Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

ASCO Highlights

DAIICHI SANKYO CO., LTD.

June 7(US)/8(JP), 2022

Forward-Looking Statements

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ASCO Highlights 2022: IR conference call

Sunao Manabe
President and CEO

Ken Takeshita
Head of Global R&D

Gilles Gallant
Head of Global
Oncology Clinical Development

Date and time	Jun 8, 2022（Wed）7:30-9:00am JST
Meeting style	Virtual conference by Zoom

Content will be delivered on-demand after the meeting.

Agenda

1. **Introduction**
2. Shift the paradigm for HER2-low BC
3. Build trust in HER2+ Breast Cancer
4. Addressing further needs in BC
5. Rising Stars
6. Future news flow

5-Year Business Plan (FY2021-FY2025) for Sustainable Growth

We will achieve our 2025 Goal, **Global Pharma Innovator with Competitive Advantage in Oncology**, and will shift to further growth towards our 2030 Vision

As of FY2020

- Oncology business launched
- Edoxaban growing
- Regional value being enhanced
- AZ strategic alliance
- Increased RD investment

2030 Vision

Innovative Global Healthcare Company Contributing to the Sustainable Development of Society

- Global top 10 in Oncology
- Additional growth pillars being source of revenue and profit
- New products being source of profit in each business unit
- Contributing to sustainable development of society through our business

Strategic Pillars for the 5-Year Business Plan (FY2021-FY2025)
-1st pillar: Maximize 3ADCs-

Achieve FY2025 Goal and Shift to Further Growth

Maximize 3ADCs
- Maximize ENHERTU® and Dato-DXd through strategic alliance with AstraZeneca
- Maximize HER3-DXd without a partner
- Expand work force and supply capacity flexibly depending on changes around product potential

Profit growth for current business and products
- Maximize Lixiana® profit
- Grow Tarlige®, Nilemdo®, etc. quickly
- Transform to profit structure focused on patented drugs
- Profit growth for American Regent and Daiichi Sankyo Healthcare

Identify and build pillars for further growth
- Identify new growth drivers following 3ADCs
- Select and advance promising post DXd-ADC modalities

Create shared value with stakeholders
- Patients: Contributing to patients through "Patient Centric Mindset"
- Shareholders: Balanced investment for growth and shareholder returns
- Society: Environment load reduction across the value chain, and actions against pandemic risks
- Employees: Create one DS culture through fostering our core behaviors

- Data-driven management through DX, and company-wide transformation through advanced digital technology
- Agile decision making through new global management structure

*3ADCs: 1) ENHERTU®, Trastuzumab deruxtecan (T-DXd, DS-8201), 2) Datopotamab deruxtecan (Dato-DXd, DS-1062) and 3) Patritumab deruxtecan (HER3-DXd, U3-1402)

Launch Plan for 3ADCs
-Expand 3ADCs in broader cancer types and treatment lines-

~FY2020

ENHERTU®
- DESTINY-Breast01
- DESTINY-Gastric01

5-Year Business Plan (FY2021-FY2025)

ENHERTU®
- DESTINY-Breast03
- DESTINY-Breast04
- DESTINY-Breast06
- DESTINY-Gastric04
- DESTINY-Lung01/02
- DESTINY-CRC01/02

Dato-DXd
- TROPION-Lung01

HER3-DXd
- HERTHENA-Lung01

FY2026 & Beyond

ENHERTU®
- DESTINY-Breast05
- DESTINY-Breast09
- DESTINY-Breast11
- DESTINY-Lung04

- Early treatment lines for GC/NSCLC (combo therapy included)
- Other cancer types

Dato-DXd
- TROPION-Lung08
- TROPION-Breast01
- TROPION-Breast02

- Early treatment lines for NSCLC, I/O combo
- Early treatment lines for HER2 negative BC
- Other cancer types

HER3-DXd
- HERTHENA-Lung02

- Early treatment lines for NSCLC, osimertinib combo
- Other cancer types

Off to a great start to achieve FY2025 goal & shift to further growth towards FY2030

Only pivotal studies for new indications are included.

Strategic Pillars for the 5-Year Business Plan (FY2021-FY2025)
-3rd pillar: Identify and build pillars for further growth-

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Achieve FY2025 Goal and Shift to Further Growth

Maximize 3ADCs

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- Select and advance promising post DXd-ADC modalities

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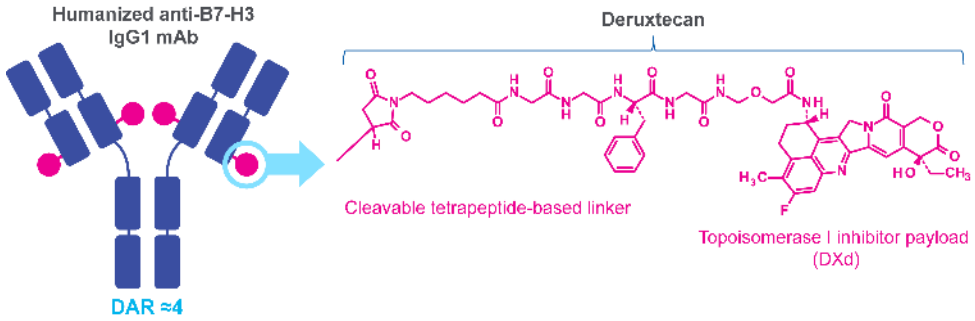
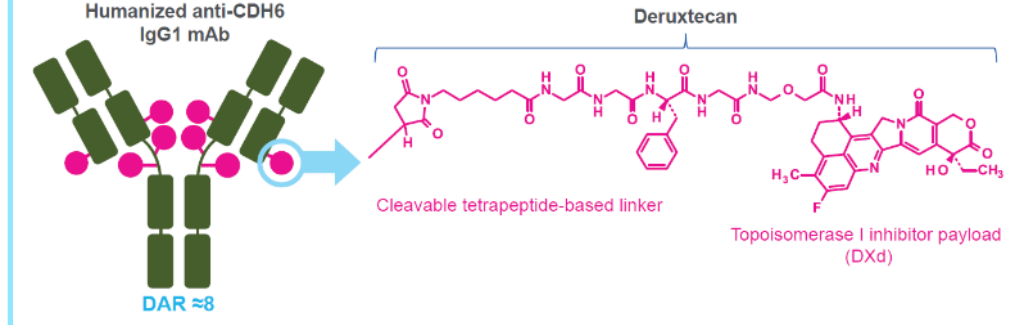
Rising Stars: DS-7300 & DS-6000

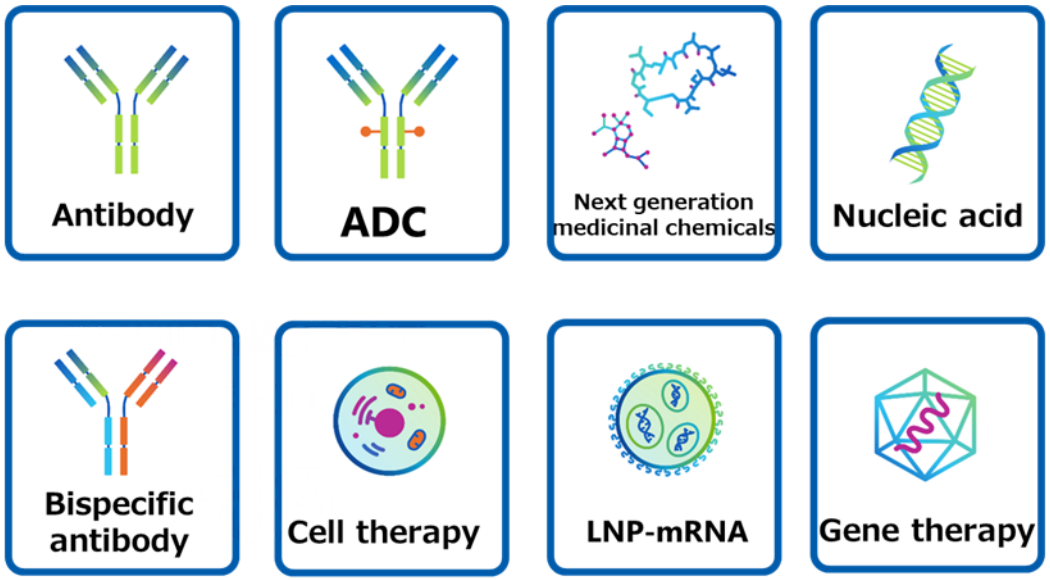
	DS-7300	DS-6000
Structure		
Development stage & target indications	**Ph1/2** **Dose escalation: solid tumors** **Dose expansion: ESCC, CRPC, sqNSCLC** **Ph2 for SCLC under preparation to start in FY2022 H1**	**Ph1** **Dose escalation & expansion: RCC & OVC** **Currently in the dose expansion part**

CRPC: castration-resistant prostate cancer, DAR: drug antibody ratio, ESCC: esophageal squamous cell carcinoma, mAb: monoclonal antibody, OVC: ovarian cancer, RCC: renal cell carcinoma, SCLC: small cell lung cancer, sqNSCLC: squamous non small cell lung cancer,

Rising Stars have potential to become new growth drivers post 3ADCs.
Development to be accelerated.

Daiichi Sankyo's Multi-modality Strategy

Optimized modality



High Unmet Medical Need

Selection of promising post DXd-ADC modalities is ongoing

- Significant knowledge of development & manufacturing accumulated for **LNP-mRNA** technology in FY2021
- Other modalities are in early research stage, further data generation is essential to assess opportunity

DS Strategy to Enrich Our Delivery to Patients

3 and Alpha strategy is evolving

3ADCs

- ENHERTU®
- Dato-DXd
- HER3-DXd

&

Alpha

- Oncology
- Specialty Medicine
- Vaccine

3ADCs Value Maximization

Rising Stars

Next Pillars

Daiichi Sankyo's Purpose and R&D Vision

Purpose	Contribute to the enrichment of quality of life around the world
R&D Vision	Source of innovation for improving patient's lives

Serve Patients Globally

by delivering our strengths worldwide:

Science & Technology

Data Highlights from ASCO & ESMO BC

ESMO BC 2022
8 Abstracts

4 Oral Presentations
2 Mini Oral Presentations
2 Poster Presentations

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4 on ENHERTU®
1 on Dato-DXd
2 on HER3-DXd

ASCO 2022
20 Abstracts

1 Plenary Session
4 Oral Presentations
13 Poster Presentations

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9 on ENHERTU®
1 on Dato-DXd
5 on HER3-DXd

DESTINY-Breast04

5th BTD in US for ENHERTU®

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron

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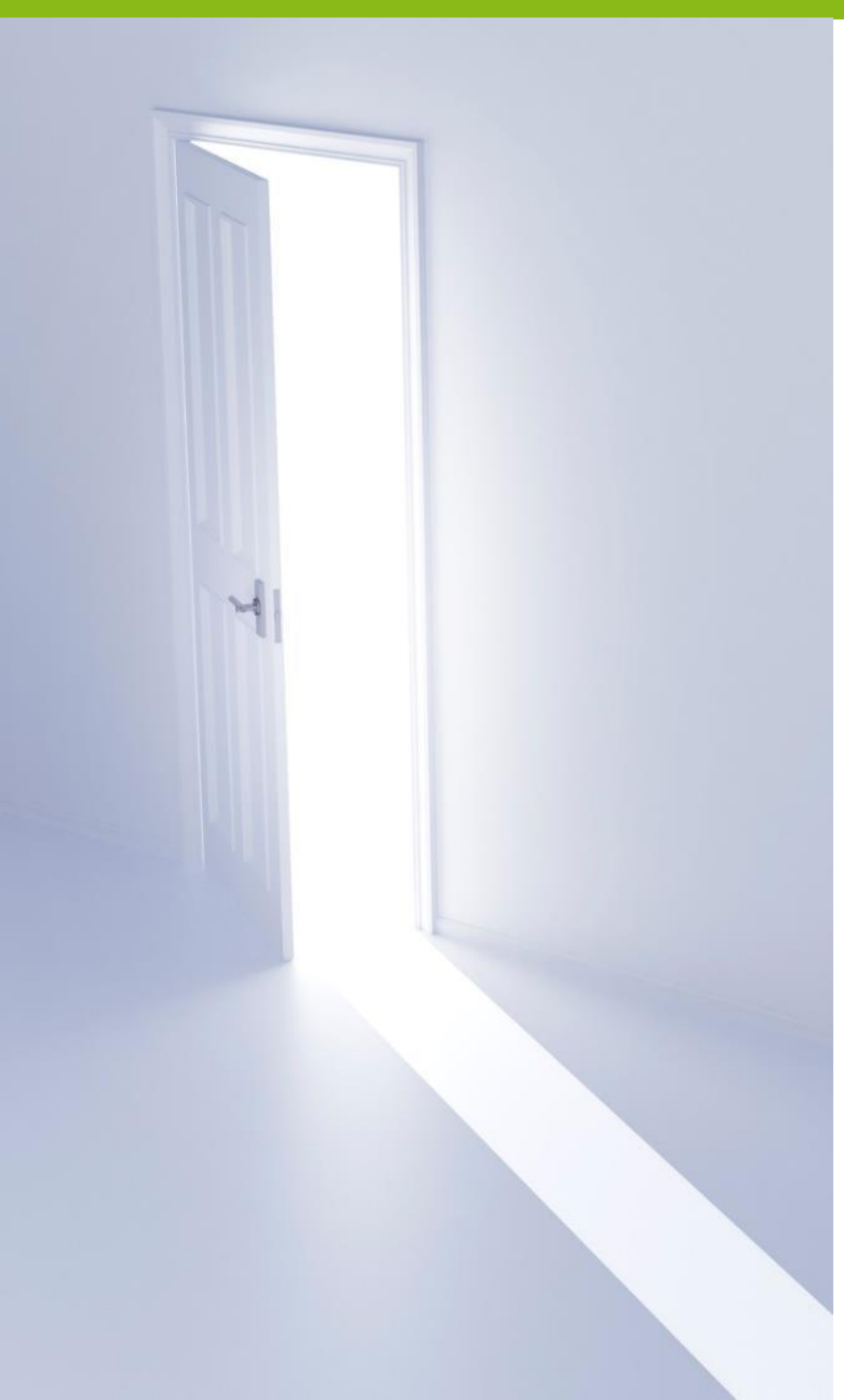

Opening a new treatment paradigm for patients with HER2-low Breast Cancer

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DESTINY-Breast04

Trastuzumab Deruxtecan (T-DXd) vs Treatment of Physician's Choice in Patients with HER2-low Unresectable and/or Metastatic Breast Cancer: Results of DESTINY-Breast04, a Randomized, Phase 3 Study

Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, USA

Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

DESTINY-Breast04 Summary and Impact

DESTINY-Breast04

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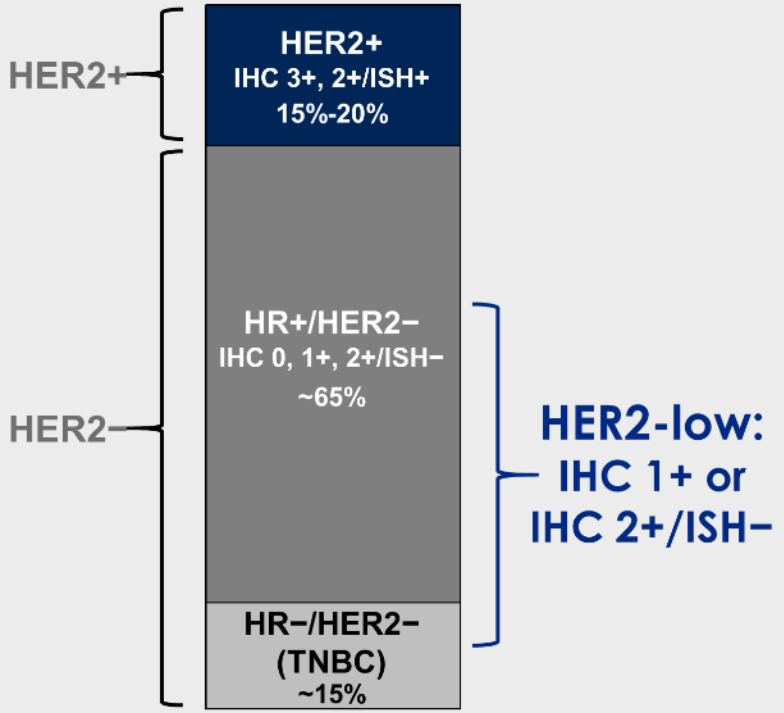
T-DXd treatment showed unprecedented improvement in efficacy for patients with HER2-low mBC

Current mBC paradigm[1,2]



The new mBC paradigm

- T-DXd is the first HER2-targeted therapy to demonstrate improved efficacy in HER2-low mBC
- DESTINY-Breast04 establishes T-DXd as the new standard of care for HER2-low mBC
- Potential improvement for ~50% of all mBC patients

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962.

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

DESTINY-Breast04

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An open-label, multicenter study (NCT03734029)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

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

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

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

Baseline Characteristics

DESTINY-Breast04

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	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes misstratified patients.

Prior Therapies

DESTINY-Breast04

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	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS in HR+ and All Patients

DESTINY-Breast04

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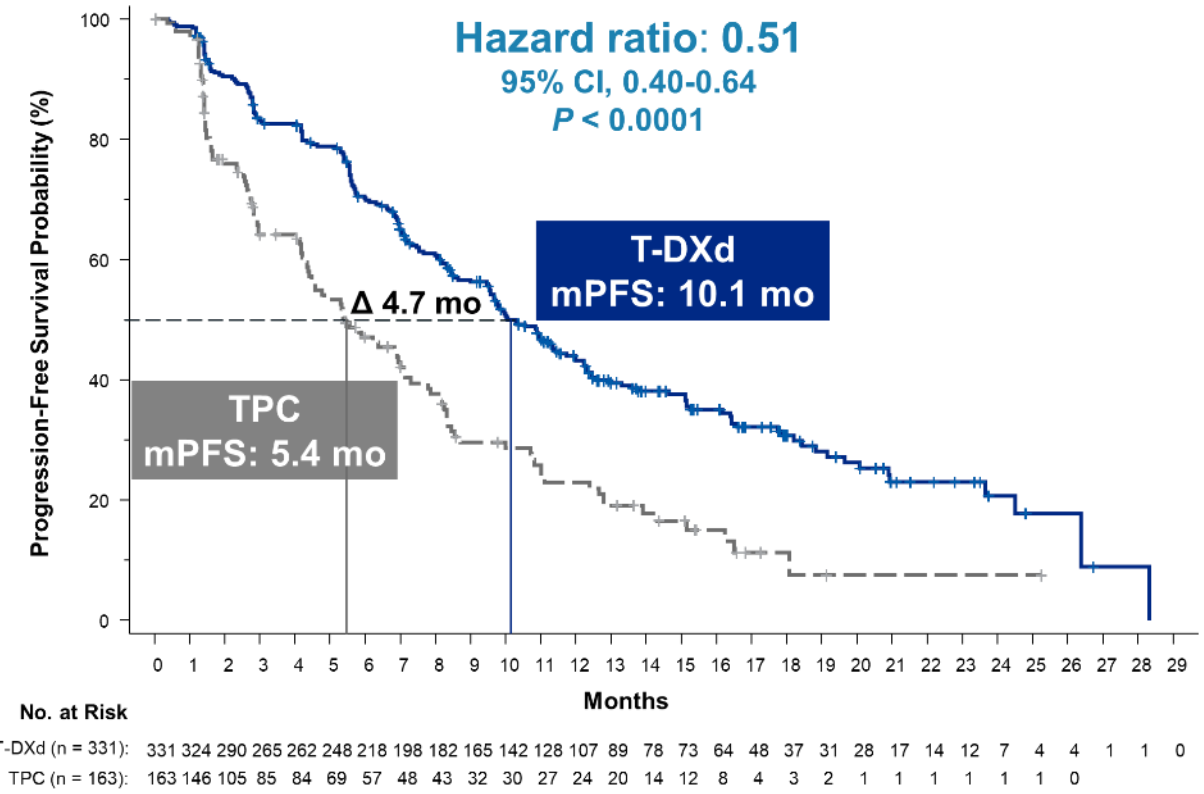
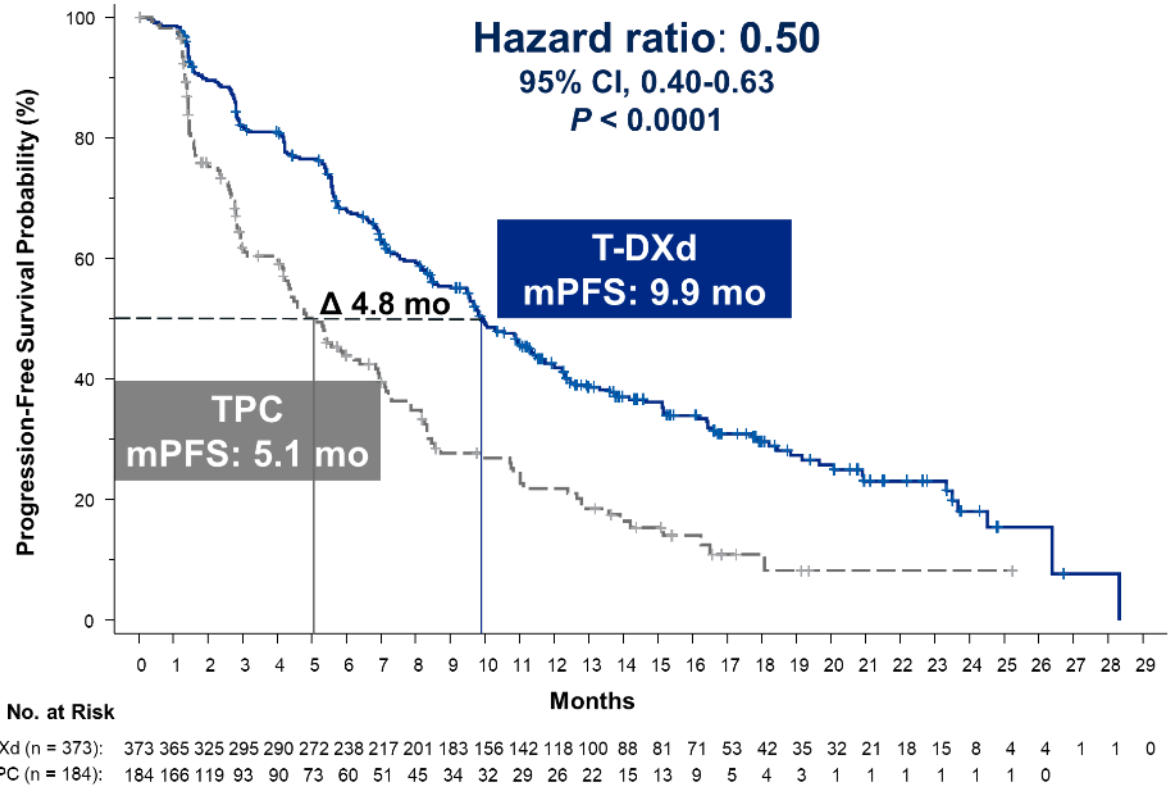
Hormone receptor–positive



All patients



PFS by blinded independent central review.

HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

DESTINY-Breast04

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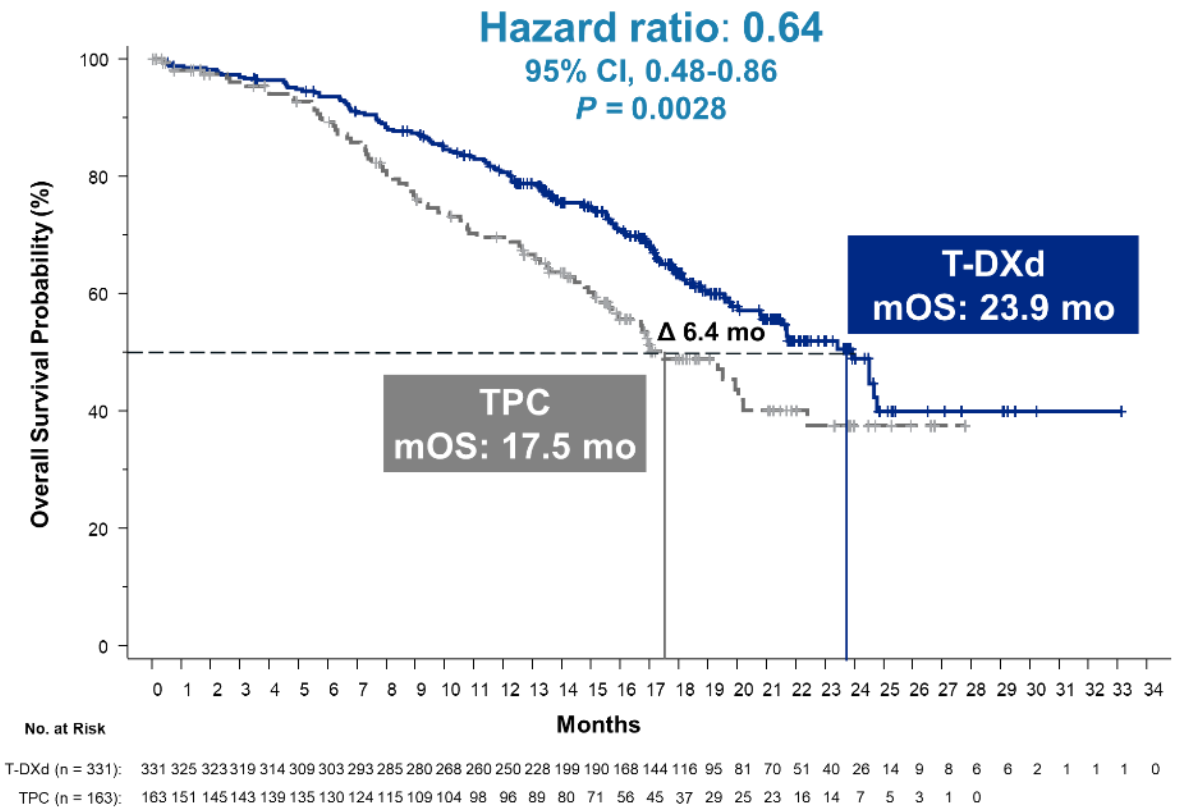
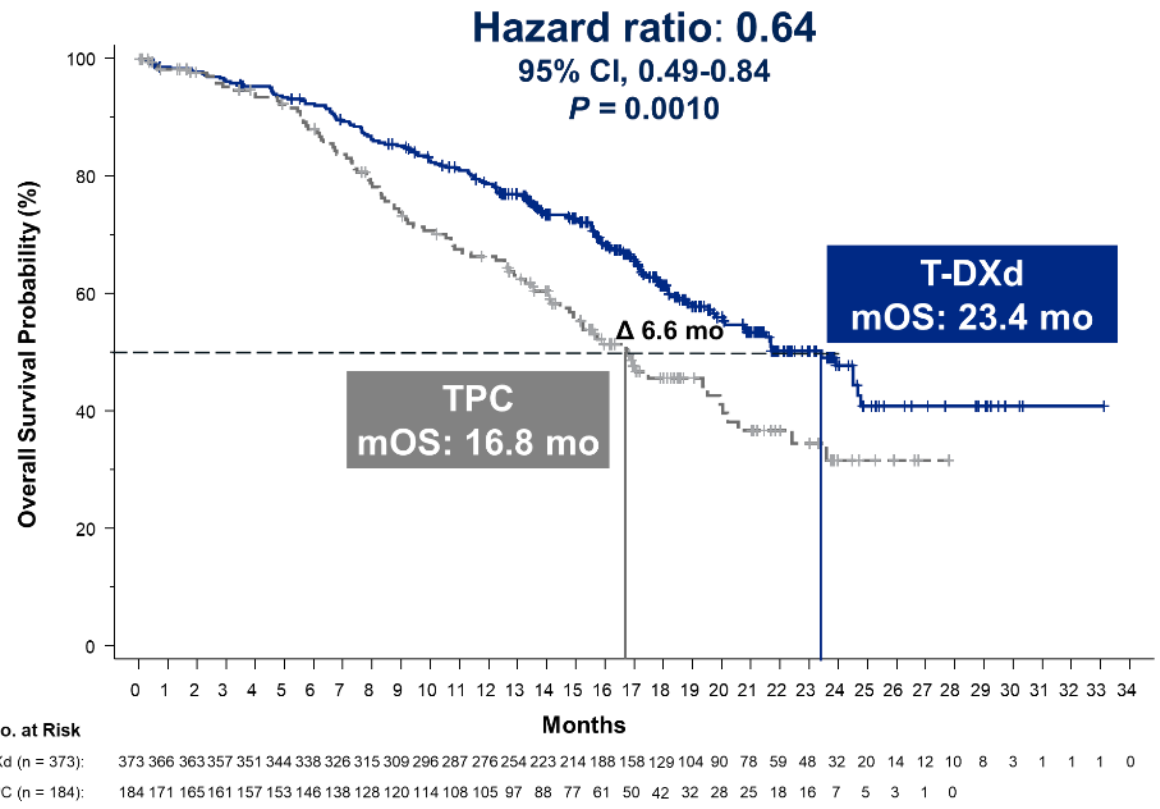
Hormone receptor–positive



All patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS and OS in HR− (Exploratory Endpoints)

DESTINY-Breast04

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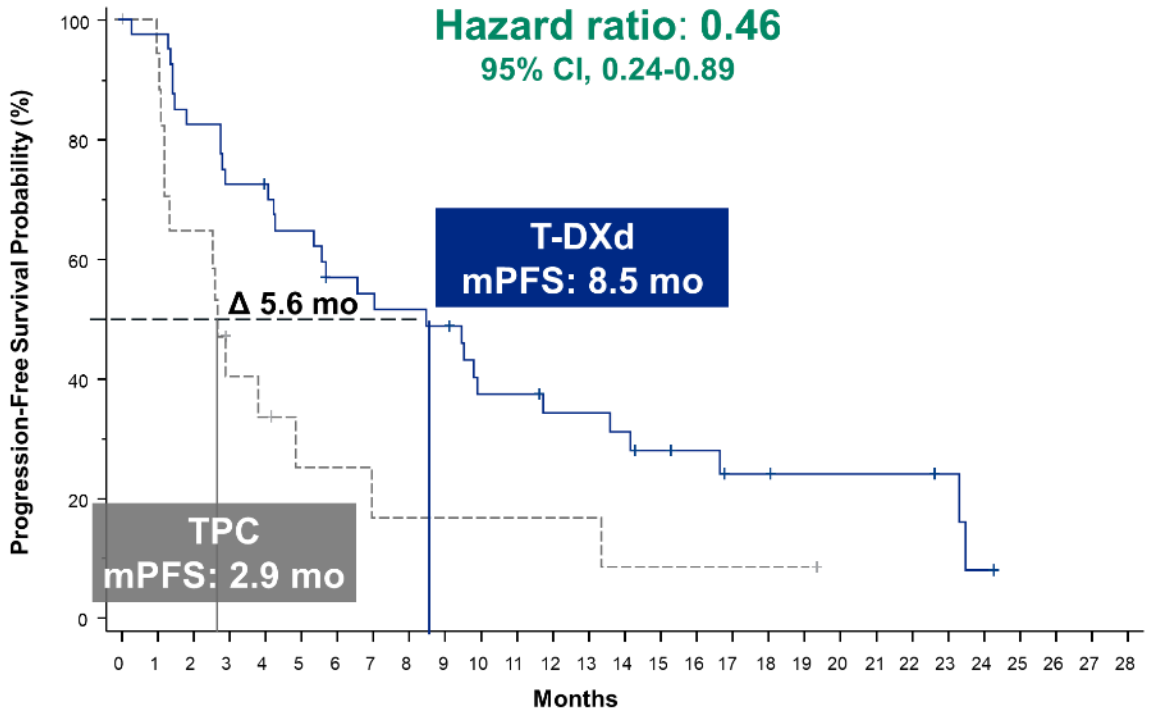
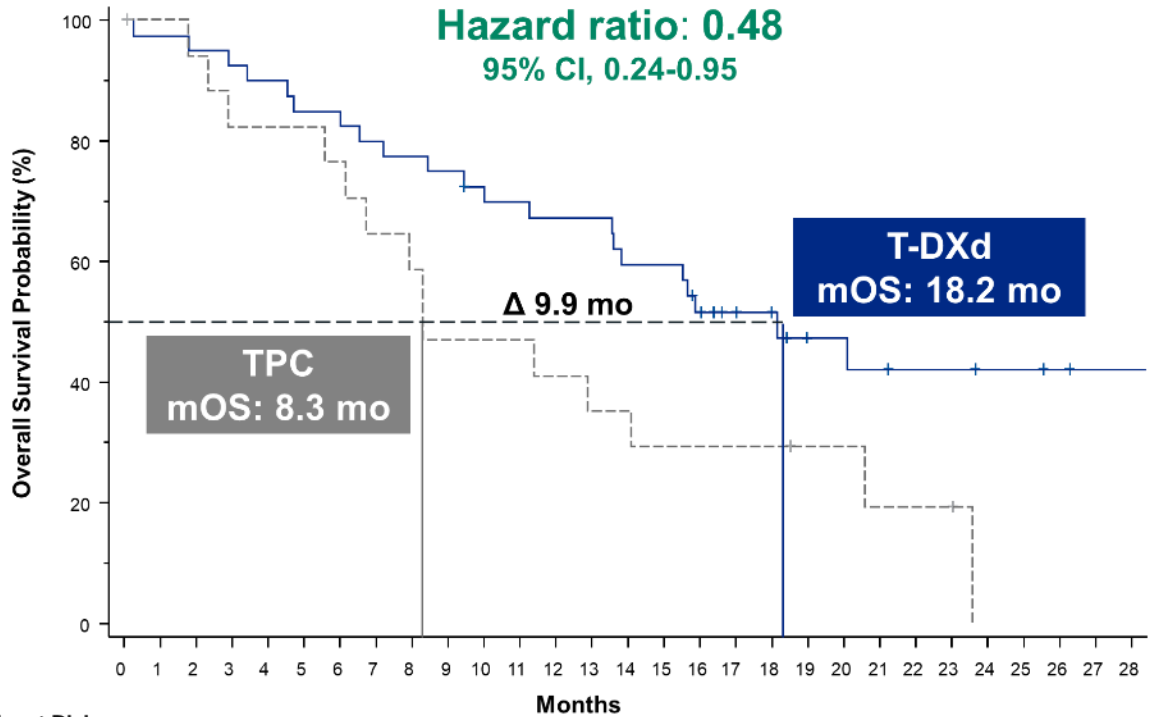
PFS



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	3	1	0
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0				

OS



No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

Subgroup Analysis: PFS in HR+

DESTINY-Breast04

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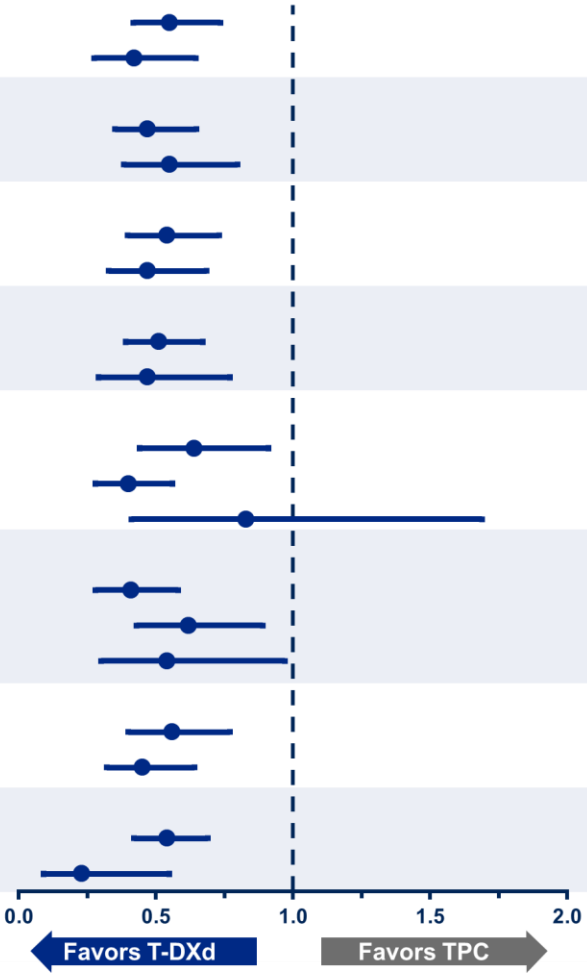
	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)

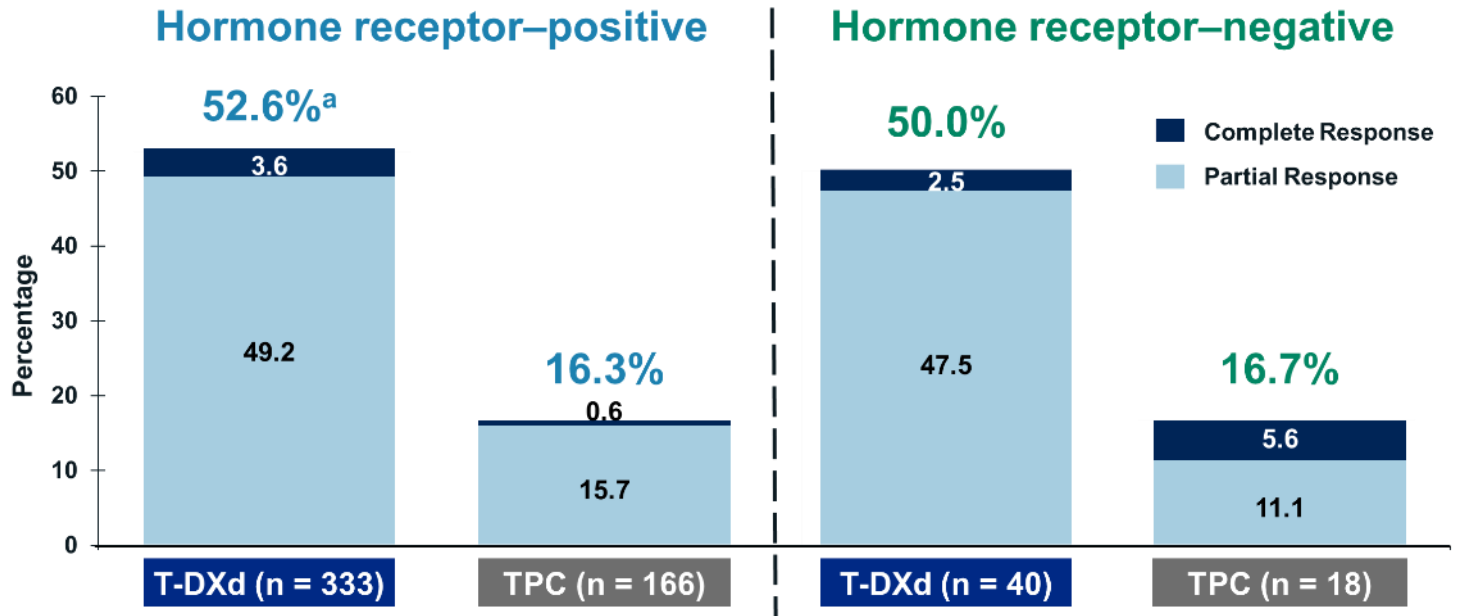


PFS by blinded independent central review. Based on derived data, which include protocol deviations.

CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Confirmed ORR

Confirmed Objective Response Rate



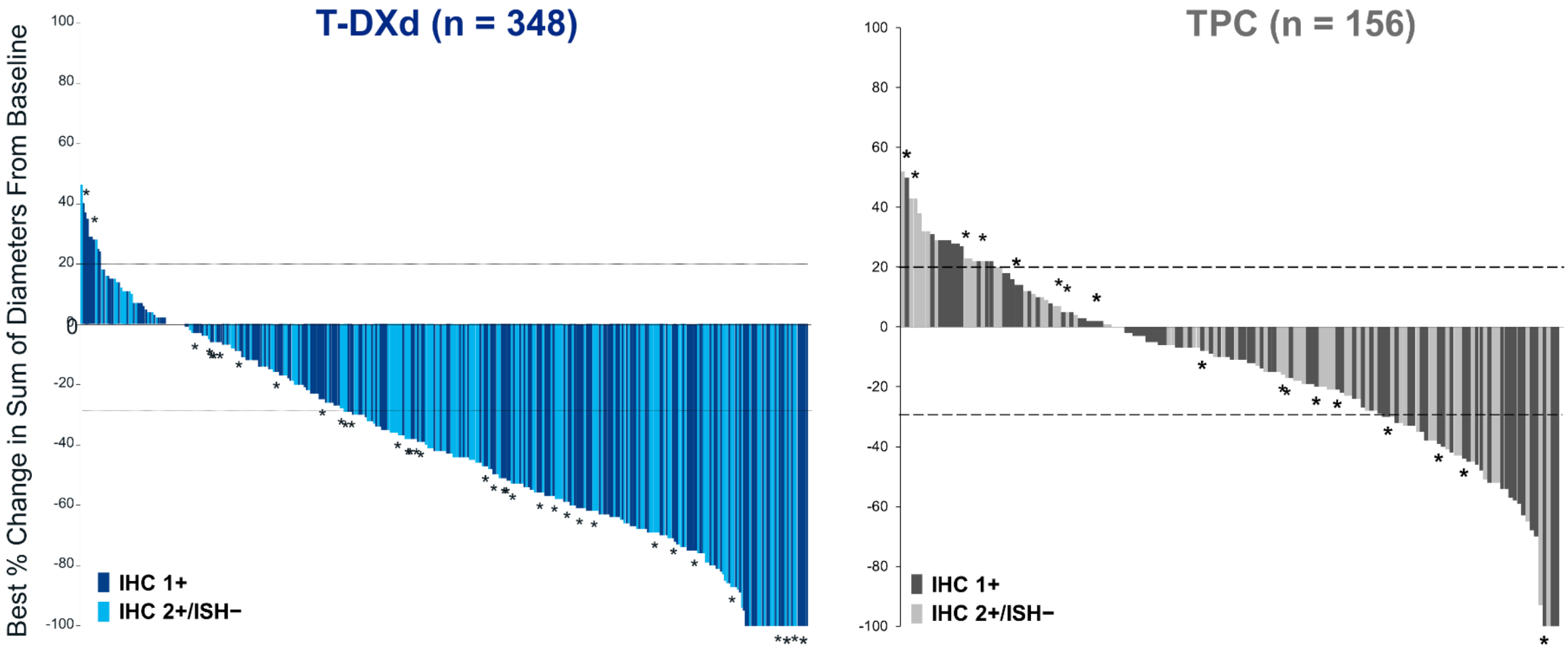
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

Best Change in Target Lesions (All Patients)

DESTINY-Breast04

Daiichi-Sankyo



*Patients with HR− disease

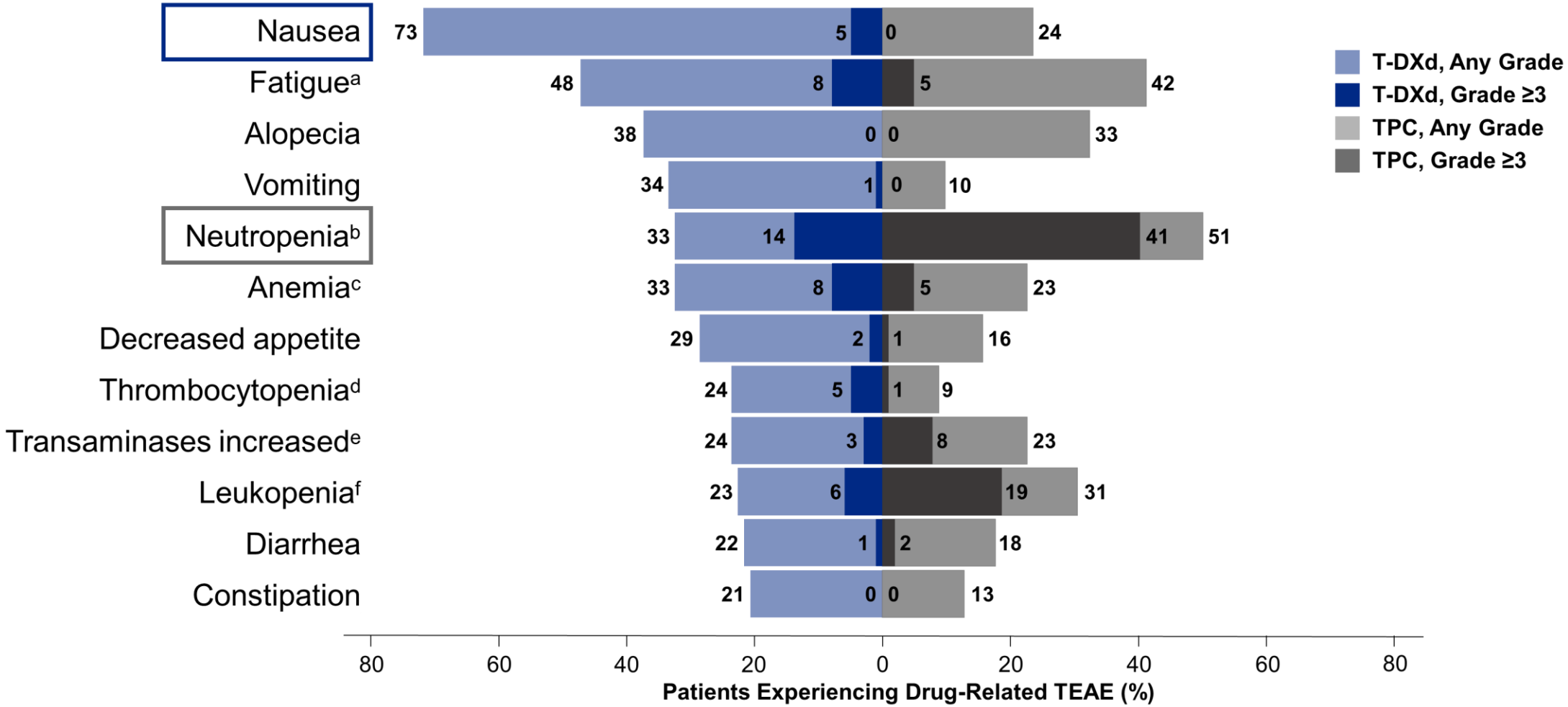
Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumor size (partial response).

HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Drug-Related TEAEs in ≥20% of Patients

DESTINY-Breast04

Daiichi-Sankyo



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Overall Safety Summary

DESTINY-Breast04

Daiichi-Sankyo

n (%)	Safety analysis set[a] T-DXd (n = 371)	TPC (n = 172)
Total patient-years of exposure, years[b]	283.55	63.59
TEAEs	369 (99)	169 (98)
Grade ≥3	195 (53)	116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuations	60 (16)	14 (8)
TEAEs associated with dose interruptions	143 (39)	72 (42)
TEAEs associated with dose reductions	84 (23)	66 (38)
TEAEs associated with deaths	14 (4)	5 (3)

- **Median treatment duration**
  - **T-DXd: 8.2 months (range, 0.2-33.3)**
  - **TPC: 3.5 months (range, 0.3-17.6)**
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]Patient-years of exposure are the treatment duration with year as unit. [c]Grouped term. [d]Fatigue includes the preferred terms fatigue, malaise, and asthenia; neutropenia included the preferred terms of neutropenia and neutrophil count decreased. [e]On-treatment death was defined as any death that occurred from the date of the first dose to 47 days after the last dose of study drug irrespective of the cause; the TEAEs associated with deaths represent a subset of on-treatment deaths reported by the investigators as adverse events.

Adverse Events of Special Interest

DESTINY-Breast04

Daiichi-Sankyo

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

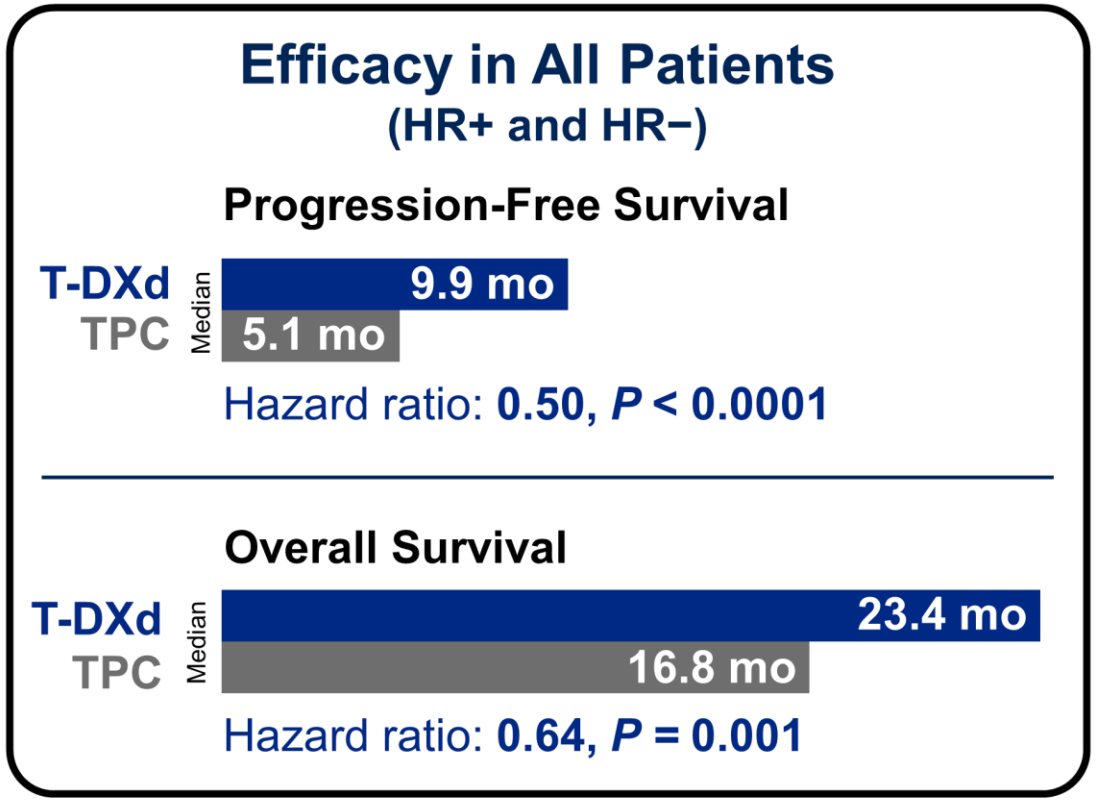
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

DESTINY-Breast04 Establishes T-DXd as the New Standard of Care in HER2-low, HR+/HR− mBC

DESTINY-Breast04

Daiichi-Sankyo

- T-DXd is the first HER2-targeted therapy to demonstrate unprecedented statistically significant and clinically meaningful improvement in PFS and OS versus TPC
- Similar magnitude of benefit across all subgroups, including HER2 IHC status and prior CDK4/6i use
- Safety is consistent with the known safety profile and showed an overall positive benefit-risk
- DESTINY-Breast04 establishes HER2-low (IHC 1+, IHC 2+/ISH−) mBC as a new targetable patient population, with T-DXd as a new standard of care



CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Retrospective study to estimate the prevalence of HER2-low breast cancer (BC) and describe its clinicopathological characteristics

Giuseppe Viale, MD, FRCPath[1]; Naoki Niikura, MD, PhD[2]; Eriko Tokunaga, MD[3]; Mark Basik, MD[4]; Naoki Hayashi, MD[5]; JoohyukSohn, MD, PhD[6]; Ciara O'Brien, PhD[7]; Gavin Higgins, PhD[8]; Della Varghese, PhD[9]; Gareth D. James[10]; Akira Moh, MD, PhD[11]; Nana Scotto, MD[12]

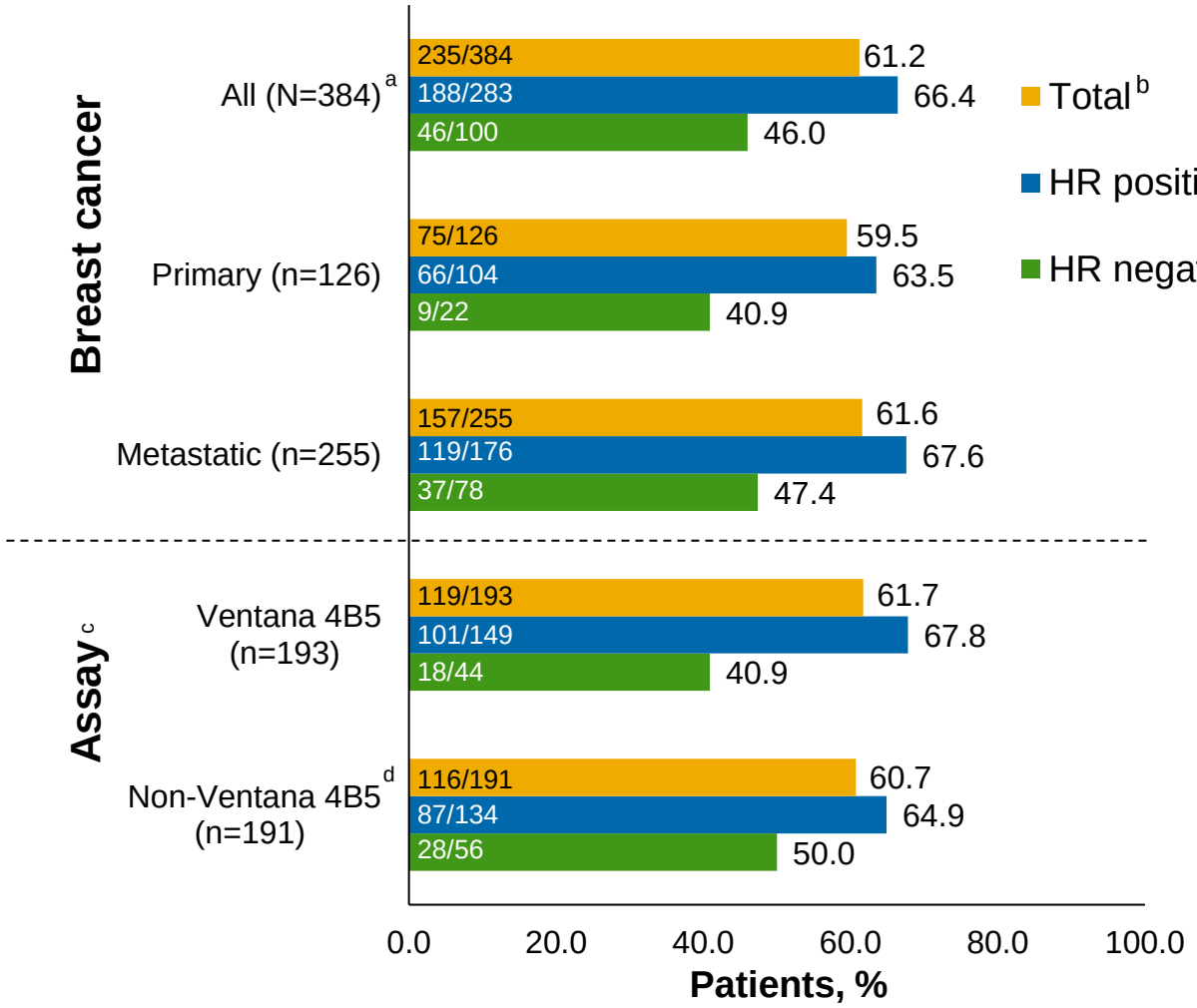
[1]European Institute of Oncology IRCCS and University of Milan, Milan, Italy; [2]Tokai University School of Medicine, Kanagawa, Japan; [3]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [4]Jewish General Hospital, McGill University, Montreal, QC, Canada; [5]St. Luke's International Hospital, Tokyo, Japan; [6]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; [7]The Christie NHS Foundation Trust, Manchester, UK; [8]Victoria Cancer Biobank, Melbourne, VIC, Australia; [9]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD; [10]Medical Statistics Consultancy Ltd, London, UK; [11]Daiichi Sankyo Inc., Basking Ridge, NJ; [12]AstraZeneca Pharmaceuticals, Cambridge, UK

ASCO 2022 #1087 Poster

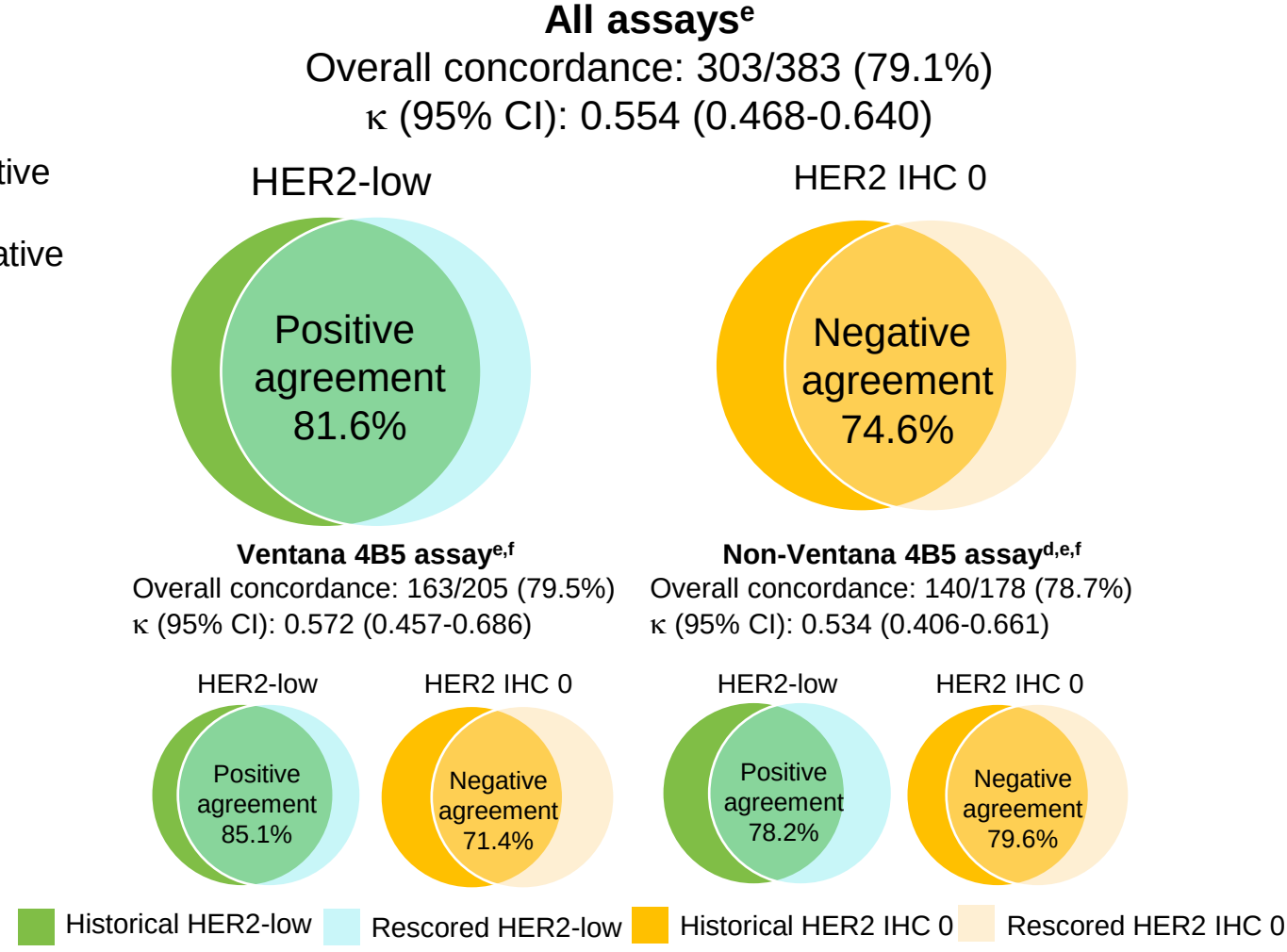
On behalf of the investigators

Results: Prevalence and Concordance

Prevalence of HER2-low in HER2-neg mBC



Concordance between rescores and historical scores



HER2, human epidermal growth factor receptor 2; HR, hormone receptor, IHC, immunohistochemistry mBC, metastatic breast cancer. [a] Only patients with available HER2 score (HER2-low or HER2 IHC 0) contribute to prevalence calculations. [b] Patients with presently unknown HR status included in total category only. [c] Ventana and non-Ventana groups based on the rescore results. [d] Includes HercepTest, Bond Oracle, or unknown. [e] Only patients with available historical scores were included. [f] Ventana and non-Ventana groups based on the historical score.

Conclusions

- In this study of mBC samples, prevalence of HER2-low BC was 61.2%
  - HER2-low prevalence was numerically higher among patients with HR-positive mBC compared with HR-negative mBC (66.4% and 46.0%, respectively)
  - Data on HER2-low prevalence in BC are limited, but this estimated prevalence is similar to that in a previous study of HER2-negative BC samples (≈60%)[1]
- Overall concordance rate for HER2 status classification between historical and rescored slides was 79.1% (κ [95% CI], 0.554 [0.468-0.640]) indicating that historical scores were relatively accurate in identifying patients with HER2-low–expressing BC
  - Overall concordance was similar in the Ventana 4B5 and non-Ventana 4B5 cohorts (79.5% and 78.7%, respectively)
  - HER2-low and HER2 IHC 0 groups had similar demographic and baseline disease characteristics
- As HER2-targeted therapies such as T-DXd for the treatment of patients with HER2-low BC are emerging,[2-6] a greater understanding of patients with HER2-low expression who may benefit from these therapies is important

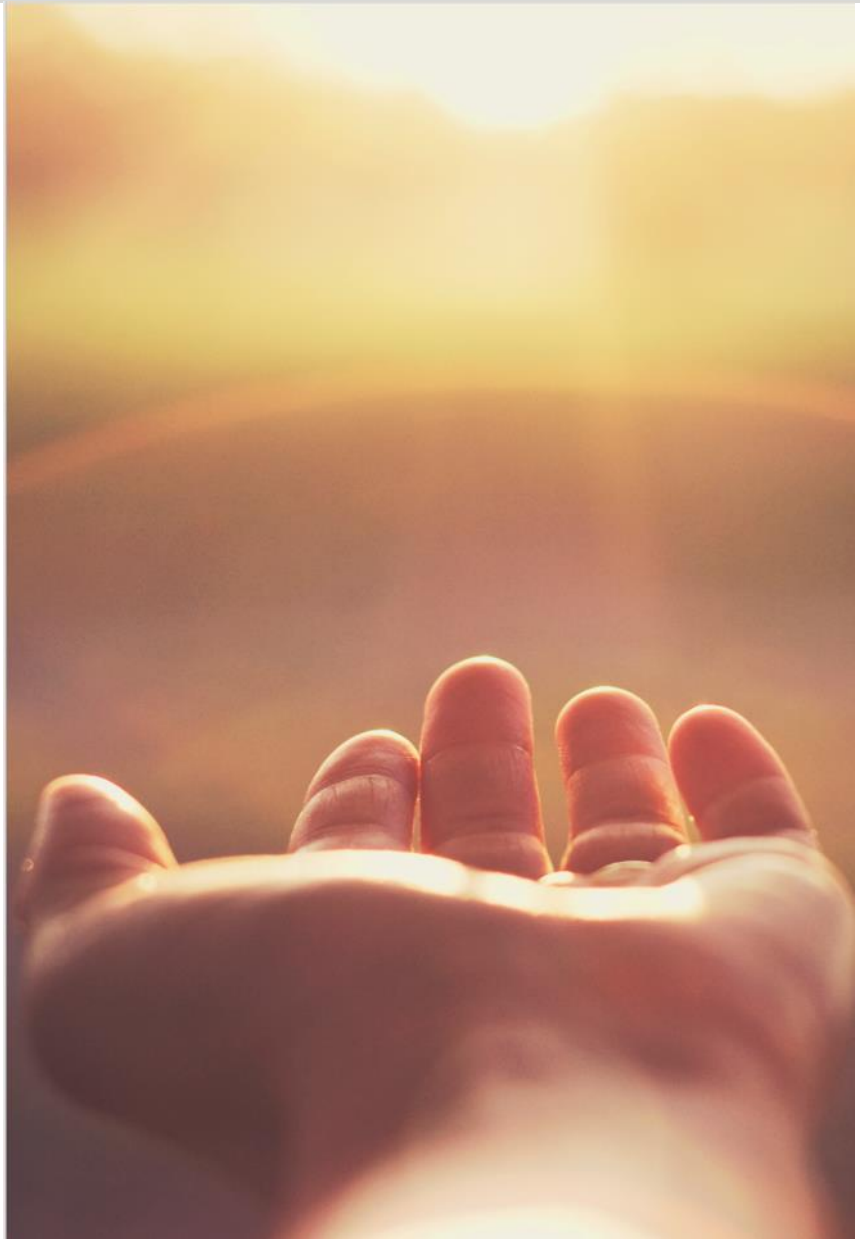
BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor, IHC, immunohistochemistry; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan.

1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. AstraZeneca. Enhertu significantly improved both progression-free and overall survival in DESTINY-Breast04 trial in patients with HER2-low metastatic breast cancer. Accessed April 26, 2022. https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-improves-pfs-and-os-in-her2-low-bc.html. 3. Modi S, et al. *J Clin Oncol*. 2020;38(17):1887-1896. 4. Diéras V, et al. Presented at: San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, Texas. Abstract PD8-02. 5. Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium; December 8-11, 2020; virtual. Abstract OT-03-09. 6. Modi S, et al. Presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, Texas. Abstract OT1-07-02.

ENHERTU®: HER2-low Breast Cancer Clinical Development Highlights

	Neoadjuvant	Post-neoadjuvant/Adjuvant	1L Metastatic	2L Metastatic	3L Metastatic
HER2+ ~ 20% of patients	**DESTINY-Breast11** Phase 3 ENHERTU® vs ENHERTU® / THP vs AC / THP	**DESTINY-Breast05** Phase 3 Monotherapy vs T-DM1	**DESTINY-Breast09** Phase 3 ENHERTU® ± pertuzumab vs THP	**DESTINY-Breast03** Phase 3 Monotherapy vs T-DM1 APPROVED	**DESTINY-Breast01** Phase 2 Monotherapy LAUNCHED
			DESTINY-Breast07 Phase 1b/2 Combination (Part 2)		**DESTINY-Breast02** Phase 3 Monotherapy vs PC
					DESTINY-Breast07 Phase 1b/2 Combination(Part 1)
Hormone-receptor positive (HR+) ~ 65% of patients	**HER2-low ~ 60% of patients that are not HER2+**			**DESTINY-Breast06** Phase 3 Monotherapy vs PC (chemotherapy naïve)	
			DESTINY-Breast08 Phase 1b Combination		**DESTINY-Breast04** Phase 3 Monotherapy vs PC (2L+ chemotherapy) **BTD in US**
Triple-negative (TNBC) ~ 15% of patients			**BEGONIA** Phase 1b/2 Combo with durvalumab		

HER2-low Breast Cancer Key Takeaways



- DESTINY-Breast04 demonstrated statistically significant and clinically meaningful improvement in both PFS and OS for T-DXd vs. TPC in HER2-low mBC consistent across HR status and IHC scores
  - Granted BTD by FDA
- ~50% of all breast cancer patients are reclassified as HER2-low – a new targetable patient segment
- Phase 3 in chemo naïve patients (DESTINY-Breast06) is on-going, and we are also exploring opportunities to target HER2-low BC in earlier lines with combinations

ENHERTU® pioneers the first targeted therapy for HER2-low Breast Cancer

DB-04 regulatory submission planned in FY2022 H1

Agenda

1. Introduction
2. Shift the paradigm for HER2-low BC
3. **Build trust in HER2+ Breast Cancer**
4. Addressing further needs in BC
5. Rising Stars
6. Future news flow

ENHERTU® Approved in the U.S. for 2L HER2+ BC

May 05, 2022

- Approval was granted under the FDA's RTOR program following the recent Priority Review and Breakthrough Therapy Designation
- Approval broadens indication for ENHERTU® to earlier use in metastatic breast cancer
- Based on groundbreaking DESTINY-Breast03 results showing ENHERTU® reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1)

