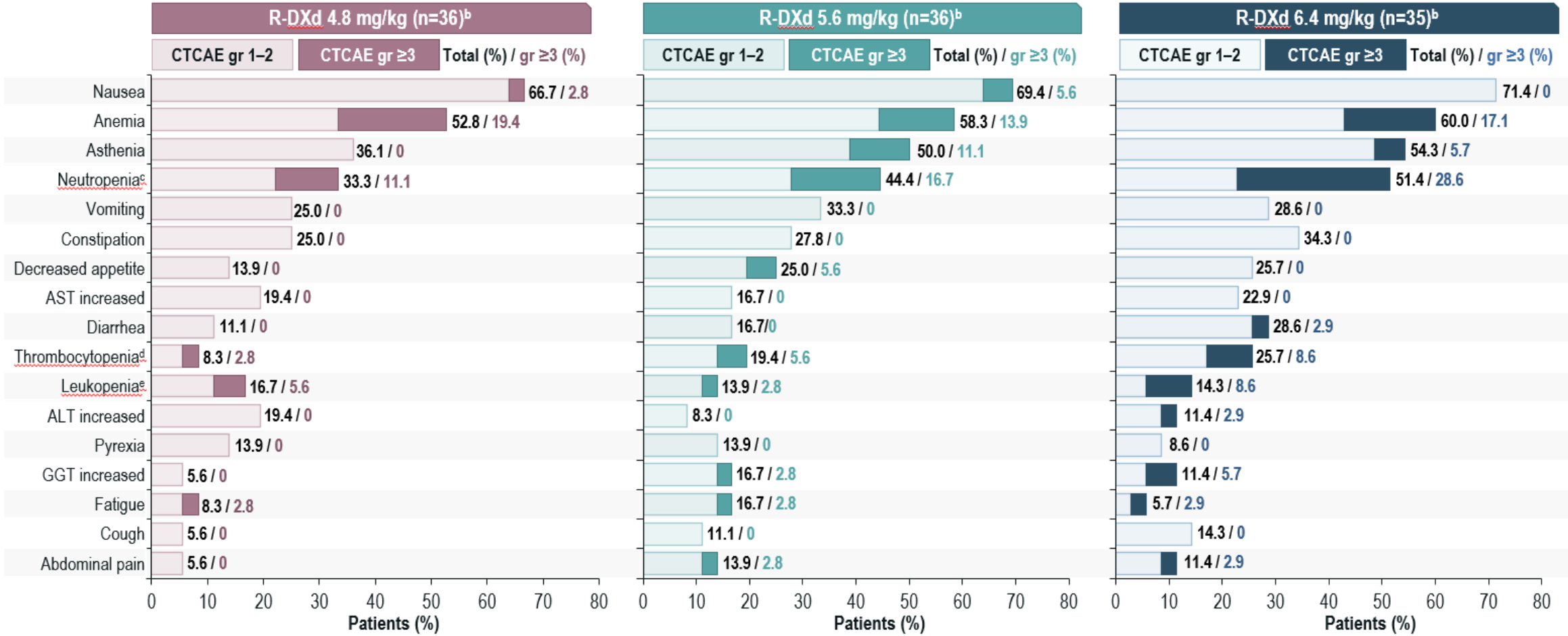
Data cutoff: February 26, 2025.

Reported safety events are defined using MedDRA Preferred Terms and CTCAE criteria.

[a]Grade 5 events were hepatic failure, ovarian cancer, and malignant neoplasm progression. [b]Grade 5 events were ovarian cancer and aspiration. [c]Grade 5 event was influenza infection. [d]Dose modifications associated with treatment-related TEAEs defined as: dose discontinuation, no subsequent administration of R-DXd; dose reduction, R-DXd dose was reduced at next administration; dose delay, study drug was not administered at the next scheduled cycle but was administered at a later date. [e]ILD/pneumonitis events were adjudicated by an independent ILD adjudication committee. [f]ILD/pneumonitis Grade ≥3 event (adjudicated as treatment related) was grade 3.

CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Most common TEAEs (≥10% of overall population)[a]



Nausea, anemia, asthenia and neutropenia were the most common TEAEs across all doses

Data cutoff: February 26, 2025.

[a]TEAEs reported in ≥10% of all patients who received R-DXd 4.8–6.4 mg/kg. Reported safety events are defined by MedDRA preferred terminology. [b]Grade 4 hematologic TEAEs reported at 4.8 mg/kg: neutropenia[c] (n=2), thrombocytopenia[d] (n=1); at 5.6 mg/kg: neutropenia[c] (n=2), thrombocytopenia[d] (n=1), leukopenia[e] (n=1); at 6.4 mg/kg: neutropenia[c] (n=3), thrombocytopenia[d] (n=1), lymphopenia (n=1). No grade 5 hematologic TEAEs were reported at any dose. Grade 3 febrile neutropenia was reported in 2 patients, one each in the R-DXd 5.6 and 6.4 mg/kg cohorts. [c]Neutropenia was defined as the grouped incidence of events reported under the preferred terms '*neutropenia*' and '*neutrophil count decreased*', with a maximum of one event per patient per grouped preferred term. [d]Thrombocytopenia was defined as the grouped incidence of events reported under the preferred terms '*thrombocytopenia*' and '*platelet count decreased*', with a maximum of one event per patient per grouped preferred term. [e]Leukopenia was defined as the preferred term '*white blood cell count decreased.*'

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma-glutamyltransferase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Conclusions

- In this dose-optimization analysis, 107 patients with platinum-resistant OC received R-DXd at doses of 4.8–6.4 mg/kg
  - In total, 94.1% of tumors demonstrated positive CDH6 membrane expression by IHC
- After a minimum of 18 weeks of follow-up, R-DXd demonstrated promising efficacy across all evaluated doses:
  - The confirmed ORR was 50.5%, including three CRs (2.8%)
  - Clinically meaningful tumor responses were observed across a range of CDH6 expression levels
  - Further follow-up is required to obtain mature data on DOR and PFS
- The safety profile of R-DXd appears manageable and is consistent with the safety findings reported in the Phase 1 study[1,2]
  - One adjudicated treatment-related Grade ≥3 ILD event (Grade 3) was reported in this analysis
- Based on these efficacy and safety results, as well as PK and ER data,[3] R-DXd 5.6 mg/kg provided a positive benefit–risk profile and was considered the optimal dose
- The Phase 3 part of the REJOICE-Ovarian01 study will evaluate R-DXd 5.6 mg/kg versus treatment of physician's choice in patients with platinum-resistant OC

Data cutoff: February 26, 2025.

CR, complete response; DOR, duration of response; ER, exposure–response; IHC. immunohistochemistry; ORR, objective response rate; OC, ovarian cancer; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response.

1. Moore KN, et al. Oral presentation at the European Society for Medical Oncology congress. October 20–24, 2023; Madrid, Spain. Presentation 745MO. 2. Moore KN, et al. Oral presentation at the Society of Gynecologic Oncology 2024 Annual Meeting on Women's Cancer. March 16–18, 2024; San Diego, CA, USA. 3. Daiichi Sankyo, Inc. Data on file.

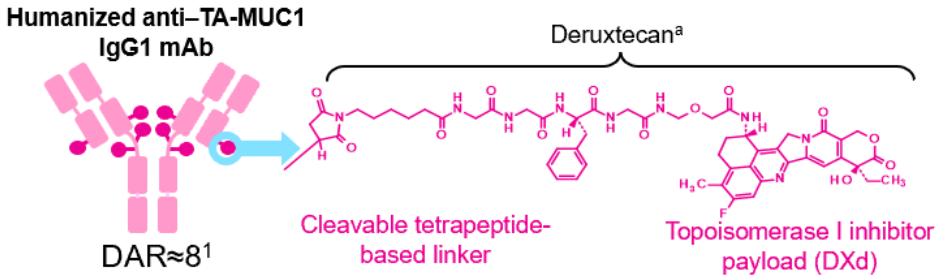
DS-3939, a tumor-associated mucin 1 (TA-MUC1)–directed antibody–drug conjugate, in patients with advanced/metastatic solid tumors: Initial results from a first-in-human study

Manish R. Patel,[1] Toshihiko Doi,[2] Noboru Yamamoto,[3] Ignacio Garrido-Laguna,[4] Satoshi Nishioka,[5] Sutan Wu,[5] Christian Ostheimer,[5] Keiko Nakajima,[5] Benedito A. Carneiro[6]

[1]Sarah Cannon Research Institute at Florida Cancer Specialists, Sarasota, FL, USA; [2]National Cancer Center Hospital East, Kashiwa, Japan; [3]National Cancer Center Hospital, Tokyo, Japan; [4]Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA; [5]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [6]Legorreta Cancer Center at Brown University, Providence, RI, USA.

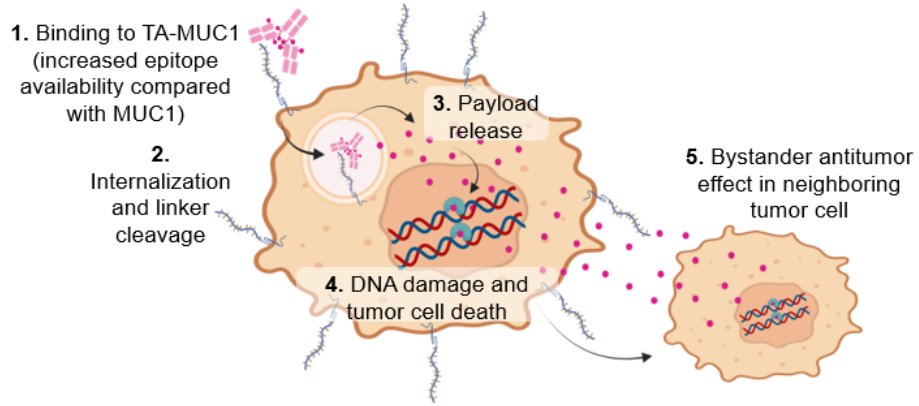
DS-3939: Novel TA-MUC1–directed ADC with significant preclinical activity

- **DS-3939** was designed with 3 components[1–5]:



- **DS-3939 specifically binds to TA-MUC1** by recognizing both its glycan and backbone peptide moieties, promoting **high payload delivery into tumor cells**[1–3,6]

DS-3939 MOA[1,6]

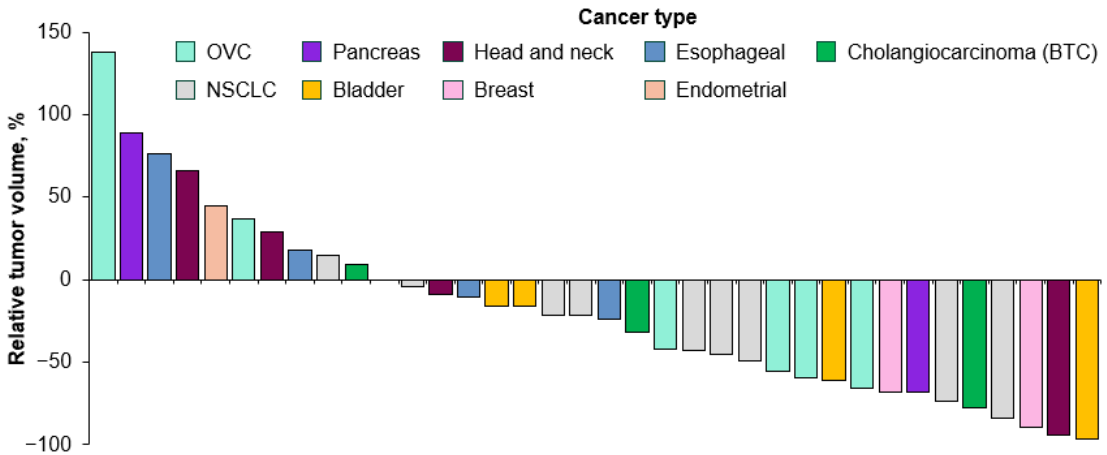


Created with BioRender.com. Adapted from Yukiura M, et al. AACR 2024.[6]