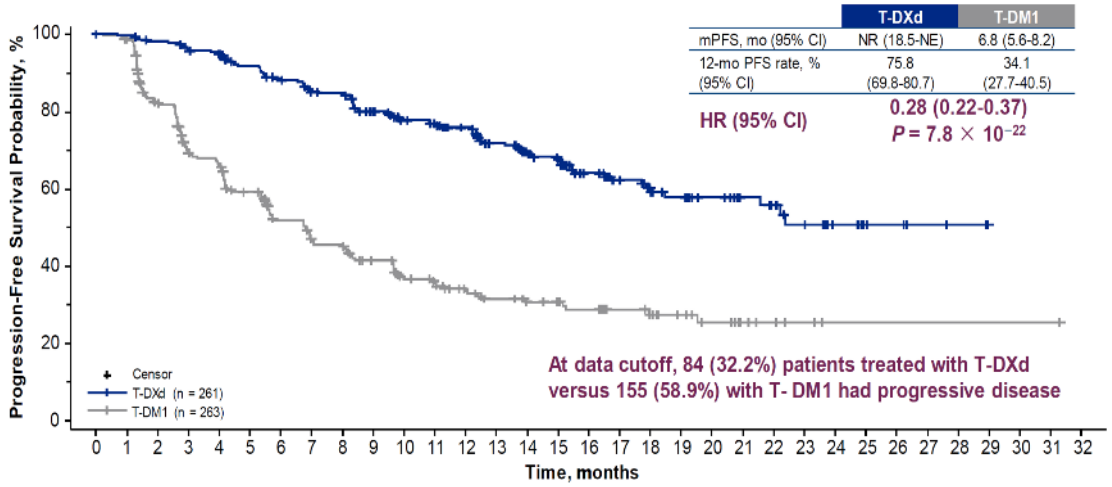
ENHERTU®: DESTINY-Breast03 study

DESTINY-Breast03

Daiichi-Sankyo

Primary endpoint: PFS by BICR

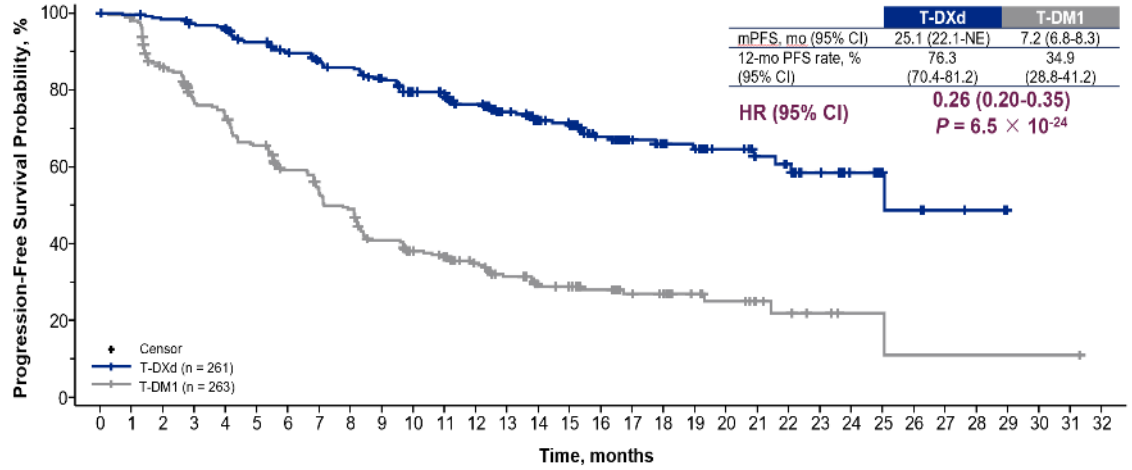
ESMO 2021



- 72% reduction in risk of disease progression or death compared to T-DM1

Secondary endpoint: PFS by investigator assessment

ESMO 2021



- ENHERTU® demonstrated 25.1m median PFS while T-DM1 demonstrated 7.2m median PFS

BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and was 13.9 months (range, 11.8-15.1) for T-DM1.
Cortés et al. *N Engl J Med*. 2022; 286:1143-54

- ENHERTU® demonstrated **unparalleled** improvement in PFS compared to T-DM1 and no grade 4/5 ILD in patients with HER2+ BC, data published in NEJM
- Approved in US in May 2022, regulatory approval planned in JP/EU in FY2022

Transform the course of HER2 positive breast cancer

NEJM: the New England Journal of Medicine

Daiichi-Sankyo

DESTINY-Breast03

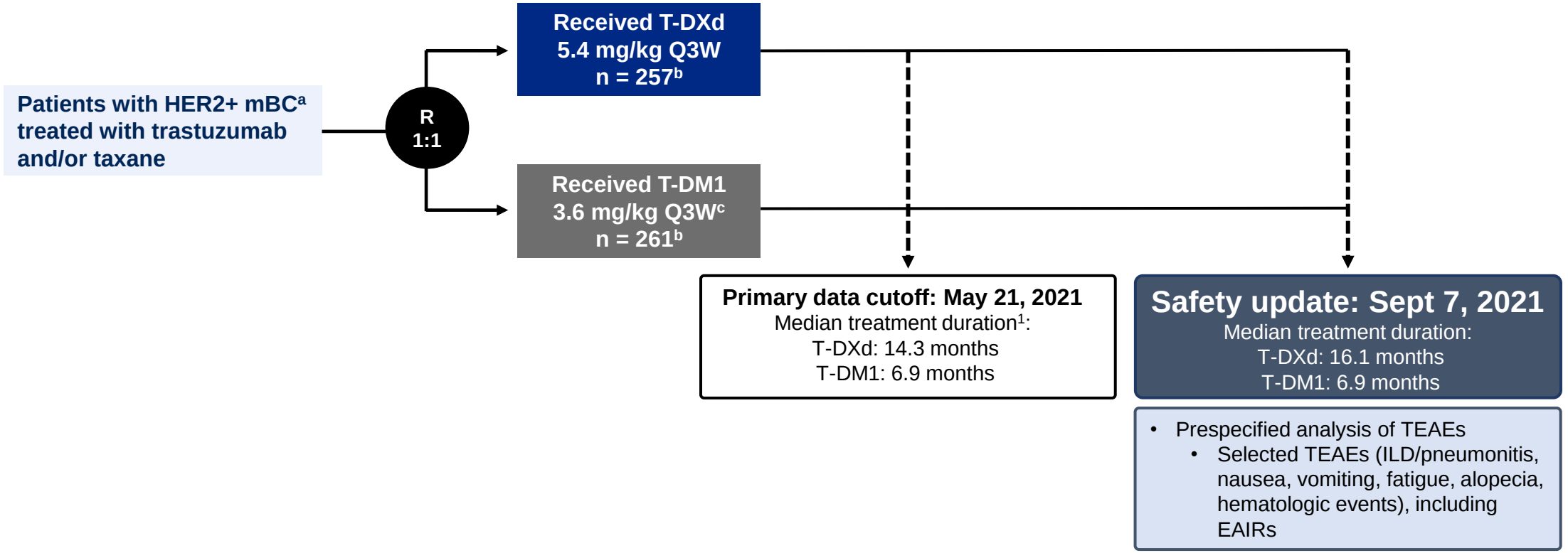
Trastuzumab Deruxtecan vs Trastuzumab Emtansine in Patients With HER2-Positive Unresectable and/or Metastatic Breast Cancer: Safety Follow-up of the Randomized, Phase 3 Study DESTINY-Breast03

Erika Hamilton, MD,[a] Vanessa Petry, Winnie Yeo, Sung-Bae Kim, Giampaolo Bianchini, Toshinari Yamashita, Kan Yonemori, Kenichi Inoue, Giuseppe Curigliano, Sara A. Hurvitz, Javier Cortés, Hiroji Iwata, Jillian Cathcart, Yali Liu, Caleb Lee, Emarjola Bako, Rachel Kim, Seock-Ah Im
On behalf of the DESTINY-Breast03 investigators

[a]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

DESTINY-Breast03 Study Design

DESTINY-Breast03



Objective of the study was to provide updated safety data with additional analyses in patients with HER2+ mBC treated with T-DXd or T-DM1 in DESTINY-Breast03

EAIRs, exposure-adjusted incidence rates; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mBC, metastatic breast cancer; Q3W, every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

[a]Central testing of archived sample for HER2 status. [b]Number of treated patients (not the randomized number of patients). [c]Or in accordance with the local label.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

Safety Update Overview (September 7, 2021)

DESTINY-Breast03

Daiichi-Sankyo

n (%)	T-DXd n = 257	T-DM1 n = 261
Patients discontinued from study treatment	141 (54.9)	222 (85.1)
Any grade TEAE	256 (99.6)	249 (95.4)
Grade ≥3 TEAE	137 (53.3)	130 (49.8)
Any grade serious TEAE	54 (21.0)	50 (19.2)
Grade ≥3 serious TEAE	39 (15.2)	38 (14.6)
TEAE associated with drug discontinuation	38 (14.8)	19 (7.3)
TEAE associated with dose reduction	59 (23.0)	36 (13.8)

- Rates of TEAEs (any grade and grade ≥3) and serious TEAEs were similar between the T-DXd and T-DM1 arms
- TEAEs associated with drug discontinuation occurred in 38 patients (14.8%) in the T-DXd arm and 19 patients (7.3%) in the T-DM1 arm

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

Safety update: Sept 7, 2021

Exposure-Adjusted Incidence Rates (EAIRs)[a]

DESTINY-Breast03

Daiichi-Sankyo

	Exposure-adjusted incidence per total patient-years of exposure	
	T-DXd n = 257	**T-DM1 n = 261**
Patients remaining on treatment, n (%)	116 (45.1)	39 (14.9)
Treatment duration, median (range), months	**16.1 (0.7-33.0)**	**6.9 (0.7-28.5)**
Exposure, patient-years[b]	327.2	186.3
EAIR, grade ≥3 TEAE	0.42	0.70
EAIR, any grade serious TEAE	0.17	0.27
EAIR, grade ≥3 serious TEAE	0.12	0.20
EAIR, TEAE associated with drug discontinuation	0.12	0.10
EAIR, TEAE associated with dose reduction	0.18	0.19

- EAIRs were measured to account for differences in treatment duration exposure between T-DXd and T-DM1 and provide a more meaningful comparison
- EAIRs per patient-year were lower in the T-DXd arm than the T-DM1 arm except for TEAEs associated with drug discontinuation, which were primarily associated with ILD/pneumonitis in the T-DXd arm
  - EAIR for grade ≥3 TEAEs was 0.42 for T-DXd and 0.70 for T-DM1
  - EAIR for any grade serious TEAEs was 0.17 for T-DXd and 0.27 for T-DM1

EAIRs, exposure-adjusted incidence rates; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]EAIR was the number of patients with at least 1 event incidence divided by the sum of patient-years of exposure over patients in the safety analysis set (total patient-years of exposure). [b]Patient years of exposure were the treatment duration with year as unit.

Safety update: Sept 7, 2021

Drug-Related TEAEs[a] Reported in ≥20% of Patients in Either Treatment Arm

DESTINY-Breast03

Daiichi-Sankyo

n (%)	T-DXd n = 257		T-DM1 n = 261	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	189 (73.5)	17 (6.6)	72 (27.6)	1 (0.4)
Fatigue	118 (45.9)	16 (6.2)	76 (29.1)	2 (0.8)
Vomiting	114 (44.4)	4 (1.6)	15 (5.7)	1 (0.4)
Neutropenia	111 (43.2)	51 (19.8)	30 (11.5)	8 (3.1)
Alopecia	97 (37.7)	1 (0.4)	7 (2.7)	0
Anemia	82 (31.9)	16 (6.2)	37 (14.2)	11 (4.2)
Leukopenia	79 (30.7)	17 (6.6)	21 (8.0)	2 (0.8)
Decreased appetite	68 (26.5)	3 (1.2)	34 (13.0)	0
Thrombocytopenia	65 (25.3)	19 (7.4)	137 (52.5)	65 (24.9)
Diarrhea	61 (23.7)	1 (0.4)	11 (4.2)	2 (0.8)
Constipation	60 (23.3)	0	25 (9.6)	0

- Most of the selected drug-related TEAEs in either treatment arm were hematologic or gastrointestinal

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse events.
Selected TEAEs (and preferred terms included): anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased); neutropenia (neutrophil count decreased, neutropenia); thrombocytopenia (platelet count decreased, thrombocytopenia); fatigue (fatigue, asthenia, malaise).
[a]Based on nonclinical data, clinical data, epidemiology data, and reported data from drugs in a similar class (anti-HER2 therapies), selected TEAEs for T-DXd were reviewed for additional characterization.

Safety update: Sept 7, 2021

Time to First Onset of TEAEs

DESTINY-Breast03

Daiichi-Sankyo

Median time to event, days	T-DXd n = 257	T-DM1 n = 261
TEAE associated with treatment discontinuation	224	147
TEAE associated with first dose reduction	96	19
Selected TEAEs		
Anemia	70.0	42.0
Lymphopenia	196.0	168.0
Thrombocytopenia	132.0	8.0
Fatigue	22.0	24.0
Leukopenia	74.5	92.0
Neutropenia[a]	64.0	105.0
Nausea	2.0	3.0
Vomiting	10.0	6.0
Alopecia	27.0	43.0

- TEAEs associated with first drug discontinuation or first dose reduction occurred later with T-DXd treatment than with T-DM1 treatment
- Median time to any TEAE associated with first dose reduction was longer in the T-DXd arm at 96 days compared with the T-DM1 arm at 19 days

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Selected TEAEs (and preferred terms included): anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased); lymphopenia (lymphocyte count decreased, lymphopenia); neutropenia (neutrophil count decreased, neutropenia); thrombocytopenia (platelet count decreased, thrombocytopenia); leukopenia (white blood cell count decreased, leukopenia); fatigue (fatigue, asthenia, malaise).
[a]11.7% of patients in the T-DXd group and 2.3% of patients in the T-DM1 group were treated with G-CSF within 28 days after onset of neutropenia, including febrile neutropenia.

Safety update: Sept 7, 2021

Adjudicated Drug-Related ILD/Pneumonitis

DESTINY-Breast03

Daiichi-Sankyo

	T-DXd n = 257	T-DM1 n = 261
Any grade, n (%)	28 (10.9)	5 (1.9)
Grade 1	7 (2.7)	4 (1.5)
Grade 2	19 (7.4)	1 (0.4)
Grade 3	2 (0.8)	0
Grade 4	0	0
Grade 5	0	0
Time to first onset, median (range), days	181 (33-507)	289 (80-499)
Outcome of worst event, n (%)		
Fatal	0	1 (20.0)[a]
Not recovered/not resolved	8 (28.6)	0
Ongoing	0	0
Recovering/resolving	2 (7.1)	0
Recovered/resolved with sequelae	2 (7.1)	0
Recovered/resolved	16 (57.1)	4 (80.0)

For this safety update:

- Majority of adjudicated ILD/pneumonitis cases were low grade and no new grade 4 or 5 events occurred in either treatment arm
- One additional grade 2 adjudicated drug-related ILD/pneumonitis occurred
- The majority of events resolved with ongoing follow-up

ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]Patient had an event of pulmonary embolism that the investigator considered to be grade 5. This was initially reported as respiratory failure but subsequently updated to pulmonary embolism. The ILD adjudication committee adjudicated this event as drug-related grade 1 ILD/pneumonitis. The death was not evaluable for adjudication. The investigator recorded disease progression as the primary cause of death.[1]

1. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154 (supplementary appendix).

Safety update: Sept 7, 2021

Conclusions

- **No new safety signals were observed for T-DXd in patients with HER2+ mBC in this safety update,[1-3] and in-depth analysis demonstrated that:**
  - Most TEAEs were grade 1 or 2, and exposure-adjusted incidence rates of grade ≥3 TEAEs and serious TEAEs were lower with T-DXd than T-DM1
  - Risk of nausea, vomiting, fatigue, and alopecia was higher for T-DXd in the initial treatment cycles
  - Prevalence of nausea and vomiting was higher for T-DXd in the initial treatment cycles and was consistent over time for alopecia and fatigue
    - In the T-DXd arm, the increased risk and higher prevalence of these events that persisted throughout treatment duration necessitates ongoing supportive care
  - There were no additional grade 3 adjudicated ILD/pneumonitis events with T-DXd (overall rate = 0.8%), and no grade 4 or 5 events overall

These data reinforce the established favorable benefit/risk profile of T-DXd over T-DM1 in HER2+ mBC

HER2, human epidermal growth factor receptor-2; ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

1. Modi S et al. *J Clin Oncol*. 2020;38:1887-1896. 2. Modi S et al. *N Engl J Med*. 2020;382:610-621. 3. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

Safety update: Sept 7, 2021

Guidelines and recommendations for the multidisciplinary diagnosis and management of ILD/pneumonitis in patients receiving T-DXd (1/2)

Daiichi-Sankyo

Workup

In the following situations, ILD/pneumonitis should be considered:

- Patient develops radiographic changes potentially consistent with ILD/pneumonitis
- Patient develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever

Patient evaluations should include the following:

- High-resolution CT
- Pulmonologist consultation
- Infectious disease consultation as clinically indicated
- Blood culture and CBC; other blood tests could be considered as needed
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests and pulse oximetry (SpO_2)
- Arterial blood gases if clinically indicated
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible
- Other tests could be considered, as needed

We suggest:

- **Use of a multidisciplinary team in evaluating for an ILD/pneumonitis diagnosis, including the medical oncologist, primary physician, nurse practitioner, pulmonologist, thoracic surgeon, pathologist, infectious disease specialist, and radiologist**
- **If blood tests are being considered, consider tests for atypical infection, such as serum beta-d glucan and galactomannan, and for serum markers such as KL-6, SP-A, and SP-D[a]**

If the event is confirmed to have an etiology other than ILD/pneumonitis, follow routine clinical practice. If the event is confirmed to be ILD/pneumonitis, follow the ILD/pneumonitis management guidelines according to ILD/pneumonitis severity as outlined below

Continued on the next slide

These guidelines are based on guidelines published by Modi et al 2020 and the US, EU, and Canada prescribing information. Minor updates to the guidelines from Modi et al were published by Li et al 2021 and are included here.. [a] KL-6, SP-A, and SP-D are used as markers in Japan but may not be used clinically in all countries. [b] In the event a dose reduction is needed, per the US, EU, and Canada prescribing information, dose reductions from the indicated dose of 5.4 mg/kg for patients with breast cancer are 4.4 and 3.2 mg/kg for the first and second dose-level reductions, respectively. Per the US prescribing information, dose reductions from the indicated dose of 6.4 mg/kg for patients with gastric cancer are 5.4 and 4.4 mg/kg for the first and second dose-level reductions, respectively. If further dose reductions are required, treatment should be discontinued. [c] The EU and Canada prescribing information and Li et al indicate that for grade ≥ 2 ILD, steroids should be continued for ≥ 14 days or until complete resolution of clinical and chest CT findings, while the US prescribing information indicates that steroids should be continued for ≥ 14 days. CBC, complete blood count; CT, computed tomography; ILD, interstitial lung disease; IV, intravenous; KL-6, Krebs von den Lungen-6; PK, pharmacokinetics; SP-A, surfactant protein-A; SP-D, surfactant protein-D; SpO2, oxygen saturation; T-DXd, trastuzumab deruxtecan.

Source: Swain SM et al. Cancer Treatment Reviews (2022): 102378

Guidelines and recommendations for the multidisciplinary diagnosis and management of ILD/pneumonitis in patients receiving T-DXd (2/2)

ILD/pneumonitis severity	Grade 1	Grade 2	Grade 3 or 4
	We suggest that the medical oncologist manage and treat the ILD/pneumonitis jointly with a multidisciplinary team, including a primary care physician, nurse practitioner, pulmonologist, pathologist, pharmacist, infectious disease specialist, and radiologist. The pulmonologist should be involved early to benefit from their expertise in managing the lung injury		
T-DXd dosing modification	• **Interrupt T-DXd** • T-DXd can be resumed if the ILD/pneumonitis fully resolved to grade 0 – If resolved in ≤28 days from day of onset, maintain dose – If resolved in >28 days from day of onset, reduce dose 1 level[b] – If ILD/pneumonitis occurs beyond day 22 and has not resolved within 49 days from the last infusion, discontinue T-DXd	**Permanently discontinue T-DXd**	**Permanently discontinue T-DXd**
ILF/pneumonitis management	• Monitor and closely follow up in 2-7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks or as clinically indicated • Consider starting systemic steroids (eg. ≥0.5 mg/kg/day of prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks *If diagnostic observations worsen despite initiation of steroids, then follow grade 2 guidelines* **We suggest considering steroids for selected grade 1 cases that show extensive lung involvement or in patients at increased risk for progression of ILD/pneumonitis**	• Promptly start systemic steroids (eg. ≥1.0 mg/kg/day of prednisone or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks[c] • Monitor symptoms closely • Reimage as clinically indicated • If worsening or no improvement in clinical or diagnostic observations in 5 days: – Consider increasing dose of steroids (eg. 2.0 mg/kg/day of prednisone or equivalent), and administration may be switched to IV (eg. methylprednisolone) – Reconsider additional workup for alternative etiologies as described above – Escalate care as clinically indicated	• Hospitalization required • Promptly start empirical high-dose methylprednisolone IV treatment (eg. 500-1000 mg/day for 3 days), followed by ≥1.0 mg/kg/day of prednisone (or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks • Reimage as clinically indicated • If still no improvement within 3-5 days: – Reconsider additional workup for alternative etiologies as described above – Consider other immunosuppressants (eg. infliximab or mycophenolate mofetil) and/or treat per local practice

Patients with ILD/pneumonitis regardless of severity or seriousness should be followed up until complete resolution of clinical and/or chest CT findings, including after drug discontinuation

Refer to footnotes on the previous slide

Source: Swain SM et al. Cancer Treatment Reviews (2022): 102378

Daiichi-Sankyo

DESTINY-Breast03

PATIENT-REPORTED OUTCOMES FROM DESTINY-Breast03, A RANDOMIZED PHASE 3 STUDY OF TRASTUZUMAB DERUXTECAN (T-DXd) VS TRASTUZUMAB EMTANSINE (T-DM1) IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

GIUSEPPE CURIGLIANO, KYLE DUNTON, MATS ROSENLUND, MARTIN JANEK, JILLIAN CATHCART, YALI LIU, PETER A. FASCHING, HIROJI IWATA

Giuseppe Curigliano, MD
European Institute of Oncology IRCCS, University of Milan,
Milan, Italy

ESMO BC 2022 #1630 Oral

On behalf of the investigators

DESTINY-Breast03 PRO & Hospitalization Endpoints & Analyses

DESTINY-Breast03

Daiichi-Sankyo

Endpoint	Description	Measures of interest	Main analyses
EORTC QLQ-C30	Oncology-specific questionnaire	• Global health status (GHS)/QoL[a] • Functioning scales: physical, role, emotional, cognitive, and social • Symptom scales: pain	• Change from baseline • Time to definitive deterioration (TDD)[b,c]
EORTC QLQ-BR45	Breast cancer-specific questionnaire	• Symptom scales: arm and breast	• TDD[b,c]
EQ-5D-5L	Generic questionnaire	• Self-rated health status (visual analog scale [VAS])	• TDD[c]
Hospitalization	Records assessment	• Date of admission to hospital • Status/date of discharge	• Time to first hospitalization • Length of stay

- Completion compliance for HRQoL patient questionnaires was high in both treatment groups, with **>97% completion at baseline** and **>82% completion from cycles 3-27** in both arms

EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HRQoL, health-related quality of life; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

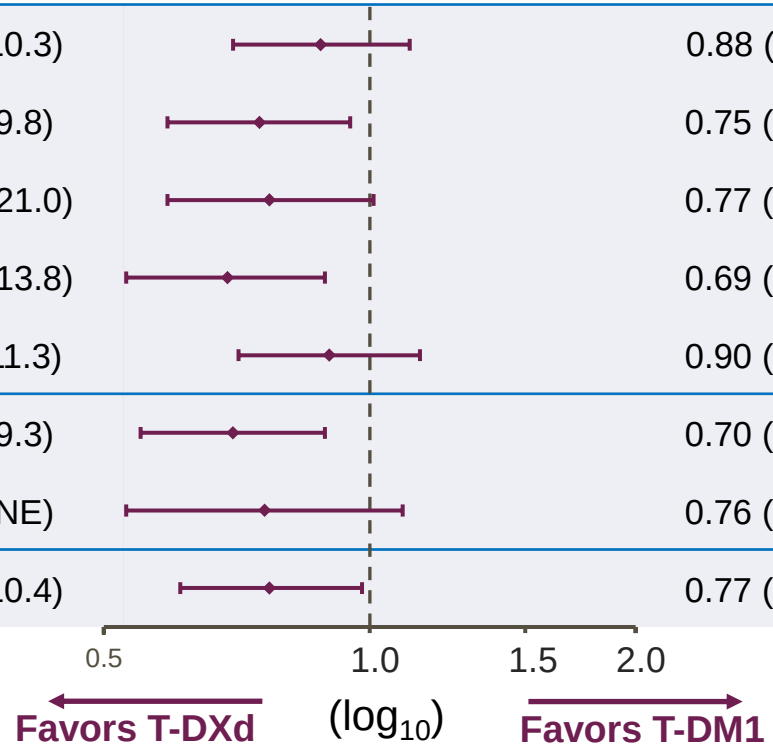
[a]Primary PRO variable of interest. [b]Clinically meaningful deterioration defined as a change of 10 points or more in the GHS and subscale scores. [c]Not all variables measured were assessed for TDD.