Preclinical activity of DS-3939

- **DS-3939** has exhibited **significant antitumor effects** in multiple TA-MUC1–positive preclinical CDX and PDX models, including in OVC, PDAC, NSCLC, BC, UC, and BTC[1]
- **DS-3939** exhibited antitumor effects in bladder PDX and TNBC PDX models following treatment with other cytotoxic ADCs[1]

Tumor regression was exhibited in 25/36 PDX models treated with DS-3939[1]



Adapted from Takano K, et al. *Mol Cancer Ther.*[1]

[a]Refers to the linker and payload.

ADC, antibody–drug conjugate; BC, breast cancer; BTC, biliary tract cancer; CDX, cell-derived xenograft; DAR, drug-to-antibody ratio; IgG1, immunoglobulin G1; mAb, monoclonal antibody; MOA, mechanism of action; NSCLC, non-small cell lung cancer; OVC, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; PDX, patient-derived xenograft; TA-MUC1, tumor-associated mucin 1; TNBC, triple-negative breast cancer; UC, urothelial carcinoma.

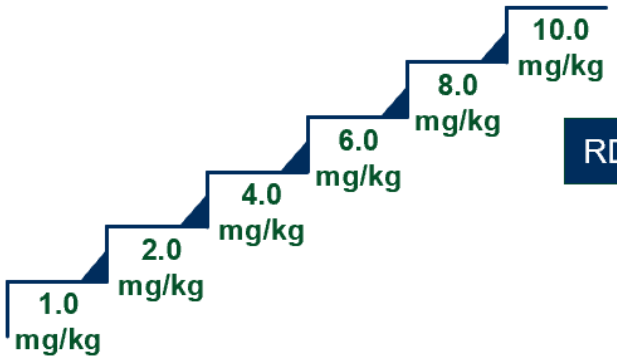
1. Takano K, et al. *Mol Cancer Ther*. Published online July 10, 2025. 2. Danielczyk A, et al. *Cancer Immunol Immunother*. 2006;55:1337–1347. 3. Fan XN, et al. *Pathol Res Pract*. 2010;206:585–589. 4. Nakada T, et al. *Bioorg Med Chem Lett*. 2016;26:1542–1545. 5. Ogitani Y, et al. *Bioorg Med Chem Lett*. 2016;26:5069–5072. 6. Yukiura M, et al. Oral presentation at the AACR Annual Meeting. April 5–10, 2024; San Diego, CA. Abstract 6579.

DS3939-077: First-in-human study (NCT05875168)[1,2]

Key eligibility criteria (Part 1):

- Adults with histologically or cytologically documented locally advanced, metastatic, or unresectable solid tumors not amenable to SOC therapy
- ECOG PS 0–1
- Adequate organ function
- No history of, current, or suspected ILD/pneumonitis
- No prior treatment targeting MUC1 or TA-MUC1
- Patients who received prior treatment with a DXd ADC can be eligible (Part 1 only)

Part 1: Dose escalation (N=64)



RDE(s)

DS-3939 monotherapy IV Q3W

Part 2: Dose expansion

Multiple expansion cohorts targeting various advanced solid tumors

Dose expansion, including dose optimization, is ongoing

Primary endpoints:

- Safety (DLTs [Part 1 only], TEAEs, SAEs)
- ORR[a] (Part 2 only)

Secondary endpoints:

- ORR[a] (Part 1 only)
- DCR[a]
- DOR[a]
- TTR[a]
- PFS[a]
- OS
- TA-MUC1 expression detected by IHC at baseline and correlation with DS-3939 efficacy
- Pharmacokinetics
- Immunogenicity

Exploratory endpoints:

- Antitumor activity by G-score
- Exposure–response relationships

- In the dose-escalation portion of this Phase 1/2 study, patients with BC, BTC, CRC, NSCLC, OVC, PDAC, and UC were enrolled due to broad TA-MUC1 expression in these cancer types
- **Results from the dose-escalation portion of the study are presented here**

Data cutoff: August 1, 2025.

[a]By investigator per RECIST 1.1.

ADC, antibody–drug conjugate; BC, breast cancer; BTC, biliary tract cancer; CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ILD, interstitial lung disease; IV, intravenous; MUC1, mucin 1; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; OVC, ovarian cancer; PDAC, pancreatic ductal carcinoma; PFS, progression-free survival; Q3W, once every 3 weeks; RDE, recommended dose for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SAE, serious adverse event; SOC, standard-of-care; TA-MUC1, tumor-associated mucin 1; TEAE, treatment-emergent adverse event; TTR, time to response; UC, urothelial carcinoma.

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05875168. Accessed September 16, 2025. 2. Yamamoto N, et al. *Cancer Res*. 2024; 84(Suppl. 7). Abstract CT291.

DS-3939: Baseline Characteristics and Disposition

- At the August 1, 2025 data cutoff, 64 patients had been enrolled and received treatment with DS-3939, with a median follow-up of 8.8 months (range, 0.6–22.9)
- ~Two-thirds of patients had an ECOG PS of 1 (62.5%), over half of patients had ≥3 prior LOTs in the locally advanced/metastatic setting (53.1%), and over one-third of patients had treatment with prior topoisomerase I inhibitors (37.5%)
- 15/64 patients (23.4%) had ongoing DS-3939 treatment; 49/64 patients (76.6%) discontinued treatment, including 34/64 (53.1%) due to clinical or disease progression and 13/64 (20.3%) due to TEAEs[a]

DS-3939 dose, mg/kg	1.0 (n=3)	2.0 (n=3)	4.0 (n=19)	6.0 (n=17)	8.0 (n=21)	10.0 (n=1)	Total (N=64)
Age, median (range), years	68.0 (66–69)	56.0 (52–64)	66.0 (32–82)	66.0 (46–78)	64.0 (39–79)	52.0 (52–52)	64.5 (32–82)
Male sex, n (%)	2 (66.7)	0	10 (52.6)	6 (35.3)	15 (71.4)	1 (100)	34 (53.1)
ECOG PS, n (%)							
0	1 (33.3)	3 (100)	4 (21.1)	5 (29.4)	10 (47.6)	1 (100)	24 (37.5)
1	2 (66.7)	0	15 (78.9)	12 (70.6)	11 (52.4)	0	40 (62.5)
Primary diagnosis, n (%)							
BC	0	0	3 (15.8)	2 (11.8)	0	0	5 (7.8)
BTC	1 (33.3)	0	1 (5.3)	0	5 (23.8)	0	7 (10.9)
CRC	0	0	5 (26.3)	0	2 (9.5)	0	7 (10.9)
NSCLC	0	0	6 (31.6)	9 (52.9)	1 (4.8)	0	16 (25.0)
OVC	0	3 (100)	1 (5.3)	2 (11.8)	2 (9.5)	0	8 (12.5)
PDAC	2 (66.7)	0	1 (5.3)	2 (11.8)	7 (33.3)	0	12 (18.8)
UC	0	0	2 (10.5)	2 (11.8)	4 (19.0)	1 (100)	9 (14.1)
Prior LOTs for locally adv/met disease, median (range)	2.0 (1–3)	4.0 (3–8)	2.0 (1–8)	4.0 (1–17)	3.0 (1–8)	3.0 (3–3)	3.0 (1–17)
1, n (%)	1 (33.3)	0	6 (31.6)	3 (17.6)	3 (14.3)	0	13 (20.3)
2, n (%)	1 (33.3)	0	7 (36.8)	4 (23.5)	5 (23.8)	0	17 (26.6)
3, n (%)	1 (33.3)	1 (33.3)	2 (10.5)	1 (5.9)	3 (14.3)	1 (100)	**9 (14.1)**
≥4, n (%)	0	2 (66.7)	4 (21.1)	9 (52.9)	10 (47.6)	0	**25 (39.1)**
Prior topoisomerase I inhibitor,[b] n (%)	3 (100)	0	8 (42.1)	4 (23.5)	9 (42.9)	0	**24 (37.5)**
Treatment duration, median (range), months	1.4 (1.4–2.1)	9.4 (5.6–17.3)	3.2 (1.4–14.5)	3.5 (0.7–14.8)	3.4 (0.7–10.8)	4.7 (4.7–4.7)	3.4 (0.7–17.3)
DS-3939 treatment ongoing, n (%)	0	1 (33.3)	4 (21.1)	4 (23.5)	6 (28.6)	0	**15 (23.4)**

Data cutoff: August 1, 2025.

[a]Included investigator-reported pneumonitis (n=9), cough (n=2), cerebrovascular accident (n=1), and intracranial hemorrhage (n=1). [b]Included 20 patients who received irinotecan, 2 patients who received trastuzumab deruxtecan, and 2 patients who received both trastuzumab deruxtecan and sacituzumab govitecan.

Adv/met, advanced/metastatic; BC, breast cancer; BTC, biliary tract cancer; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; LOT, line of therapy; NSCLC, non-small cell lung cancer; OVC, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; TEAE, treatment-emergent adverse event; UC, urothelial carcinoma.

DS-3939: Safety summary

DS-3939 dose, mg/kg	1.0 (n=3)	2.0 (n=3)	4.0 (n=19)	6.0 (n=17)	8.0 (n=21)	10.0 (n=1)	Total (N=64)
TEAEs, n with event (%)							
Any grade	3 (100)	3 (100)	18 (94.7)	17 (100)	21 (100)	1 (100)	**63 (98.4)**
Treatment-related	2 (66.7)	3 (100)	13 (68.4)	17 (100)	20 (95.2)	1 (100)	**56 (87.5)**
Grade ≥3	0	0	7 (36.8)	7 (41.2)	15 (71.4)	1 (100)	30 (46.9)
Treatment-related	0	0	3 (15.8)	5 (29.4)	13 (61.9)	1 (100)	22 (34.4)
Serious	0	0	4 (21.1)	4 (23.5)	9 (42.9)	0	17 (26.6)
Treatment-related	0	0	3 (15.8)	1 (5.9)	4 (19.0)	0	8 (12.5)
Associated with:							
Treatment discontinuation	0	1 (33.3)	4 (21.1)	2 (11.8)	6 (28.6)	0	13 (20.3)[b]
Treatment-related	0	1 (33.3)	3 (15.8)	2 (11.8)	5 (23.8)	0	11 (17.2)
Dose reduction	0	0	1 (5.3)	2 (11.8)	7 (33.3)	1 (100)	11 (17.2)
Treatment-related	0	0	1 (5.3)	2 (11.8)	7 (33.3)	1 (100)	11 (17.2)
Treatment interruption[c]	0	0	2 (10.5)	5 (29.4)	1 (4.8)	0	8 (12.5)
Treatment-related[c]	0	0	1 (5.3)	5 (29.4)	1 (4.8)	0	7 (10.9)
Treatment delay[d]	0	0	5 (26.3)	9 (52.9)	8 (38.1)	1 (100)	23 (35.9)
Treatment-related[d]	0	0	4 (21.1)	6 (35.3)	7 (33.3)	1 (100)	18 (28.1)
Death	0	0	1 (5.3)	0	2 (9.5)	0	3 (4.7)
Treatment-related	0	0	0	0	1 (4.8)	0	1 (1.6)
DLTs	0	0	1 (5.3)	1 (5.9)	2 (9.5)[a]	0	**4 (6.3)[a]**