TDD in PRO Measures of Interest

DESTINY-Breast03

Daiichi-Sankyo

		Median (95% CI) TDD, months		HR (95% CI)	Nominal *P* value
		T-DXd (n = 261)	T-DM1 (n = 263)		
EORTC QLQ-C30	Global health status/QoL[a]	9.7 (7.3-12.5)	8.3 (7.0-10.3)	0.88 (0.70-1.11)	0.2829
	Pain symptoms[b]	10.8 (8.3-14.0)	8.3 (6.6-9.8)	0.75 (0.59-0.95)	0.0146
	Physical functioning[b]	16.7 (14.5-NE)	10.3 (8.3-21.0)	0.77 (0.59-1.01)	0.0529
	Emotional functioning[b]	16.4 (14.1-19.9)	10.5 (9.0-13.8)	0.69 (0.53-0.89)	0.0049
	Social functioning[b]	11.1 (7.3-13.4)	9.0 (7.1-11.3)	0.90 (0.71-1.14)	0.3577
EORTC QLQ-BR45	Arm symptoms[b]	11.1 (8.5-14.8)	7.0 (5.6-9.3)	0.70 (0.55-0.89)	0.0033
	Breast symptoms[b]	26.4 (26.4-NE)	NE (NE-NE)	0.76 (0.53-1.09)	0.1329
EQ-5D-5L	VAS[b]	13.2 (10.1-15.3)	8.5 (7.3-10.4)	0.77 (0.61-0.98)	0.0354



EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HR, hazard ratio; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline. [a]Primary PRO variable of interest. [b]Secondary PRO variable of interest.

Hospitalization-Related Endpoints

DESTINY-Breast03

Daiichi-Sankyo

Parameter	T-DXd (n = 261)	T-DM1 (n = 263)
Subjects with hospitalization, n (%)	18 (6.9)	19 (7.2)
Median (range) time to first hospitalization,[a] days	219.5 (0-723)	60.0 (0-399)
Median (range) length of hospital stay, days	10.5 (1-181)	9.0 (2-25)
Died, n (%)	2 (0.8)	1 (0.4)
Discharged home, n (%)	15 (5.7)	16 (6.1)
Discharged to home health care, n (%)	1 (0.4)	1 (0.4)

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Time to first hospitalization is defined as the time from the date of randomization to the date of the first hospitalization during the study treatment (from date of first dose to 47 days after last dose). Time for subjects whose first hospitalization date was prior to treatment start date was calculated as 0.

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Conclusions

DESTINY-Breast03

Daiichi-Sankyo

- **Overall health status and QoL was maintained with T-DXd,** based on mean change from baseline of EORTC QLQ-C30 GHS scale (primary PRO variable of interest) and other specified subscales of interest
- Median (range) treatment duration was longer in the T-DXd arm (14.3 [0.7-29.8] months) than in the T-DM1 arm (6.9 [0.7-25.1] months)[1]
- For all prespecified PRO variables of interest, the HR for TDD numerically favored T-DXd over T-DM1 (HR range, 0.69-0.90), indicating **T-DXd treatment delays the deterioration of QoL in patients with mBC**
  - **Delayed TDD of pain symptoms with T-DXd** (HR, 0.75) is particularly salient, given its profound impact on QoL[2,3]
- Time to **first hospitalization was delayed with T-DXd** versus T-DM1: median 219.5 days versus 60.0 days, respectively (interpretation limited by low rates of hospitalization in both arms)
- This evidence of **maintained QoL while on treatment with T-DXd and delayed definitive deterioration across prespecified scales versus T-DM1** further supports the improved efficacy (including superior PFS) and manageable safety profile of T-DXd versus T-DM1,[1] thus supporting **T-DXd as a standard of care for patients with HER2+ mBC**

EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; HR, hazard ratio; mBC, metastatic breast cancer; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Dueñas M, et al. *J Pain Res.* 2016;9:457–467. 3. Dams L et al. *Supportive Care Cancer.* 2022;doi: 10.1007/s00520-022-06805-0.

”Is ENHERTU® Effective in Brain Metastasis?”

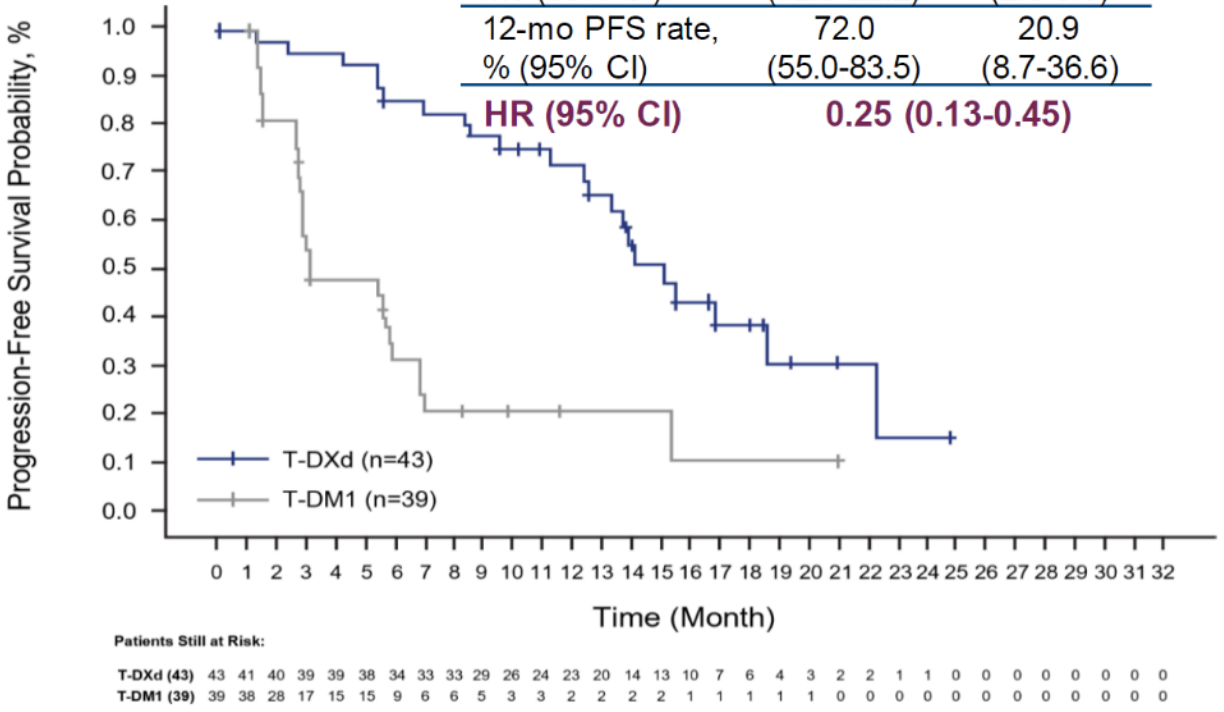
PFS KM Curves for Patients With and Without BM

SABCS 2021

DESTINY-Breast03 Subgroup Analysis (Limited to Stable BM)

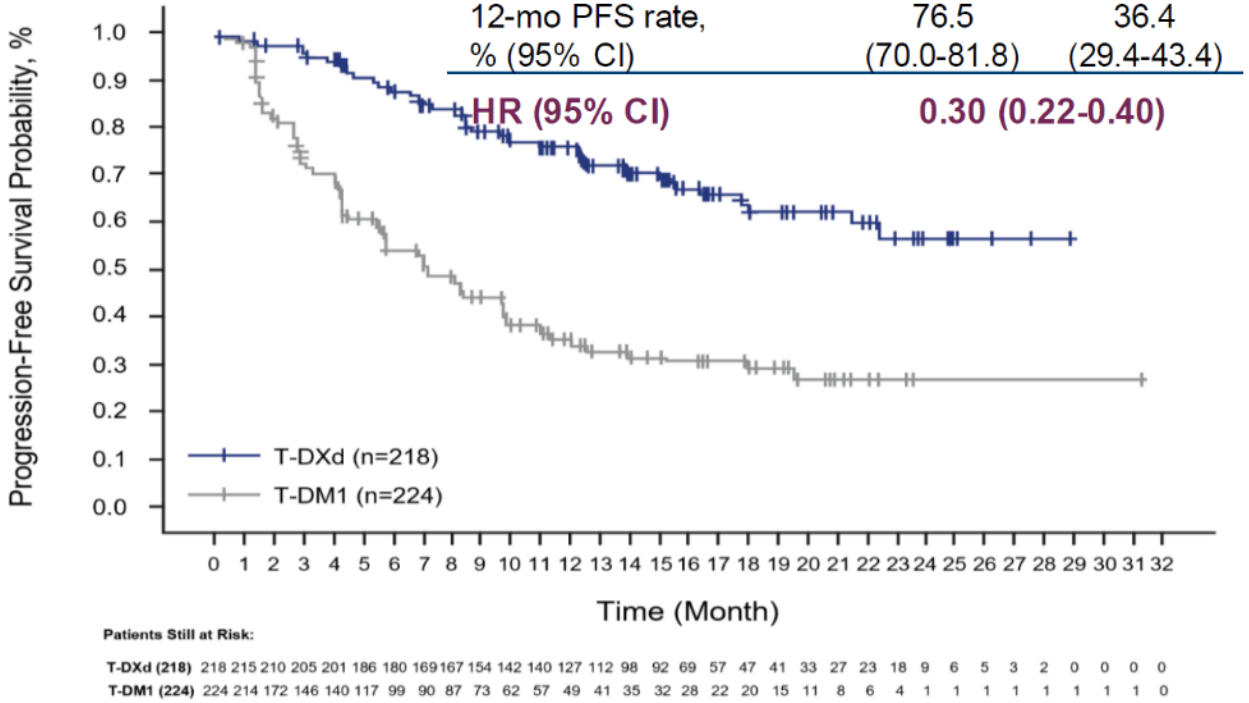
Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	0.25 (0.13-0.45)	



No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	0.30 (0.22-0.40)	



At data cutoff, in patients with BM at baseline, PD was observed:

- In 21/43 treated with T-DXd versus 27/39 with T-DM1
  - In the brain in 9/21 treated with T-DXd versus 11/27 with T-DM1

At data cutoff, in patients without BM at baseline, PD was observed:

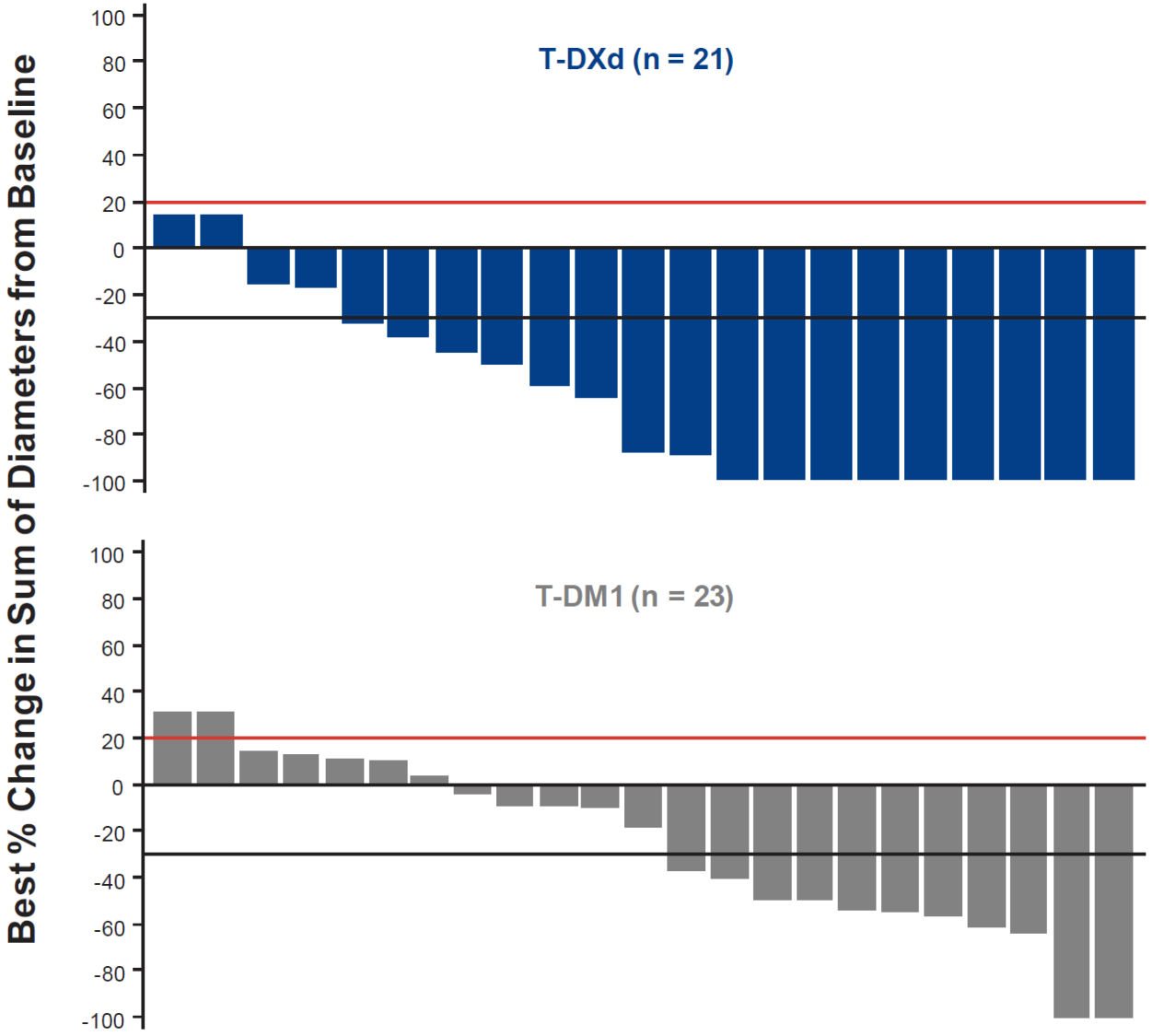
- In 63/218 treated with T-DXd versus 128/224 with T-DM1
  - In the brain in 4/63 treated with T-DXd versus 1/128 with T-DM1

mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Intracranial Response per BICR using RECIST 1.1

SABCS 2021

Daiichi-Sankyo



	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients with active brain metastases: Primary outcome analysis from the TUXEDO-1 trial

Rupert Bartsch[1], Anna Sophie Berghoff[1], Julia Furtner[2], Maximilian Marhold[1], Elisabeth Sophie Bergen[1], Sophie Roider-Schur[3], Angelika Martina Starzer[1], Heidrun Forstner[1], Beate Rottenmanner[1], Karin Dieckmann[4], Zsuzsanna Bago-Horvath[5], Georg Widhalm[6], Aysegül Ilhan-Mutlu[1], Christoph Minichsdorfer[1], Thorsten Fuereder[1], Christian Singer[7], Ansgar Weltermann[8], Rainer Puhr[1], Matthias Preusser[1]

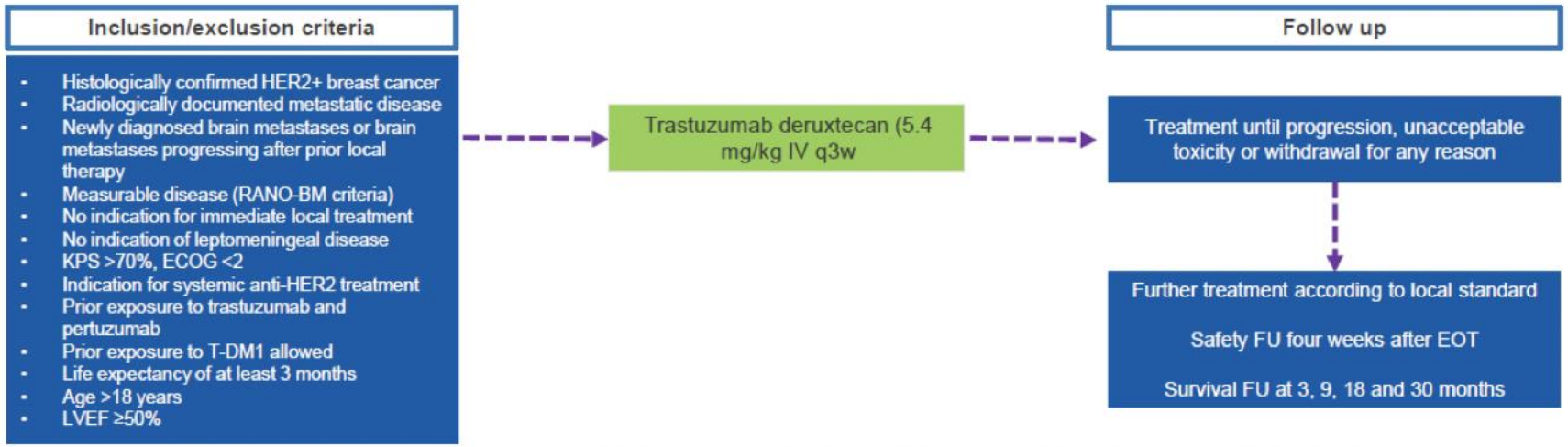
[1] Department of Medicine 1, Division of Oncology, Medical University of Vienna; [2] Department of Radiology, Medical University of Vienna, Vienna, Austria; [3] Department Oncology, St. Joseph's Hospital, Vienna, Austria; [4] Department of Radio-Oncology, Medical University of Vienna, Vienna, Austria; [5] Department of Pathology, Medical University of Vienna, Vienna, Austria; [6] Department of Neurosurgery, Medical University of Vienna, Vienna, Austria; [7] Department of Gynaecology, Medical University of Vienna, Vienna, Austria; [8] Department of Medicine 1, Elisabethinen Hospital Linz, Ordensklinkum Linz, Linz, Austria

Investigator-Initiated Study

Study Design

Primary Endpoint: ORR (CNS) by RANO-BM criteria
Secondary Endpoints:
- Clinical Benefit Rate (CR+PR+SD ≥6 months)
- Extracranial Response rate
- PFS
- OS
- Safety
- Ouality of Life

TUXEDO-1 (NCT04752059)



BM, brain metastasis; BW, body weight; CNS, central nervous system; D1, day 1; EOT, end of treatment; FU, follow up; IV, intravenous; KPS, Karnofsky performance; LVEF, left ventricular ejection fraction; q3w, once every 3 weeks; RANO, response assessment in neuro-oncology; T-DXd, trastuzumab deruxtecan.
EudraCT: 2020-000981-41.

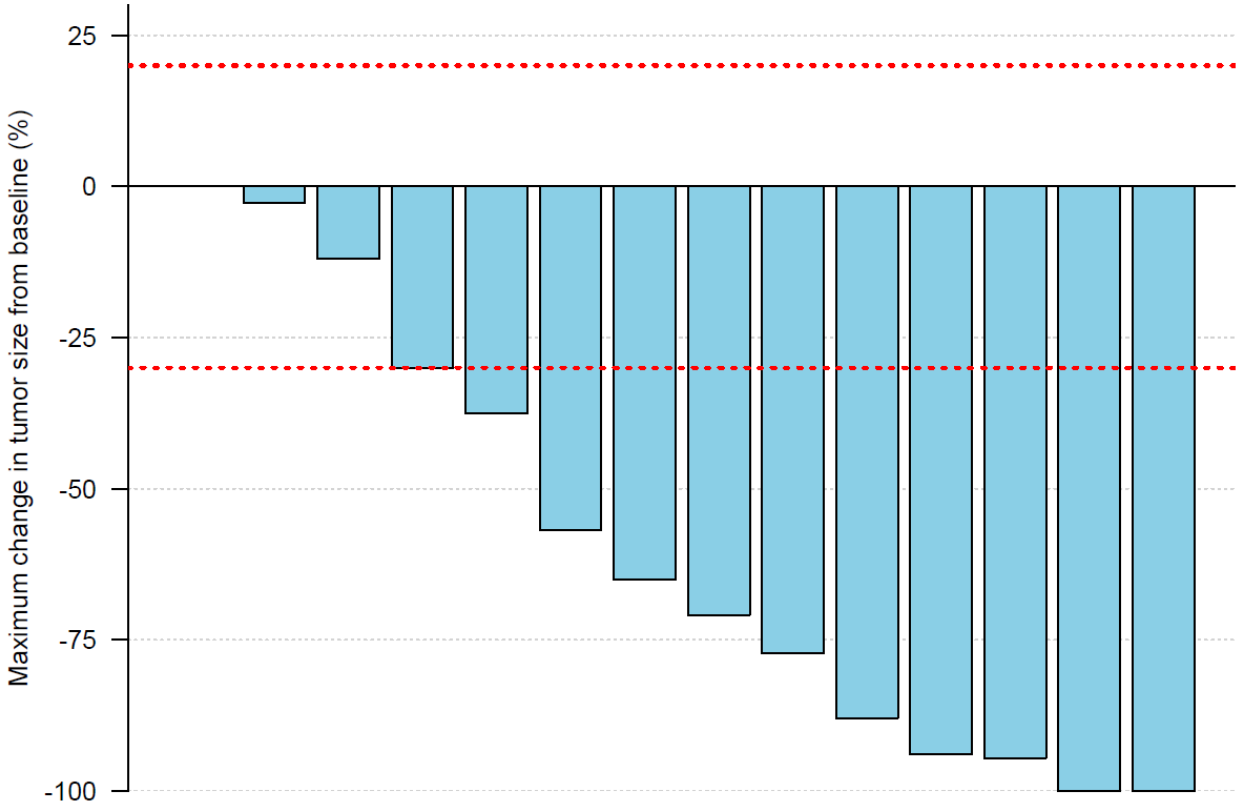
Simon Two Stage Design
- RR (CNS) >60% suggests clinically relevant activity
- RR (CNS) <26% suggests no benefit compared to previous systemic treatment options
- Stage 1: 6 pts. (at least three responses); Stage 2: 9 pts; overall 15 pts. (at least 7 responses)
- Type 1 error rate 5%; power 80%

Primary Endpoint

TUXEDO-1 trial

Objective Response Rate (RANO-BM criteria)

ORR (intention-to-treat population; *n*=15): 73.3% (95% CI 48.1-89.1)



One patient with dural metastases

RR (per-protocol-population; *n*=14): 78.6%

ESMO BC 2022 #165 Mini Oral

Conclusions

TUXEDO-1 trial

- Trastuzumab-deruxtecan was active in patients with HER2-positive breast cancer brain metastases
  - TUXEDO-1 met its primary endpoint
  - Response rate (intention-to-treat population) 73.3%
  - Comparable extra- and intracranial response rates
  - Prolonged disease control
- No new safety signals were observed
- Quality-of-life was maintained over the treatment period
- Adds to the growing body of evidence that systemic therapy is feasible in HER2-positive breast cancer with CNS metastasis
- Supports further investigation of ADCs in the context of secondary CNS malignancies

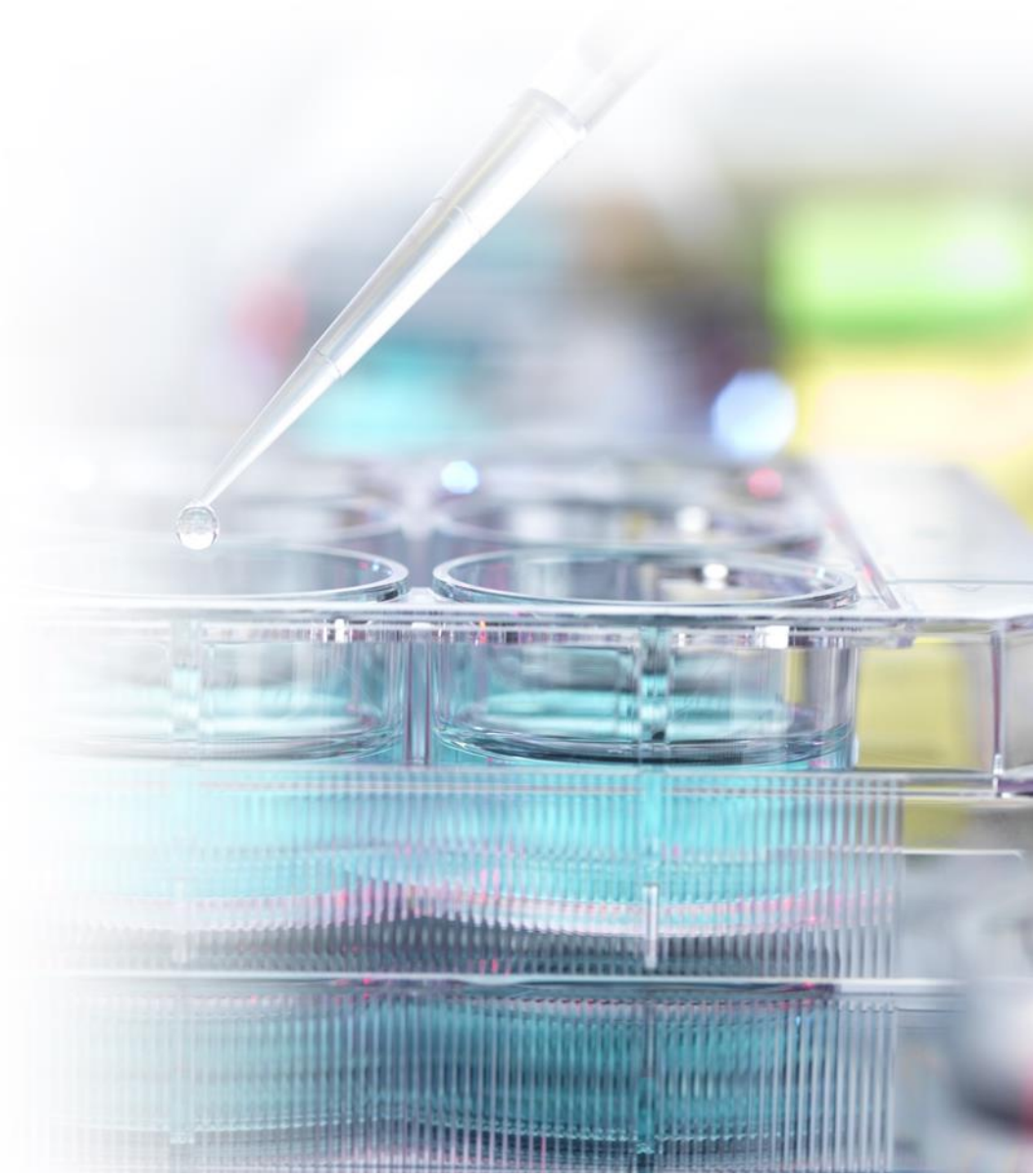
HER2+ Breast Cancer Key Takeaways

- DESTINY-Breast03 follow-up safety and PRO data supported benefit of ENHERTU® together with its efficacy in HER2+ Breast Cancer
- ENHERTU® showed preliminary efficacy in patients with active brain metastasis
  - On-going studies for further evidence
- ILD management and education are continuously important for safe use

ENHERTU® continues to build trust in HER2+ Breast Cancer therapy

Agenda

1. Introduction
2. Shift the paradigm for HER2-low BC
3. Build trust in HER2+ Breast Cancer
4. **Addressing further needs in BC**
5. Rising Stars
6. Future news flow



Address Further Unmet Needs in Breast Cancer

ENHERTU®

- **Pursuing opportunities in combinations and early diseases**
  - Support safety of nivolumab combination
    - Hamilton E et al., ESMO BC #1620 Oral
  - Preliminary data of combo dose-finding in HER2+ (DB-07) and HER low BC (DB-08)
    - Andre F et al., ASCO #3025 Poster
  - TALENT Ph2 neoadjuvant in HR+/HER2-low early BC (IIS)
    - Hurvitz S et al., ASCO #TPS623 Poster
- **Deepening science**
  - Biomarker analyses from patients from DAISY trial
    - Mosele F et al., ESMO BC #LBA1 Oral

Address Further Unmet Needs in Breast Cancer

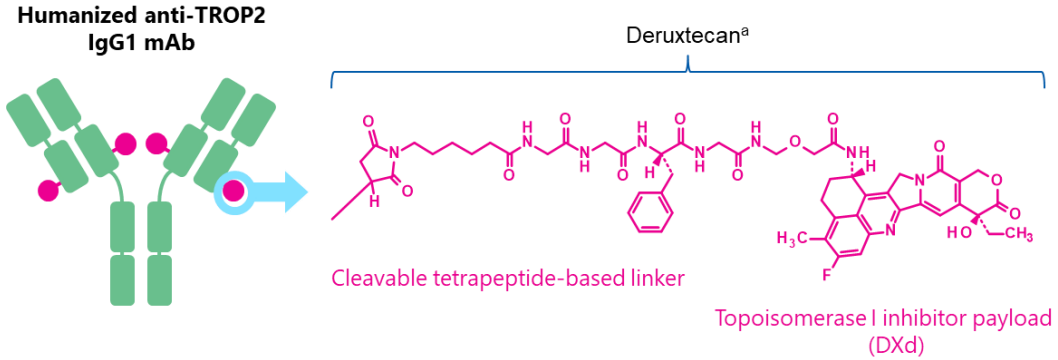
Dato-DXd

- **Promising combo opportunity in TNBC**
  - Initial results from BEGONIA study of Dato-DXd and durvalumab combo in 1L TNBC - Schmid P et al., ESMO BC #166 Mini Oral*

    * Introduced in the following slides

- **Monotherapy study in progress for TNBC and HR+/HER2-**
  - Data disclosure for future conferences

Datopotamab deruxtecan (Dato-DXd)



Designed With Key 7 Attributes

- Payload mechanism of action: topoisomerase I inhibitor [b]
- High potency of payload [b]
- Optimized drug to antibody ratio ≈4 [b,c]
- Payload with short systemic half-life [b,c]
- Stable linker-payload [b]
- Tumor-selective cleavable linker [b]
- Bystander antitumor effect [b]

- **Potential Best-In-Class TROP2 ADC**
- **Developing for BC, NSCLC and other solid tumors**

[a] Image is for illustrative purposes only; actual drug positions may vary. [b] The clinical relevance of these features is under investigation. [c] Based on animal data.

Datopotamab deruxtecan + durvalumab as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer

Initial results from BEGONIA, a phase 1b/2 study

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[1]Asan Medical Center - University of Ulsan, College of Medicine, Seoul, Korea; [2]Jagiellonian University - Medical College, Krakow, Poland; [3]Medical University of Gdańsk, Gdańsk, Poland; [4]Washington University School of Medicine, St. Louis, MO, USA; [5]Schulich School of Medicine & Dentistry, Western University, London Health Sciences Centre, London, Canada; [6]AstraZeneca, Cambridge, UK; [7]AstraZeneca, Gaithersburg, MD, USA; [8]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

BEGONIA (NCT03742102) Study Design

- Females aged ≥18 years
- Unresectable a/mTNBC
- No prior treatment for Stage IV TNBC
- ≥12 months since prior taxane therapy
- ECOG PS 0-1
- Adequate organ function
- Measurable disease per RECIST v1.1
- No prior treatment with checkpoint inhibitor or TOPO I-based ADC[a]

Part 1 (this presentation includes results from part 1)

First 20 patients:
- Paclitaxel + Durvalumab (P + D) (N=20)
- **Dato-DXd + D[c]** (N=30) Q3W until PD

All others randomized to an open cohort:
- Capivasertib + P + D (N=30)
- Oleclumab + P + D (N=30)
- T-DXd + D (N=30)

Each novel combination cohort

Primary endpoint:
Safety and tolerability
Secondary endpoints:
ORR, PFS, DoR, OS

Simon 2-stage futility analysis for Part 2 expansion[c]

Part 2 expansion (currently active/ongoing)

Randomized if multiple cohorts open:
- **Dato-DXd + D[b]** Q3W until PD
- T-DXd + D

Enroll additional 27 patients in each arm

Primary endpoint:
ORR
Secondary endpoints:
PFS, DoR, PFS6, OS

[a]ADC-cohort-specific criteria. [b]Dato-DXd 6 mg/kg + D 1120 mg. [c]Novel treatment combinations may enter Part 2 expansion if confirmed ORR is at least 57%.

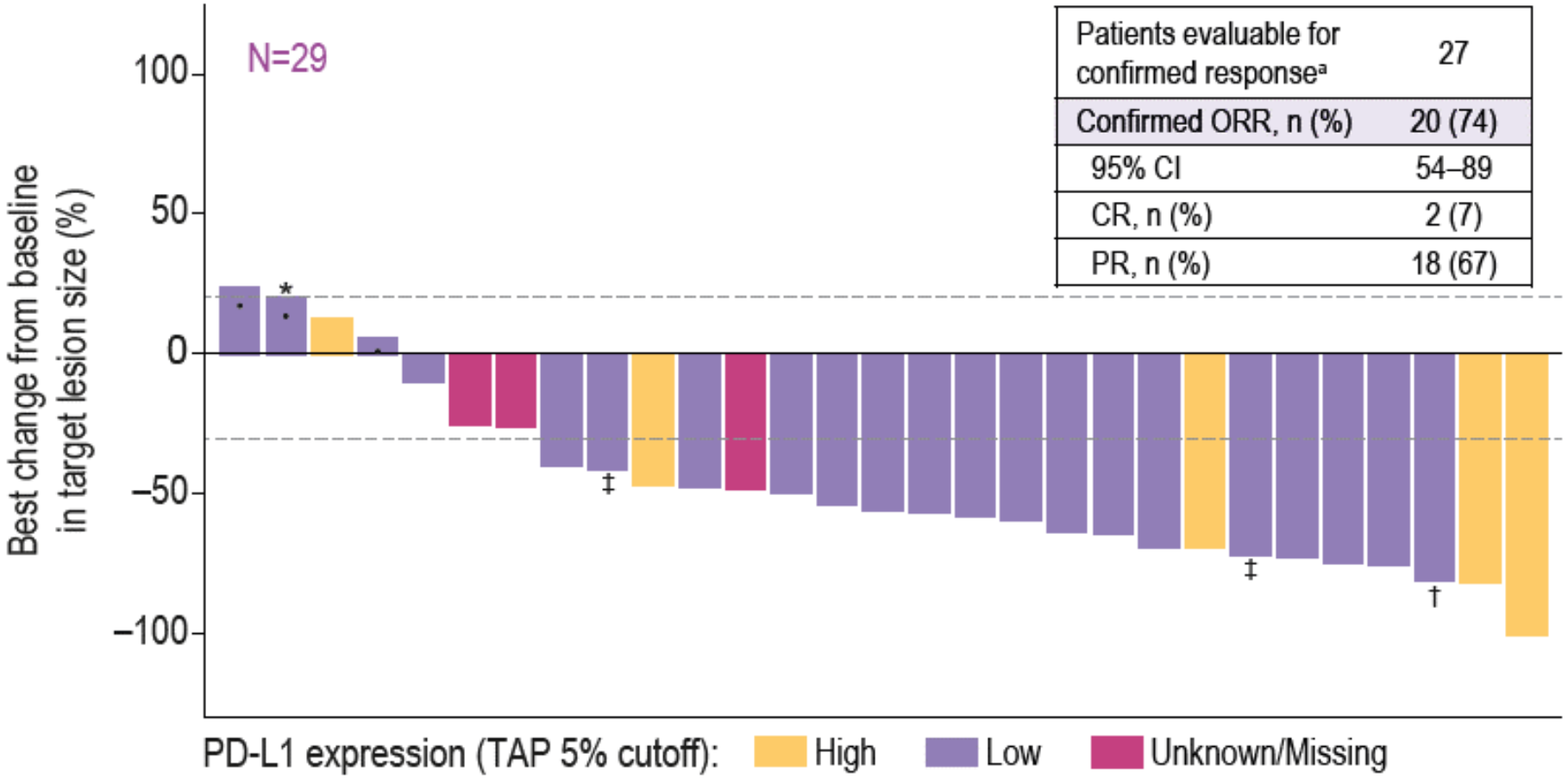
ADC, antibody-drug conjugate; a/mTNBC, locally advanced/metastatic triple negative breast cancer; DLT, dose-limiting toxicity; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance scale; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; T-DXd, trastusumab deruxtecan; TOPO I, topoisomerase I.

Data cutoff: November 15, 2021

Antitumor Responses

Dato-DXd + Durvalumab in BEGONIA Part 1

Responses observed regardless of PD-L1 expression



Patients evaluable for confirmed response[a]	27
Confirmed ORR, n (%)	20 (74)
95% CI	54–89
CR, n (%)	2 (7)
PR, n (%)	18 (67)

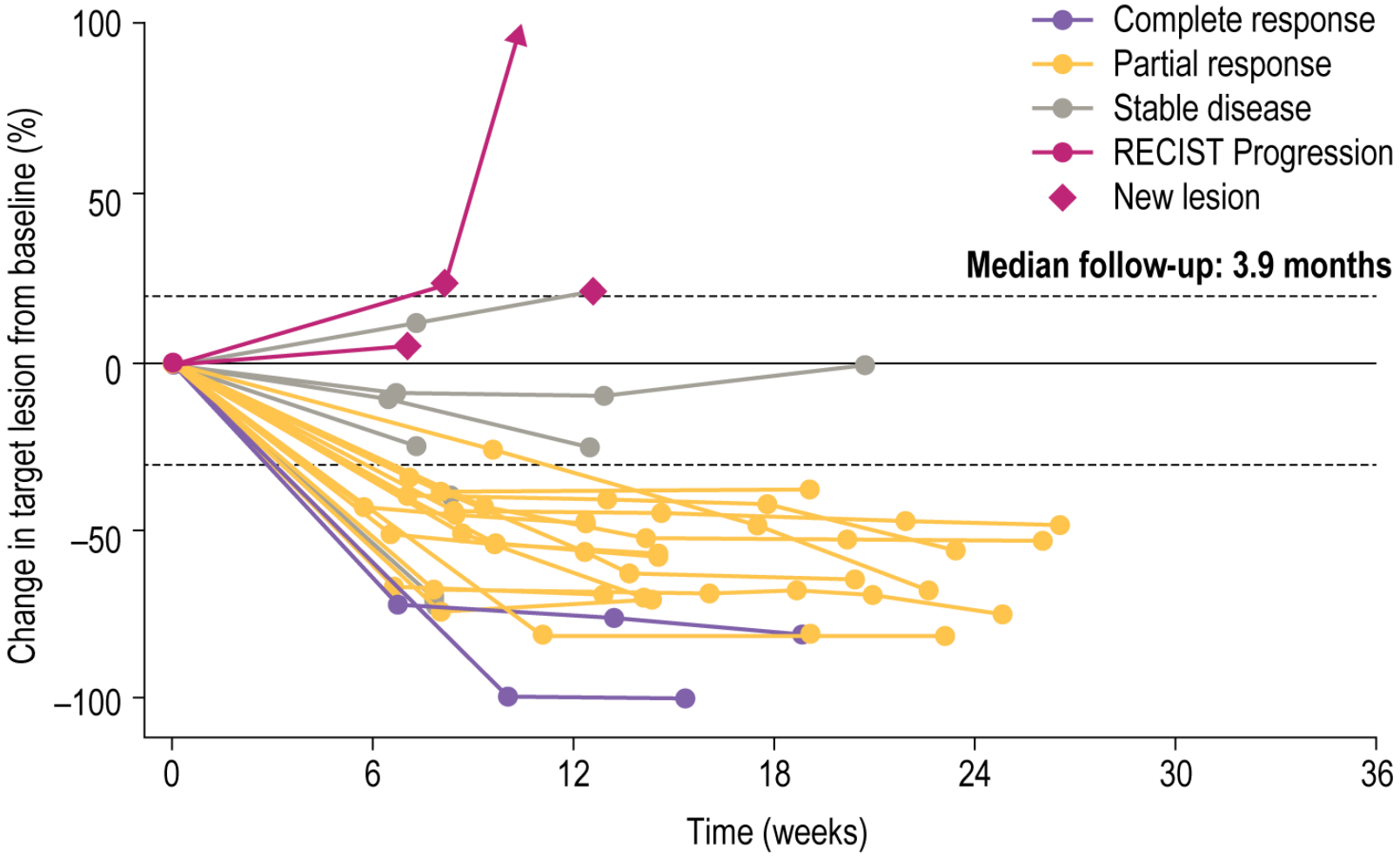
- Confirmed ORR was observed in 20/27 (74%) patients

Data cutoff: November 15, 2021

[a]Had the opportunity to have 2 postbaseline scans.
Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%).
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%.
"•" Patients with PD as best overall response. †CR with lymph node disease (CR per RECIST in lymph nodes, is <10mm). ‡ Unconfirmed response.
CR, complete response; ORR, objective response rate; PR, partial response.

Antitumor Responses

Dato-DXd + Durvalumab in BEGONIA Part 1



- Median time to response was 1.4 mos. (95% CI, 1.35–1.58)
- All patients with a response had an ongoing response at data cutoff
- Median duration of response was not reached

Data cutoff: November 15, 2021

Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%).

Safety Summary

Dato-DXd + Durvalumab in BEGONIA Part 1

No dose limiting toxicities	
Patients, n (%)	**Dato-DXd + D N=29**
Any grade AEs	29 (100)
Grade 3/4	8 (28)
Any grade treatment-related AEs	27 (93)
Grade 3/4	8 (28)
Dose adjustments	
Dato-DXd dose reduction[a]	4 (14)
Dato-DXd dose delay	1 (3)
Durvalumab dose delay	4 (14)
Serious AEs	5 (17)
AEs leading to death	1 (3)[b]
AEs leading to discontinuation of all treatments[c]	2 (7)

[a] All 4 Dato-DXd dose reductions were due to stomatitis.
[b] One patient died due to hypotension unrelated to treatment.
[c] Includes 1 case of anaphylactic reaction and 1 case of troponin increase.

Data cutoff: November 15, 2021

Most Reported Adverse Events (≥15% all grades)

Dato-DXd + Durvalumab in BEGONIA Part 1

Preferred term, n (%) AEs all causes	Dato-DXd + D N=29			
	All Grades, ≥15% of patients	Grade 1	Grade 2	Grade 3
Stomatitis	20 (69)	8 (28)	8 (28)	4 (14)
Alopecia	19 (66)	13 (45)	6 (21)	0
Nausea	19 (66)	13 (45)	6 (21)	0
Constipation	11 (38)	8 (28)	3 (10)	0
Fatigue	11 (38)	9 (31)	2 (6.9)	0
Rash	9 (31)	8 (28)	1 (3)	0
Vomiting	5 (17)	3 (10)	2 (6.9)	0

- Low rates of diarrhea reported (4 [14%]; all Grade 1)
- No cases of ILD/pneumonitis or neutropenic events were reported
- 13.7% of patients required dose reduction due to stomatitis
- Updated TMGs and prophylaxis for stomatitis are being implemented

Data cutoff: November 15, 2021

ILD, interstitial lung disease; TMG, trial management guide.

Conclusions

Dato-DXd + Durvalumab in BEGONIA Part 1

- Preliminary results of BEGONIA show that Dato-DXd + durvalumab demonstrated a robust response rate in first line a/mTNBC in a biomarker-unselected population
  - Confirmed ORR was 74%, with all patients ongoing response at the time of data cut-off
  - Responses were observed regardless of PD-L1 expression
- The combination of Dato-DXd + durvalumab had a manageable safety profile consistent with the known profile of the individual agents, with no new safety signals
  - No dose-limiting toxicities
  - Stomatitis and low-grade nausea and alopecia were the most frequent AEs
  - Low rates of diarrhea, and no cases of ILD/pneumonitis or neutropenic events, were reported
- Enrollment to Part 2 Dato-DXd + durvalumab arm is currently ongoing; follow-up continues in order to determine duration of response and PFS/OS

a/mTNBC, locally advanced/metastatic triple negative breast cancer; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate.