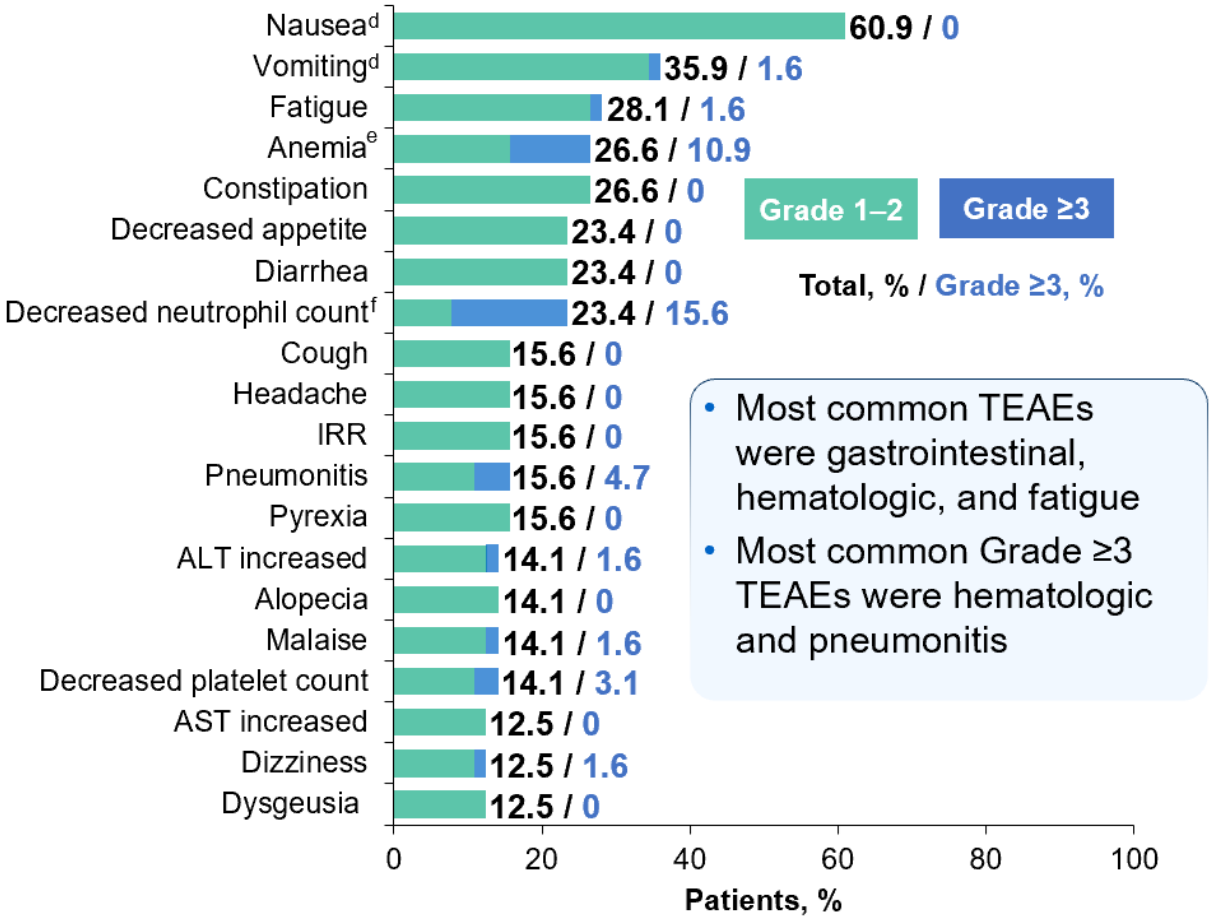
- Any-cause and treatment-related TEAEs reported in 63/64 (98.4%) and 56/64 (87.5%) patients, respectively
- Doses of ≥8 mg/kg associated with higher rates of dose reduction and treatment discontinuation
  - 6 mg/kg was determined as the RDE
- DLTs reported in 4/64 patients (6.3%)[a]
  - Grade 3 anemia needing transfusion (4.0 mg/kg)
  - Grade 3 abdominal pain (6.0 mg/kg)
  - Grade 4 decreased platelet count (8.0 mg/kg)
- Treatment discontinuations[b] and interruptions[c] were primarily due to ILD/pneumonitis and IRRs, respectively

Data cutoff: August 1, 2025.

[a]An event of Grade 1 malaise was reported as a DLT but was later confirmed as a data entry error. [b]Included investigator-reported pneumonitis (n=9), cough (n=2), cerebrovascular accident (n=1), and intracranial hemorrhage (n=1). [c]Treatment interruption: study drug infusion was temporarily stopped and then restarted during the same study visit/dosing cycle. [d]Treatment delay: study drug was not administered at the scheduled cycle/dosing visit but was administered at a later date. DLT, dose-limiting toxicity; ILD, interstitial lung disease; IRR, infusion-related reaction; RDE, recommended dose for expansion; TEAE, treatment-emergent adverse event.