Dato-DXd: Breast Cancer Clinical Development Highlights

	Neoadjuvant	Post-neoadjuvant/Adjuvant	1L Metastatic	2L Metastatic	3L Metastatic
HER2+ ~ 20% of patients		Adjuvant			
Hormone-receptor positive (HR+) ~ 65% of patients					TROPION-PanTumor01 Phase 1 Monotherapy TROPION-Breast01 Phase 3 Monotherapy vs CTx PC
Triple-negative (TNBC) ~ 15% of patients			BEGONIA Phase 1b/2 Combo with durvalumab New Study ➔ TROPION-Breast02 Phase 3 Monotherapy vs CTx	TROPION-PanTumor01 Phase 1 Monotherapy	

ENHERTU® & Dato-DXd: Breast Cancer Clinical Development Highlights

ENHERTU®
Dato-DXd

Daiichi-Sankyo

	Neoadjuvant	Post-neoadjuvant/Adjuvant	1L Metastatic	2L Metastatic	3L Metastatic
HER2+ ~ 20% of patients	**DESTINY-Breast11** Phase 3 ENHERTU® vs ENHERTU® / THP vs AC / THP	**DESTINY-Breast05** Phase 3 Monotherapy vs T-DM1	**DESTINY-Breast09** Phase 3 ENHERTU® ± pertuzumab vs THP	**DESTINY-Breast03** Phase 3 Monotherapy vs T-DM1 APPROVED	**DESTINY-Breast01** Phase 2 Monotherapy LAUNCHED
			DESTINY-Breast07 Phase 1b/2 Combination (Part 2)		**DESTINY-Breast02** Phase 3 Monotherapy vs PC
					DESTINY-Breast07 Phase 1b/2 Combination(Part 1)
Hormone-receptor positive (HR+) ~ 65% of patients					**TROPION-PanTumor01** Phase 1 Monotherapy
				DESTINY-Breast06 Phase 3 Monotherapy vs PC (chemotherapy naïve)	**TROPION-Breast01** Phase 3 Monotherapy vs CTx PC
			DESTINY-Breast08 Phase 1b Combination		**DESTINY-Breast04** Phase 3 Monotherapy vs PC (2L+ chemotherapy)
Triple-negative (TNBC) ~ 15% of patients			**BEGONIA** Phase 1b/2 Combo with durvalumab		
			BEGONIA Phase 1b/2 Combo with durvalumab		
			TROPION-Breast02 Phase 3 Monotherapy vs CTx	**TROPION-PanTumor01** Phase 1 Monotherapy	

Exploring Possibility as Another Option in Breast Cancer

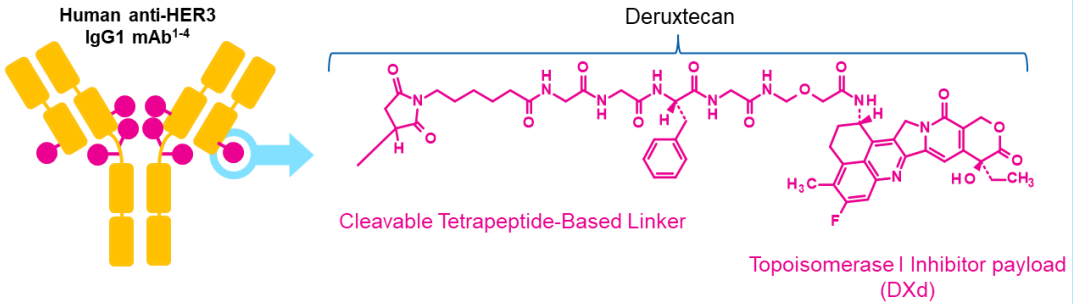
HER3-DXd

- **Breast Cancer publications at ASCO and ESMO BC**
  - HER3-expressing mBC pooled analysis – Krop I et al., ASCO #1002 Oral*

    * Introduced in the following slides

  - "Window of opportunity study" in pre-operative BC
    – Prat A et al., ESMO BC #LBA3 Oral

Patritumab Deruxtecan (HER3-DXd)



Designed With Key 7 Attributes

Payload mechanism of action: topoisomerase I inhibitor [b]
High potency of payload [b]
Optimized drug to antibody ratio ≈4 [b,c]
Payload with short systemic half-life [b,c]
Stable linker-payload [b]
Tumor-selective cleavable linker [b]
Bystander antitumor effect [b]

- **Potential First-In-Class HER3 ADC**
- **BTD by FDA for EGFR mutated NSCLC 3L+**
- **Exploring potential in Breast Cancer**

[a] The clinical relevance of these features is under investigation. [b] Based on animal data.

Results From the Phase 1/2 Study of Patritumab Deruxtecan, a HER3-Directed Antibody-Drug Conjugate (ADC), in Patients With HER3-Expressing Metastatic Breast Cancer

Ian E. Krop,[1] Norikazu Masuda,[2] Toru Mukohara,[3] Shunji Takahashi,[4] Takahiro Nakayama,[5] Kenichi Inoue,[6] Hiroji Iwata,[7] Tatsuya Toyama,[8] Yutaka Yamamoto,[9] Damien Hansra,[10] Masato Takahashi,[11] Akihiko Osaki,[12] Kumiko Koyama,[13] Tatsuya Inoue,[14] Takatoshi Yonekura,[13] Joseph Mostillo,[15] Shoichi Ohwada,[13] Yoshimi Tanaka,[13] David Sternberg,[15] Kan Yonemori[16]

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ASCO 2022 #1002 Oral

On behalf of the investigators

Study Design

Patritumab Deruxtecan : U31402-A-J101

KEY ELIGIBILITY CRITERIA

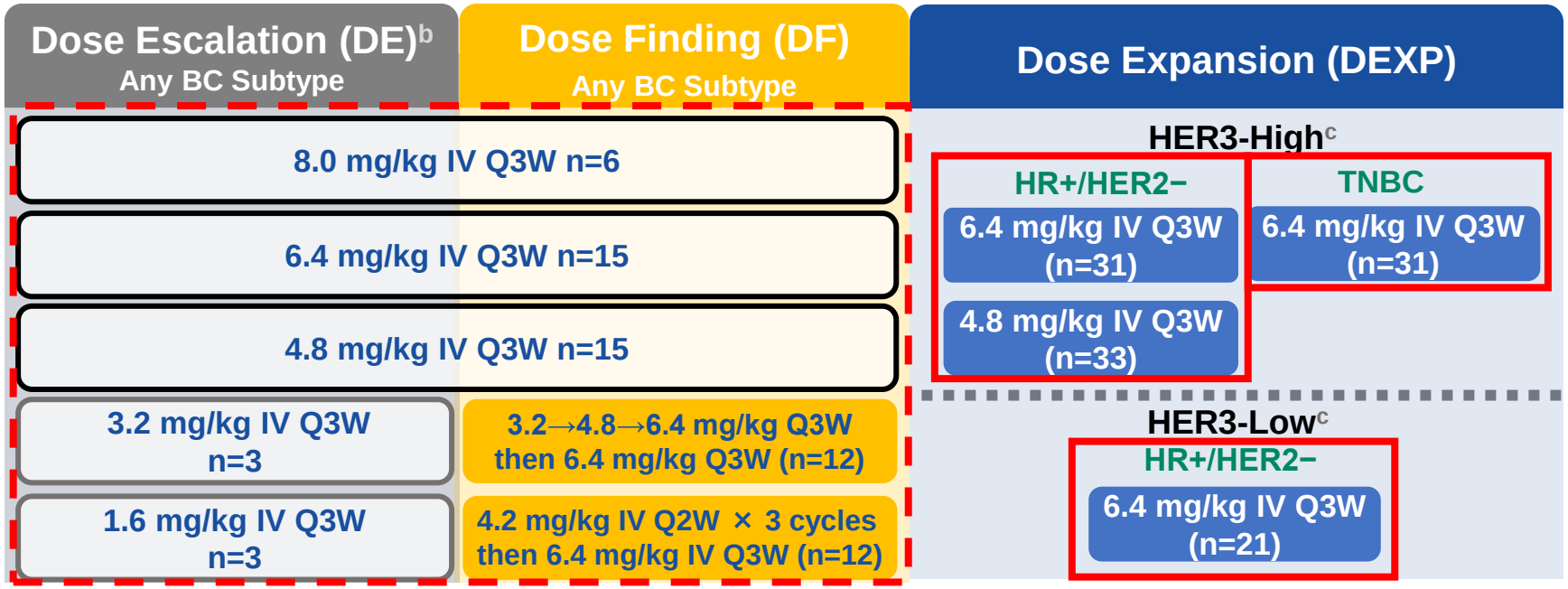
- Advanced/unresectable or metastatic breast cancer
- HER3-positive[a]

DE/DF & HR+/HER2− DEXP

- ≥2 and ≤6 lines of prior chemotherapy; ≥2 for advanced disease

Dose expansion: TNBC

- 1 to 2 prior chemotherapy regimens for advanced disease



Data for all 3 phases were pooled

- **Efficacy** is reported by BC subtype: HR+/HER2− (n=113), TNBC (n=53), and HER2+ (n=14)
- **Safety** is reported for patients who received HER3-DXd 4.8 mg/kg (n=48), 6.4 mg/kg (n=98), and all patients (N=182[d])

DE, dose escalation; DEXP, dose expansion; DF, dose finding; EWOC, escalation with overdose control; HR, hormone receptor; IHC, immunohistochemistry; mCRM, modified continuous reassessment method; Q2W, once every 2 weeks; Q3W, once every 3 weeks; R, randomized; TNBC, triple-negative breast cancer.

[a] HER3 status was determined by IHC; HER3-positive was defined as IHC 2+ and IHC 3+ for DE/DF cohorts and as ≥25% membrane positivity at 10x for DEXP cohorts. [b] Guided by mCRM with EWOC. [c] HER3-high was defined as >75% membrane positivity at 10x; HER3-low was defined as ≥25% and ≤75% membrane positivity at 10x. [d] Includes two patients with unknown BC subtype.

Clinical Activity of HER3-DXd Across BC Subtypes

Outcomes (BICR per RECIST 1.1)	HR+/HER2− (n=113) HER3-High and -Low	TNBC (n=53) HER3-High	HER2+ (n=14) HER3-High
Confirmed ORR, % (95% CI[a])	30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Best overall response, %[b]			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0.0
DOR, median (95% CI), mo	7.2 (5.3-NE)	5.9 (3.0-8.4)	8.3 (2.8-26.4)
PFS, median (95% CI), mo	7.4 (4.7-8.4)	5.5 (3.9-6.8)	11.0 (4.4-16.4)
6-month PFS rate, % (95% CI)	53.5 (43.4-62.6)	38.2 (24.2-52.0)	51.6 (22.1-74.8)
OS, median (95% CI), mo	14.6 (11.3-19.5)	14.6 (11.2-17.2)	19.5 (12.2-NE)

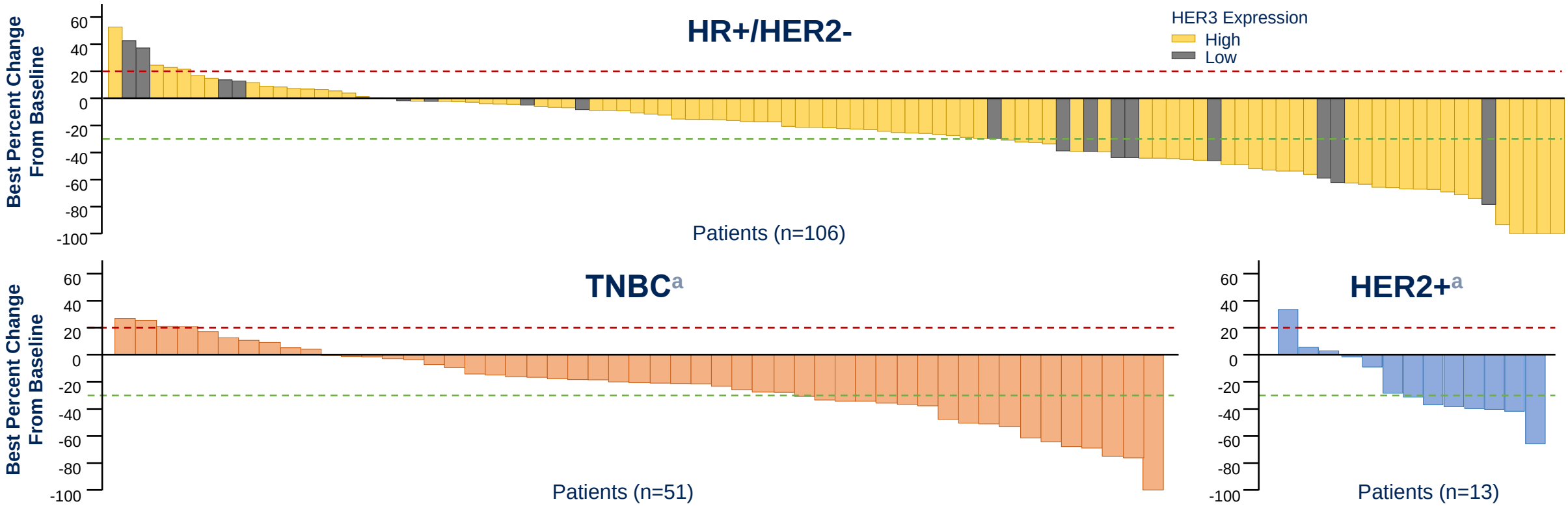
HER3-DXd demonstrated durable antitumor activity across BC subtypes

- Confirmed ORR for all patients (N=182), 28.6% (95% CI, 22.1%-35.7%); median DOR, 7.0 mo (95% CI, 5.5-8.5 months)

CR, confirmed response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a] 95% exact binomial confidence interval (by Clopper-Pearson method).
[b] No patients had a CR.

Change in Tumor Size From Baseline

Patritumab Deruxtecan : U31402-A-J101



HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes[b]

[a] Patients with TNBC and HER2+ were all HER3-high.
[b] Best percentage change from baseline in sum of diameters based on BICR for all target lesions identified is represented by patient. If any lesion measurement is missing at a post-baseline tumor assessment visit, that visit is not taken into consideration for best percent change from baseline in sum of diameters.

Overall Safety Profile of HER3-DXd

- HER3-DXd was associated with a manageable safety profile
- There was a low rate of TEAEs associated with treatment discontinuation (9.9%)
  - 18 patients had TEAEs associated with treatment discontinuation across all doses: pneumonitis (n=6), disease progression (n=2), ejection fraction decreased (n=2), ILD, malaise, peripheral edema, hepatotoxicity, gastric cancer, mental status changes, extradural hematoma, and general physical health deterioration (all n=1)
- 6.6% of patients had treatment-related ILD events[a]
  - Most were grade 1 and 2 (4.4%)
  - There was one grade 5 ILD event (0.5%)

Patritumab Deruxtecan : U31402-A-J101

Patients, n (%) **Median treatment duration: 5.9 mo (range 0.7-30.6 mo)**	**4.8 mg/kg n=48**	**6.4 mg/kg n=98**	**All Doses N=182**
Any TEAE	47 (97.9)	98 (100)	181 (99.5)
Associated with discontinuation	5 (10.4)	8 (8.2)	18 (9.9)
Associated with dose reduction	6 (12.5)	22 (22.4)	35 (19.2)
Associated with drug interruption	23 (47.9)	57 (58.2)	100 (54.9)
Associated with death	1 (2.1)[b]	6 (6.1)[b]	7 (3.8)[b]
Grade ≥3 TEAE	31 (64.6)	80 (81.6)	130 (71.4)
Treatment-related TEAE	47 (97.9)	97 (99.0)	180 (98.9)
Associated with death	0	1 (1.0)[c]	1 (0.5)[c]
Grade ≥3	27 (56.3)	76 (77.6)	120 (65.9)
Serious TEAE	7 (14.6)	23 (23.5)	38 (20.9)
Adjudicated treatment-related ILD[d]			
Grade 1	0	2 (2.0)	3 (1.6)
Grade 2	1 (2.1)	2 (2.0)	5 (2.7)
Grade 3	0	2 (2.0)	3 (1.6)
Grade 4	0	0	0
Grade 5	0	1 (1.0)	1 (0.5)
Total	**1 (2.1)**	**7 (7.1)**	**12 (6.6)**

ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] As determined by an independent adjudication committee. [b] TEAEs associated with death included disease progression (n=4), neutropenic sepsis (n=1), extradural hematoma (n=1), and choking (n=1). [c] Treatment-related TEAE associated with death was neutropenic sepsis (n=1). [d] Median time to onset, 141.5 days (95% CI; 36-584 days).

TEAEs in Patients Treated with 4.8 mg/kg and 6.4 mg/kg

Patritumab Deruxtecan : U31402-A-J101

- GI and hematologic toxicity were the most common TEAEs
- Rates of non-hematologic toxicity were similar at both doses and generally low grade
- Rates of grade ≥3 neutropenia, thrombocytopenia and leukopenia were numerically higher at 6.4 mg/kg vs 4.8 mg/kg
  - All events were managed by dose delay or reduction and were not associated with treatment discontinuation
  - No grade ≥3 TEAE of thrombocytopenia resulted in a grade ≥3 bleeding event

TEAEs (≥25% of all patients), (%)	4.8 mg/kg n=48		6.4 mg/kg n=98	
	All grade	Grade ≥3	All grade	Grade ≥3
TEAEs	**97.9**	**64.6**	**100**	**81.6**
Nausea	68.8	4.2	80.6	5.1
Platelet count decreased[a]	60.4	27.1	71.4	38.8
Neutrophil count decreased[a]	62.5	27.1	66.3	52.0
Decreased appetite	56.3	6.3	53.1	6.1
Vomiting	47.9	4.2	46.9	1.0
White blood cell count decreased[a]	45.8	10.4	45.9	23.5
Diarrhea	41.7	4.2	43.9	3.1
Anemia[a]	43.8	20.8	43.9	21.4
Aspartate aminotransferase increased	43.8	4.2	34.7	6.1
Stomatitis	25.0	0.0	34.7	1.0
Fatigue	31.3	0.0	33.7	3.1
Alanine aminotransferase increased	41.7	2.1	31.6	7.1
Constipation	22.9	0.0	29.6	0.0
Alopecia	20.8	NA	28.6	NA
Malaise	22.9	0.0	26.5	1.0

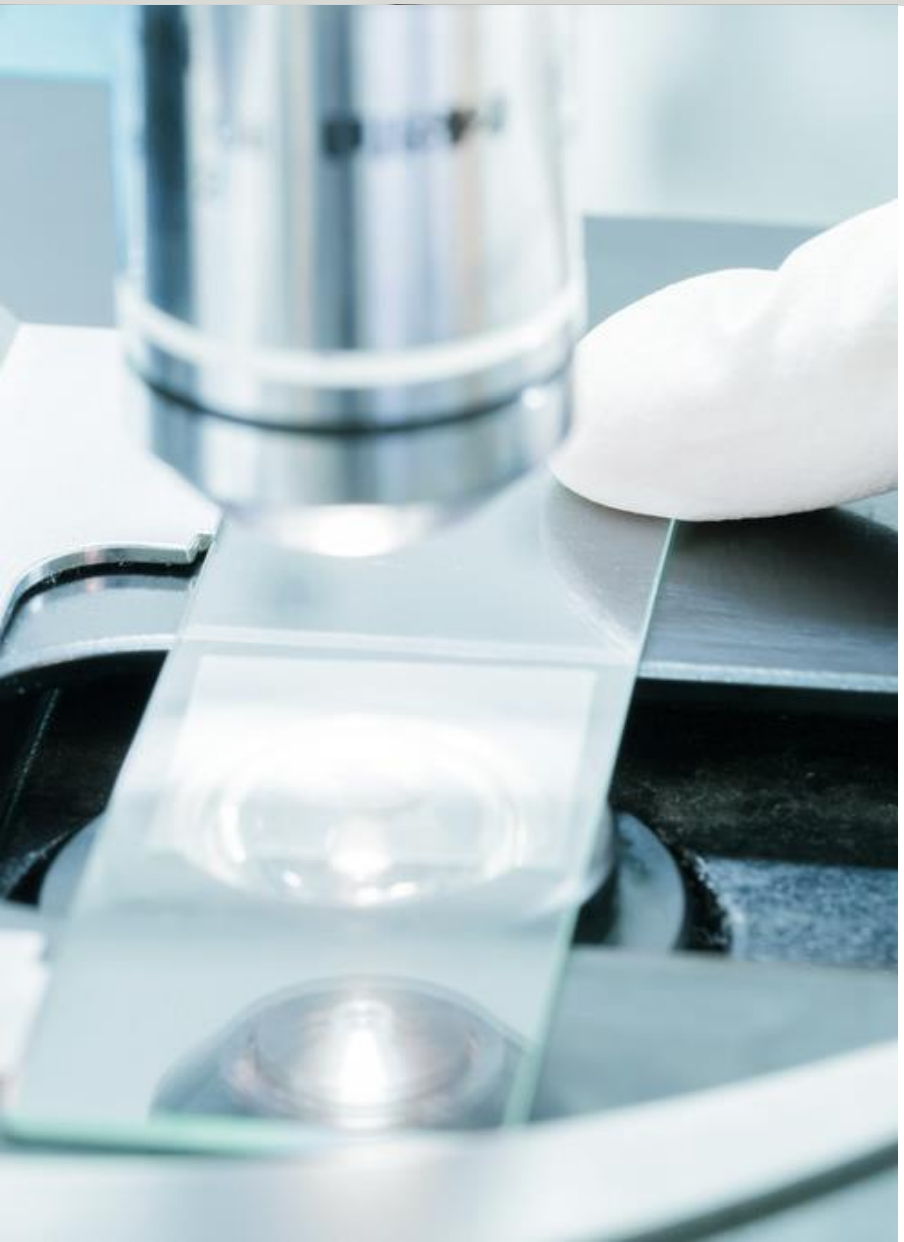
GI, gastrointestinal; NA, not applicable.
[a] Grouped terms: platelet count decreased (platelet count decreased, thrombocytopenia); neutrophil count decreased (neutrophil count decreased, neutropenia); white blood cell count decreased (leukopenia, white blood cell decreased); anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased).

Conclusions

Patritumab Deruxtecan : U31402-A-J101

- HER3-DXd demonstrated clinically meaningful and durable antitumor activity in a heavily pretreated population of patients with HER3-expressing BC
  - Durable antitumor activity was demonstrated across BC subtypes: HR+/HER2− (ORR, 30%; median DOR, 7.2 months), TNBC (ORR, 23%; median DOR, 5.9 months), and HER2+ (ORR, 43%; median DOR, 8.3 months)
  - Antitumor activity was also demonstrated across the range of HER3 expression
- The safety profile was manageable with a low rate of discontinuation due to TEAEs (10%)
  - The rate of adjudicated treatment-related ILD was 7%; most cases were grade 1 and 2
  - Grade ≥3 hematological toxicities were manageable; no grade ≥3 thrombocytopenia resulted in treatment discontinuation nor in a grade ≥3 bleeding event
- As a similar safety profile was seen with 4.8 mg/kg and 6.4 mg/kg, a 5.6 mg/kg dose, currently used in NSCLC, is being evaluated in BC to refine dose optimization
- These data provide encouraging evidence of antitumor efficacy with a manageable safety profile and warrant further evaluation of HER3-DXd across clinical and histopathological BC subtypes

Address Further Needs in Breast Cancer Key Takeaways



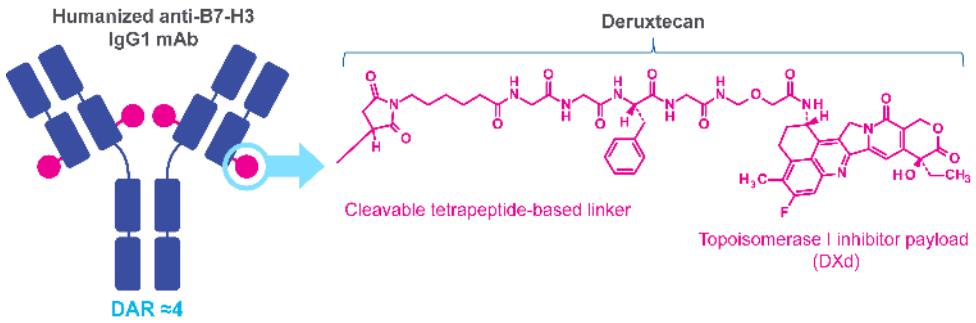
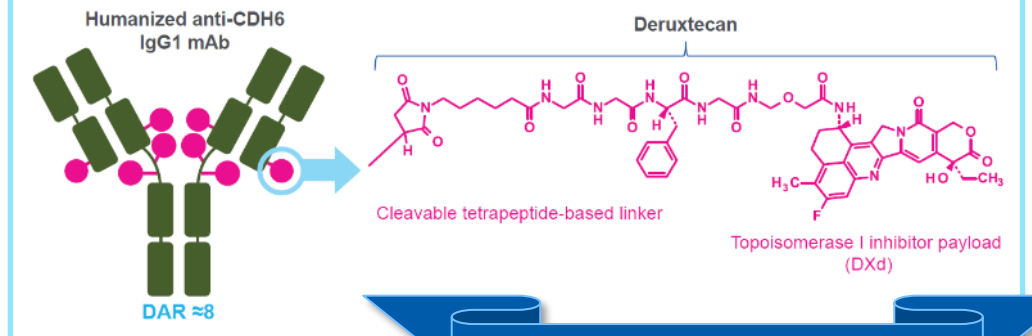
- Deepen our understanding of DXd-ADC science – mode of action/ resistance
- Seek opportunities in combinations and early disease
- Aim to overcome the disease with multiple treatment options

We continue to address remaining unmet needs in Breast Cancer

Agenda

1. Introduction
2. Shift the paradigm for HER2-low BC
3. Build trust in HER2+ Breast Cancer
4. Addressing further needs in BC
5. **Rising Stars**
6. Future news flow

Rising Stars: DS-7300 & DS-6000

	DS-7300	DS-6000
Structure		
Development stage & target indications	**Ph1/2** **Dose escalation: solid tumors** **Dose expansion: ESCC, CRPC, sqNSCLC** **Ph2 for SCLC under preparation to start in FY2022 H1**	**Ph1** **Dose escalation & expansion: RCC & OVC** **Currently in the dose expansion part**

First data disclosure in ASCO 2022

CRPC: castration-resistant prostate cancer, DAR: drug antibody ratio, ESCC: esophageal squamous cell carcinoma, mAb: monoclonal antibody, OVC: ovarian cancer, RCC: renal cell carcinoma, SCLC: small cell lung cancer, sqNSCLC: squamous non small cell lung cancer,

Rising Stars have potential to become new growth drivers post 3ADCs.
Development to be accelerated.