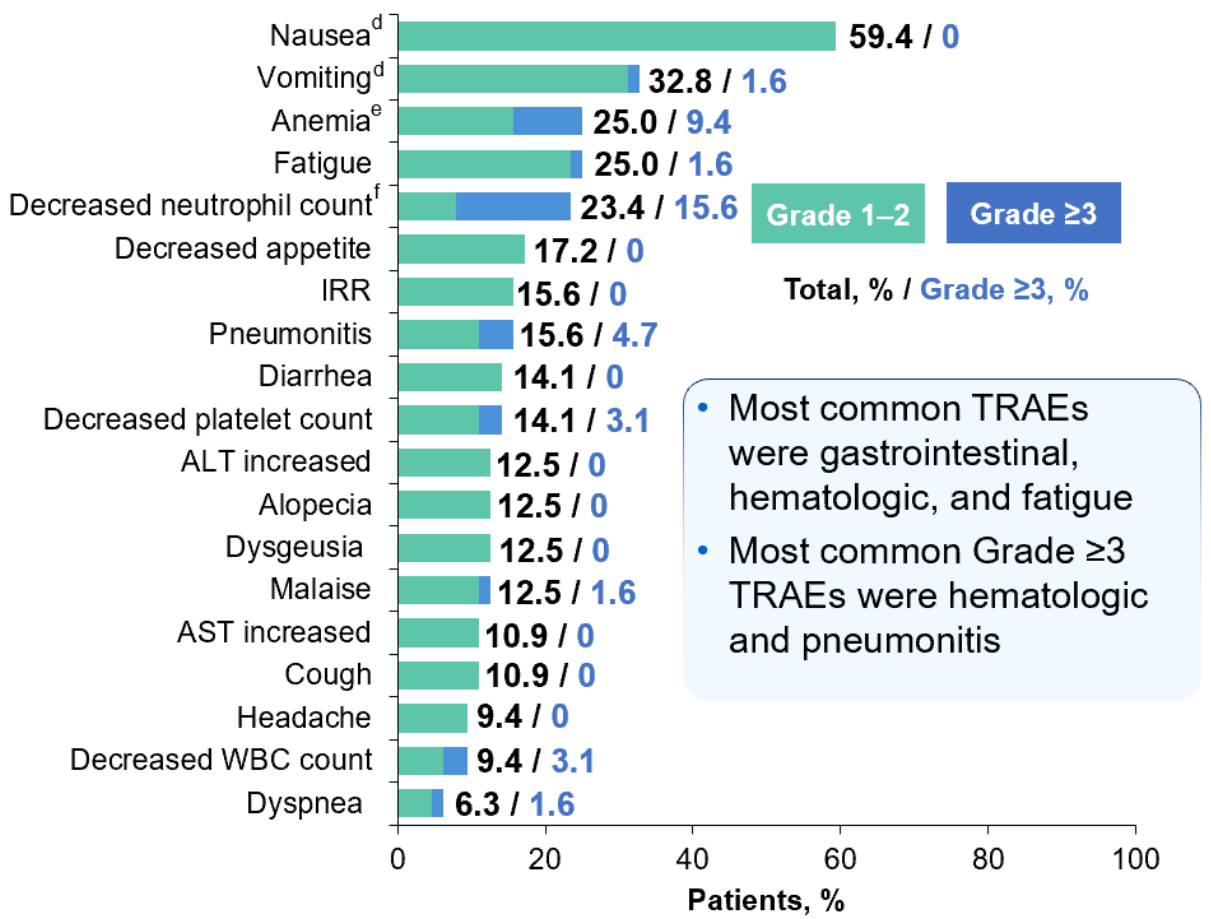
DS-3939: Most common TEAEs and TRAEs

Any-grade TEAEs (≥12% of patients)[a,b]



- Most common TEAEs were gastrointestinal, hematologic, and fatigue
- Most common Grade ≥3 TEAEs were hematologic and pneumonitis

Any-grade TRAEs (≥5% of patients)[b,c]



- Most common TRAEs were gastrointestinal, hematologic, and fatigue
- Most common Grade ≥3 TRAEs were hematologic and pneumonitis

Data cutoff: August 1, 2025.

[a]TEAEs occurring at any grade in ≥12% of patients and Grade ≥3 TEAEs occurring for those preferred terms in the overall population (N=64). [b]Adverse events were coded using the MedDRA dictionary, Version 28.0. [c]TRAEs occurring at any grade in ≥5% of patients and Grade ≥3 TRAEs occurring for those preferred terms in the overall population (N=64). [d]Premedication for the prevention of nausea and vomiting was required before each dose of DS-3939. [e]There were no Grade ≥4 anemia events. [f]Included "decreased neutrophil count" and "neutropenia." Three patients experienced Grade 4 decreased neutrophil count. One patient experienced Grade 3 febrile neutropenia (not included in figure).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WBC, white blood cell.

DS-3939: Majority of ILD and IRR events were Grade 1 or 2

Adjudicated treatment-related ILD/pneumonitis

DS-3939 dose, mg/kg	1.0 (n=3)	2.0 (n=3)	4.0 (n=19)	6.0 (n=17)	8.0 (n=21)	10.0 (n=1)	Total (N=64)
Events, n (%)							
Any grade	0	1 (33.3)	2 (10.5)	0	4 (19.0)	0	**7 (10.9)**
Grade 1	0	0	0	0	0	0	**0**
Grade 2	0	1 (33.3)	1 (5.3)	0	4 (19.0)	0	**6 (9.4)**
Grade 3	0	0	1 (5.3)	0	0	0	**1 (1.6)**
Grade ≥4	0	0	0	0	0	0	**0**

- Adjudicated treatment-related ILD/pneumonitis reported in 7/64 patients (10.9%)
  - Per protocol, DS-3939 was permanently discontinued for Grade ≥2 ILD/pneumonitis
  - Median time to onset of adjudicated treatment-related ILD/pneumonitis was 68 days
  - Post data cutoff: 2/4 ILD cases previously pending adjudication were adjudicated as Grade 5; 2 cases still pending adjudication

IRRs

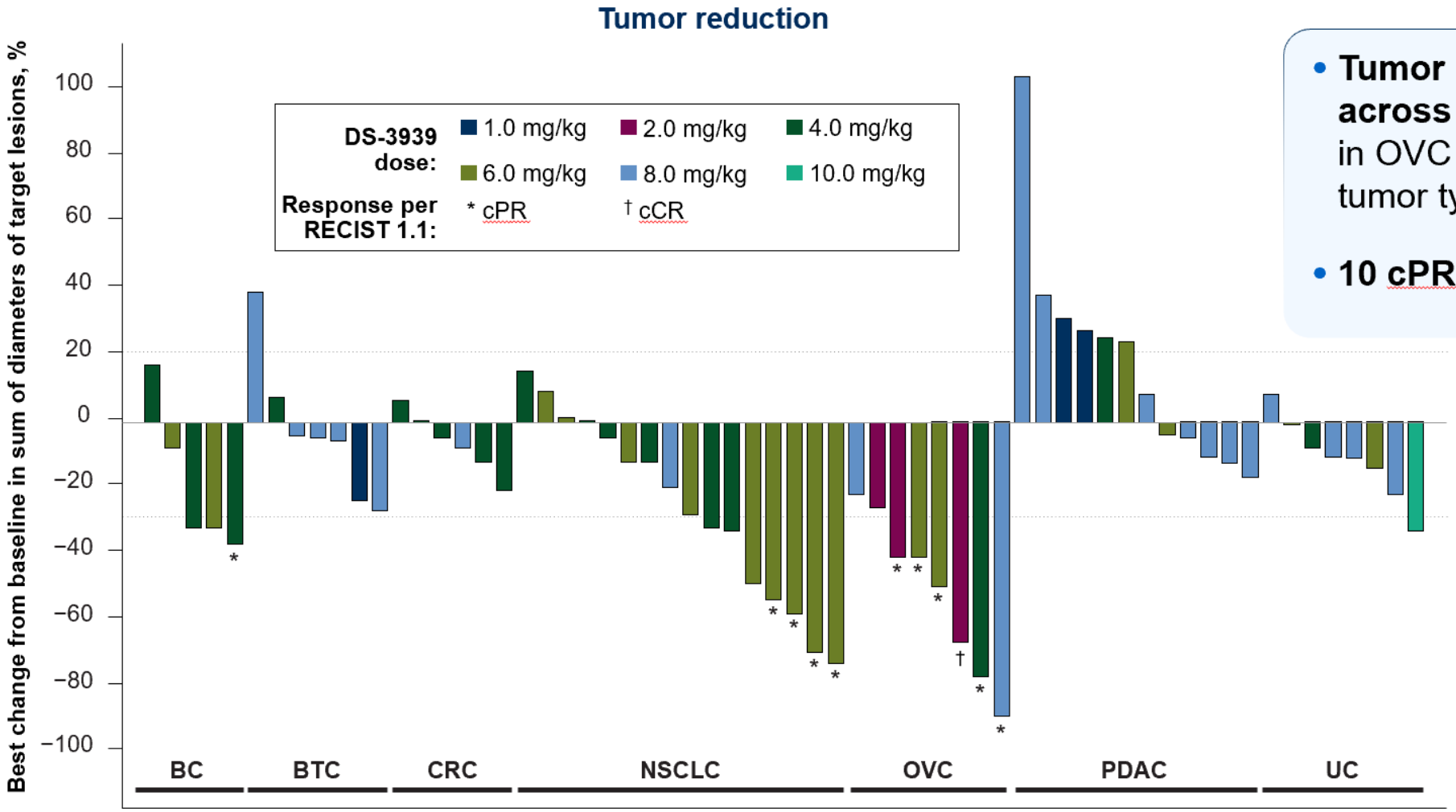
DS-3939 dose, mg/kg	1.0 (n=3)	2.0 (n=3)	4.0 (n=19)	6.0 (n=17)	8.0 (n=21)	10.0 (n=1)	Total (N=64)
Events, n (%)							
Any grade	0	1 (33.3)	1 (5.3)	6 (35.3)	2 (9.5)	0	**10 (15.6)**
Grade 1	0	1 (33.3)	0	2 (11.8)	1 (4.8)	0	**4 (6.3)**
Grade 2	0	0	1 (5.3)	4 (23.5)	1 (4.8)	0	**6 (9.4)**
Grade 3	0	0	0	0	0	0	**0**
Grade ≥4	0	0	0	0	0	0	**0**

- IRRs reported in 10/64 patients (15.6%)
  - No Grade ≥3 events
  - No treatment discontinuations due to IRRs
  - Infusion interrupted due to IRRs in 6/64 patients (9.4%)
  - 7 patients (10.9%) experienced IRRs during Cycle 1; for most of those patients, IRR did not reoccur later in treatment

Data cutoff: August 1, 2025.

ILD, interstitial lung disease; IRR, infusion-related reaction.

DS-3939: Tumor reductions across doses: 10 cPRs and 1 cCR



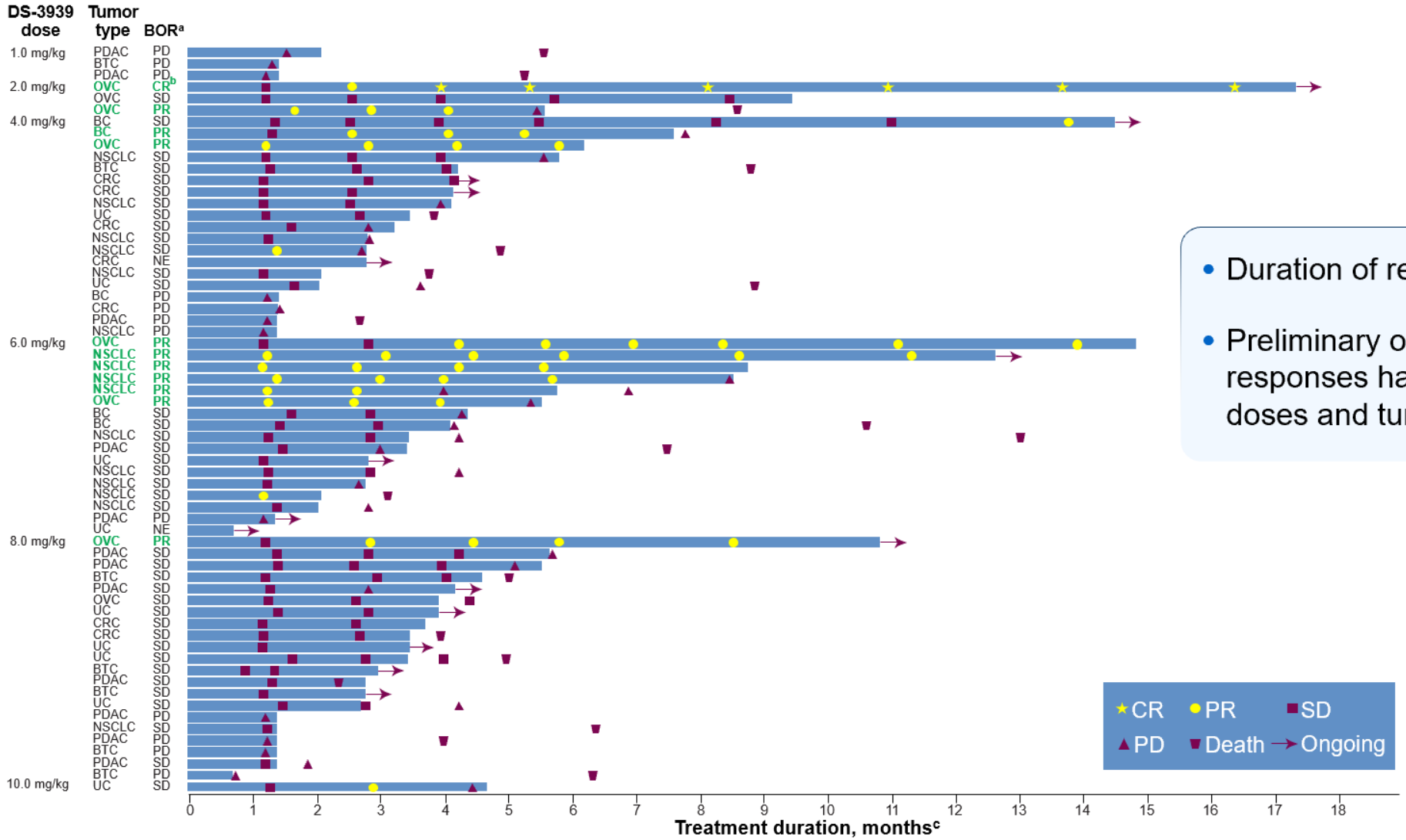
- **Tumor reduction was observed across dose levels,** from 2.0 mg/kg in OVC and 4.0 mg/kg in most other tumor types
- **10 cPRs and 1 cCR[a]**

Data cutoff: August 1, 2025. Median follow-up: 8.8 months (range, 0.6–22.9).

[a]The patient with cCR had lymph nodes only as target lesion.

BC, breast cancer; BTC, biliary tract cancer; cCR, confirmed complete response; cPR, confirmed partial response; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; OVC, ovarian cancer; PD, progressive disease; PDAC, primary ductal adenocarcinoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; UC, urothelial carcinoma.

DS-3939: Treatment duration across tumor types



- Duration of response data yet to mature
- Preliminary observation is that durable responses have been observed across doses and tumor types

Data cutoff: August 1, 2025. Median follow-up: 8.8 months (range, 0.6–22.9).

[a]BOR per RECIST 1.1; CRs and PRs were confirmed. [b]The patient had lymph nodes only as the target lesion. [c]Treatment duration (months) was calculated as (date of the last dose−date of the first dose+21)/30.4375. For patients who were still on treatment at the data cutoff date, the most recent available date of administered dose was used.

BC, breast cancer; BOR, best overall response; BTC, biliary tract cancer; CR, complete response; CRC, colorectal cancer; NE, not evaluable; NSCLC, non-small cell lung cancer; OVC, ovarian cancer; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; UC, urothelial carcinoma.

DS-3939: Conclusions

Preliminary data from the novel TA-MUC1 ADC DS-3939 FIH study, DS3939-077, show:

- **A manageable safety profile in patients with previously treated advanced/metastatic solid tumors**
  - Most common TRAEs were gastrointestinal, hematologic, and fatigue; most were Grade 1 or 2
  - Adjudicated treatment-related ILD/pneumonitis was reported in 7/64 patients (10.9%); most were Grade 2[a]
  - IRRs in 10/64 patients (15.6%); all were Grade 1 or 2
- **DS-3939 demonstrated promising preliminary antitumor activity across dose levels and tumor types in previously treated patients**
- **Dose expansion and optimization are ongoing; patients with various tumor types are being enrolled**

Data cutoff: August 1, 2025.

[a]Post data cutoff: 2/4 ILD cases previously pending adjudication were adjudicated as Grade 5; 2 cases still pending adjudication.

ADC, antibody-drug conjugate; BC, breast cancer; FIH, first-in-human; ILD, interstitial lung disease; IRR, infusion-related reaction; RDE, recommended dose for expansion; PR, partial response; TA-MUC1, tumor-associated mucin 1; TEAE, treatment-emergent adverse event.

Agenda

1. Welcome message
2. Highlights from ESMO 2025
3. **Q&A**

Contact address regarding this material

Daiichi Sankyo Co., Ltd.
Corporate Communications Department

TEL: +81-3-6225-1125
Email: DaiichiSankyoIR_jp@daiichisankyo.com