Phase I, Two-Part, Multi-Center, First-in-Human Study of DS-6000a in Subjects with Advanced Renal Cell Carcinoma and Ovarian Cancer

Erika P. Hamilton, MD[1,2]; Shekeab Jauhari, MD[1,3]; Kathleen Moore, MD[4]; Brian Rini, MD[5]; Robert McLeod, MD[6]; Jie Lin, MD[6]; Nanae Izumi[6]; Madan G. Kundu, PhD[6]; Yusuke Myobatake[6]; Abderrahmane Laadem, MD[6]; Yutaka Noguchi[7]; Julius Kirui[1]; David R. Spigel, MD[1,2]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Tennessee Oncology, PLLC, Nashville, TN; [3]Florida Cancer Specialists and Research Institute, Lake Mary, FL; [4]University of Oklahoma College of Medicine, Oklahoma City, OK; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN; [6]Daiichi Sankyo, Inc, Basking Ridge, NJ; [7]Daiichi Sankyo Co, Ltd, Tokyo, Japan

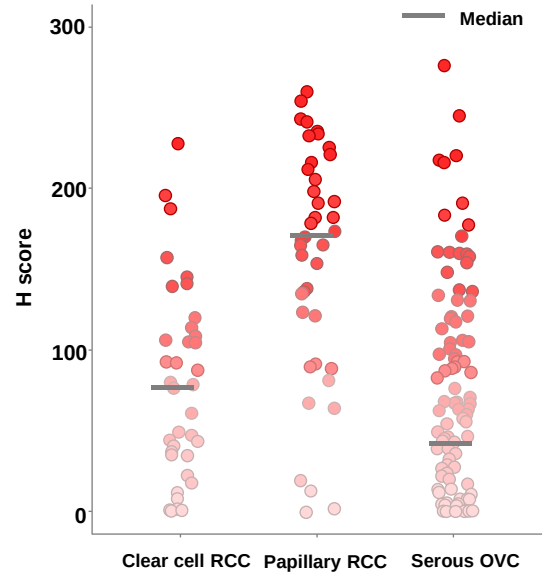
ASCO 2022 #3002 Oral

On behalf of the investigators

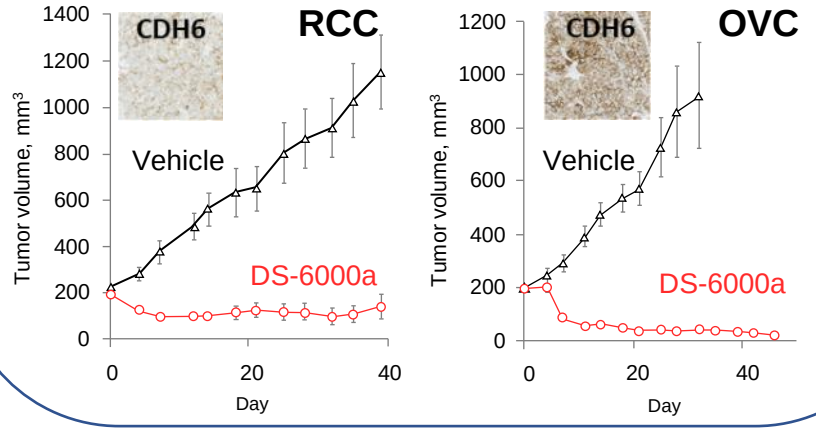
Background

- Cadherin 6 (CDH6) is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition
- CDH6 is found to be overexpressed in various cancers, particularly ovarian cancer (OVC) and renal cell carcinoma (RCC)[1]
- In preclinical studies, DS-6000a inhibited tumor growth and induced tumor regression in CDH6-expressing OVC and RCC[1]
- Here, we report initial results from the dose-escalation portion of a first-in-human trial in patients with advanced OVC and RCC (NCT04707248)

CDH6 Expression in RCC/Serous OVC[1]



Antitumor Activity of DS-6000a in RCC and OVC PDX Model[1]



PDX, patient-derived xenograft.

1. Hirokazu S, et al. ESMO 2021. Abstract 10P.

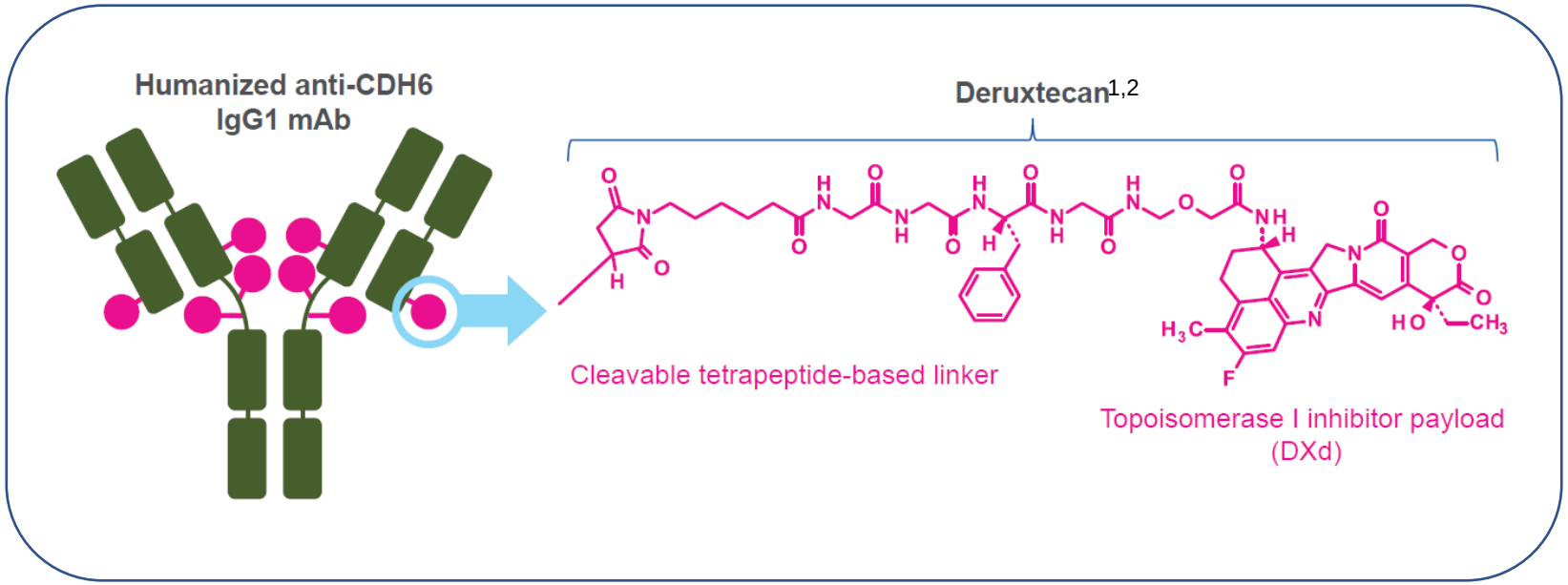
DS-6000a Was Designed With 7 Key Attributes

DS-6000a is a cadherin 6 (CDH6) directed ADC composed of 3 components:[1-3]

A humanized anti-CDH6 IgG1 monoclonal antibody covalently linked to:

A topoisomerase I inhibitor payload, an exatecan derivative, via

A tetrapeptide-based cleavable linker



- Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
- High potency of payload [a,1,2]
- High drug-to-antibody ratio ≈8 [a,1,2]
- Payload with short systemic half-life [a,b,1,2]
- Stable linker-payload [a,1,2]
- Tumor-selective cleavable linker [a,1,2]
- Bystander antitumor effect [a,1,2]

ADC, antibody-drug conjugate; DXd, a novel topoisomerase 1 inhibitor that is a derivative of exatecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.
1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. **2.** Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **3.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

Study Design

Dose Escalation (Part A)
DS-6000a IV q3w
RCC and serous OVC

Dose Expansion (Part B)
DS-6000a IV q3w at RDE

Enrollment criteria

- Advanced/metastatic RCC or OVC not amenable to SOC therapy[a]
- ECOG PS 0 to 1
- Ability to provide archived tissue for correlative testing
- No previous treatment with CDH6-targeting agents or ADCs with a linked topoisomerase I inhibitor

Primary objectives

- Safety and tolerability
- Determine MTD and RDE

Secondary objectives

- PK of DS-6000a, total anti-CDH6 antibody, and the DXd payload
- Antitumor activity per RECIST 1.1
- Immunogenicity

ADC, antibody drug conjugate; CDH6, cadherin 6; DXd, topoisomerase I inhibitor payload; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; OVC, ovarian cancer; PK, pharmacokinetics; q3w, every 3 weeks; RCC, renal cell carcinoma, RDE, recommended dose for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care.
[a] Patients with OVC must have also had prior treatment with platinum and taxane therapy.

Baseline Patient and Disease Characteristics

DS-6000a Dose Escalation	OVC (N=20)	RCC (N=9)	Total (N=30)[a]
Age, median (range), years	65.5 (51-78)	60.0 (41-72)	64.5 (41-78)
Sex, n (%)			
Female	20 (100)	4 (44.4)	25 (83.3)
Male	0	5 (55.6)	5 (16.7)
Baseline ECOG PS, n (%)			
0	10 (50)	6 (66.7)	16 (53.3)
1	10 (50)	3 (33.3)	14 (46.7)
Tumor type, n (%)			
Renal cell carcinoma			
Clear cell RCC	–	8 (88.9)	8 (26.7)
Non–clear cell RCC	–	1 (11.1)	1 (3.3)
Serous ovarian cancer	20 (100)	–	20 (66.7)
Platinum-resistant disease	17 (85)	–	17 (56.7)
No. of prior systemic regimens			
Median (range)	4.0 (1-12)	2.0 (1-6)	3.0 (1-12)
Baseline CDH6 expression H score, range	0-250	17-218	0-250[b]

Data cutoff: February 25, 2022.
CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; OVC, ovarian cancer; RCC, renal cell carcinoma.
[a] One missing primary diagnosis of OVC.
[b] Membrane CDH6 expression of 23 evaluable archival tissues.

Patient and Treatment Summary

- As of data cutoff, 30 patients enrolled in part A (dose escalation) had received DS-6000a (OVC, n=21; RCC, n=9)
  - 17 patients (56.7%) were receiving ongoing treatment with DS-6000a (OVC, n=12; RCC, n=5)
  - 13 patients (43.3%) discontinued treatment
    - 9 of 13 patients discontinued due to disease progression
    - 1 patient (3.3%) discontinued due to TEAE
- Median treatment duration was 12.1 weeks (range, 3.0-54.1 weeks)

- Data cutoff: February 25, 2022.
- OVC, ovarian cancer; RCC, renal cell carcinoma; TEAE, treatment-emergent adverse event.

Treatment Related TEAEs (Any Grade) Occurring in ≥10% of Patients

	1.6 mg/kg (n=1)	3.2 mg/kg (n=6)	4.8 mg/kg (n=6)	6.4 mg/kg (n=8)	8.0 mg/kg (n=6)	9.6 mg/kg (n=3)	Total (N=30)
Any treatment-related TEAE, n (%)	1 (100)	4 (66.7)	4 (66.7)	7 (87.5)	6 (100.0)	3 (100.0)	25 (83.3)
Nausea	0	3 (50.0)	3 (50.0)	5 (62.5)	5 (83.3)	2 (66.7)	18 (60.0)
Fatigue	0	2 (33.3)	3 (50.0)	4 (50.0)	6 (100.0)	2 (66.7)	17 (56.7)
Vomiting	0	2 (33.3)	1 (16.7)	2 (25.0)	2 (33.3)	2 (66.7)	9 (30.0)
Neutrophil count decreased	0	0	0	1 (12.5)	3 (50.0)	3 (100.0)	7 (23.3)
Decreased appetite	1 (100)	0	0	4 (50.0)	1 (16.7)	0	6 (20.0)
Diarrhea	0	0	0	2 (25.0)	1 (16.7)	1 (33.3)	4 (13.3)

- Treatment-related TEAEs occurred in 25 patients (83.3%)
- The most common treatment-related TEAEs of any grade were nausea, fatigue, and vomiting
- One patient in the 9.6-mg/kg arm experienced grade 2 pneumonitis, which led to treatment discontinuation

Data cutoff: February 25, 2022.
TEAE, treatment-emergent adverse event.

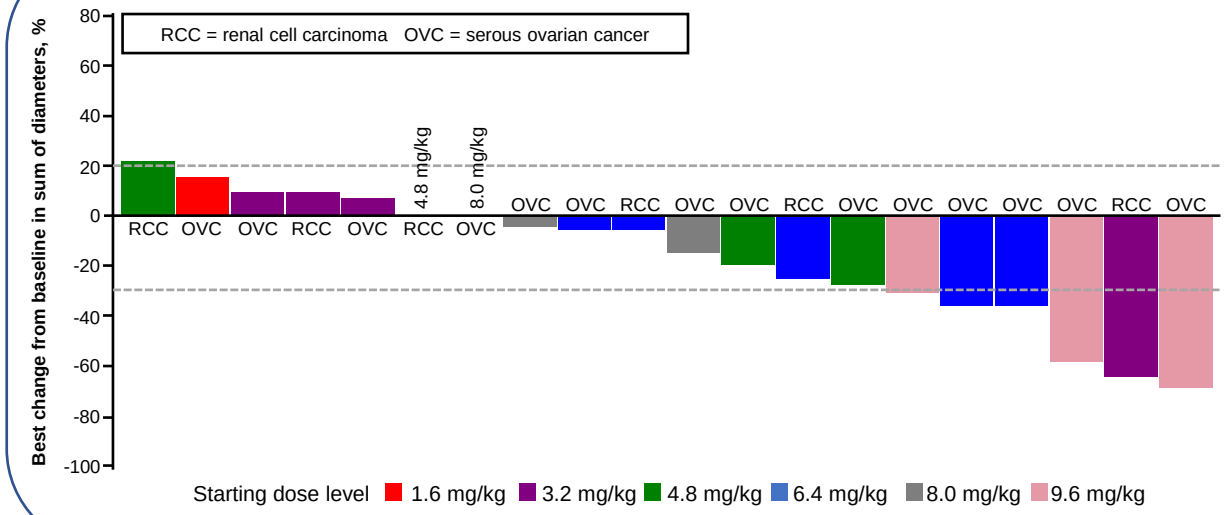
Treatment-Related TEAEs (Grade ≥3)

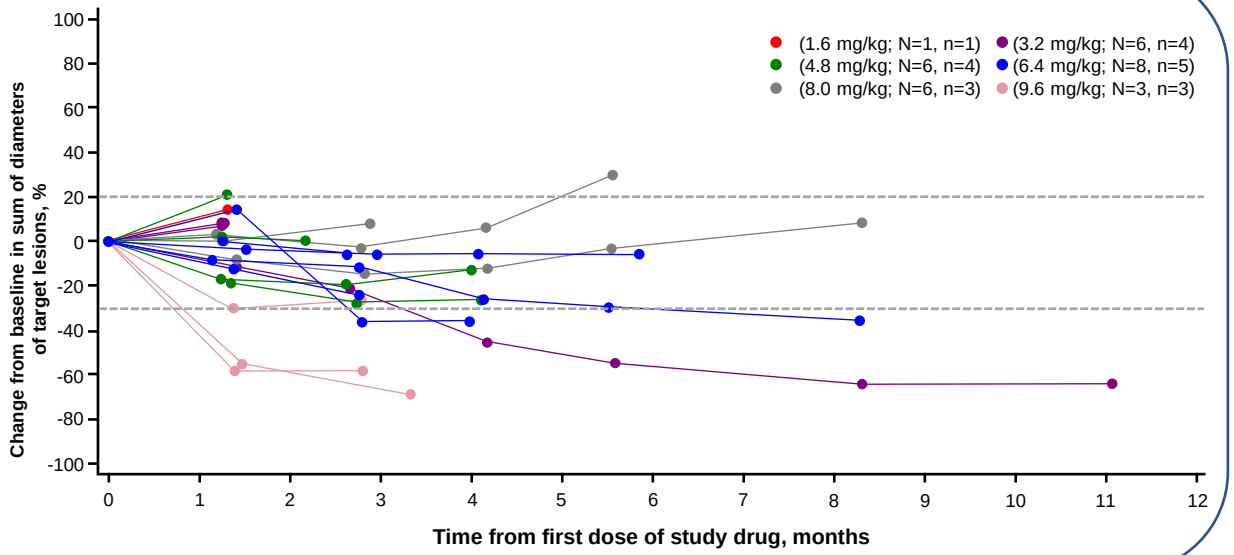
	1.6 mg/kg (n=1)	3.2 mg/kg (n=6)	4.8 mg/kg (n=6)	6.4 mg/kg (n=8)	8.0 mg/kg (n=6)	9.6 mg/kg (n=3)	Total (N=30)
Any grade ≥3 treatment-related TEAE, n (%)	0	0	0	2 (25.0)	2 (33.3)	3 (100)	7 (23.3)
Neutrophil count decreased	0	0	0	0	2 (33.3)	3 (100)	5 (16.7)
Anemia	0	0	0	1 (12.5)	0	1 (33.3)	2 (6.7)
Febrile neutropenia	0	0	0	1 (12.5)	0	1 (33.3)	2 (6.7)
Decreased appetite	0	0	0	0	1 (16.7)	0	1 (3.3)
Platelet count decreased	0	0	0	0	0	1 (33.3)	1 (3.3)

- Grade ≥3 treatment-related TEAEs occurred in 7 patients (23.3%)
- The most common treatment-related TEAEs (nausea, fatigue, and vomiting) had no grade ≥3 events
- Two patients experienced DLTs in the 9.6-mg/kg arm (grade 3 febrile neutropenia and grade 4 platelet count decreased)
- Two patients experienced grade 3 treatment-related SAEs (anemia and febrile neutropenia)

Data cutoff: February 25, 2022.
DLT, dose-limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Change From Baseline in Target Lesions: OVC and RCC Evaluable Population[a]



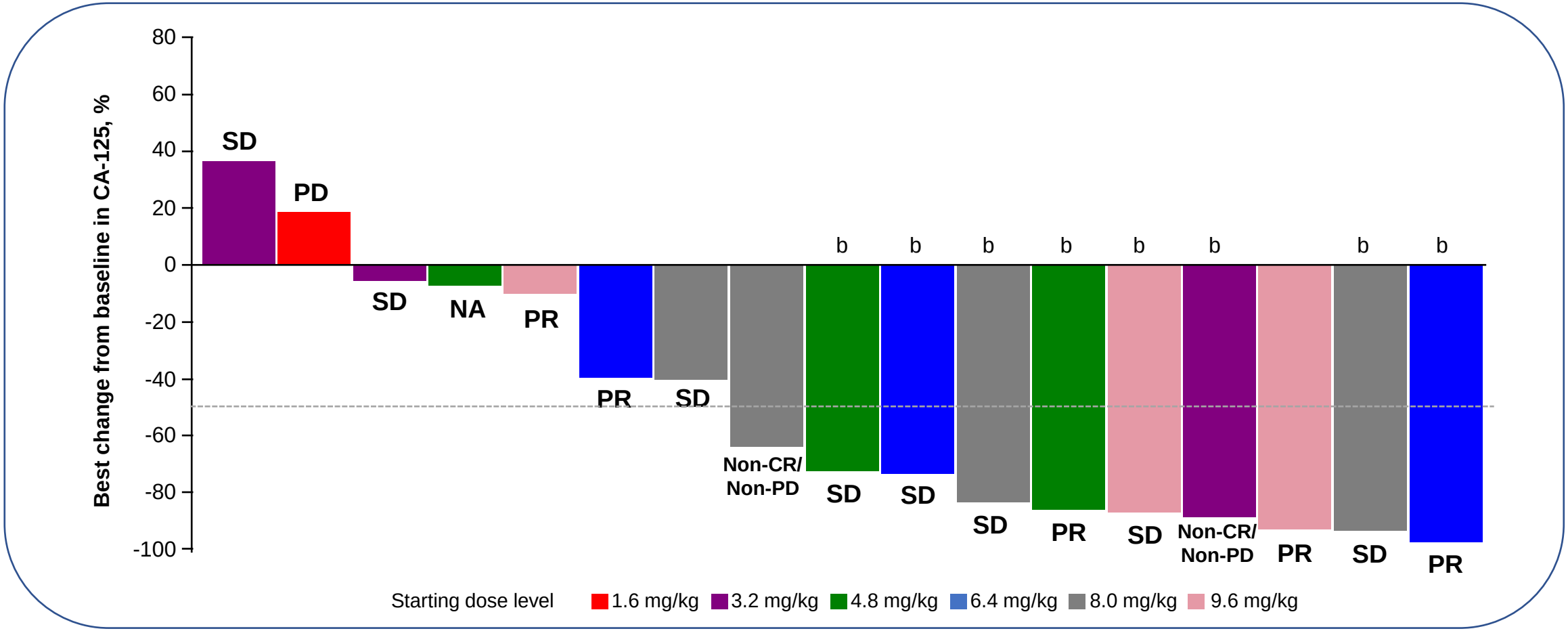


- Among 20 evaluable patients with measurable disease, there were 6 PRs (platinum-resistant OVC, n=5; RCC, n=1)
  - 4 confirmed PRs (platinum-resistant OVC, n=3; RCC, n=1)
  - 2 unconfirmed PRs (1 patient still in the trial)
- 12 patients had stable disease

Data cutoff: February 25, 2022.
OVC, ovarian cancer; PR, partial response; RCC, renal cell carcinoma.
[a] Patients who received ≥1 dose of study treatment and have completed ≥1 postbaseline tumor assessment or discontinued treatment for any reason.

Change From Baseline in CA-125 Levels

- Among 17 evaluable patients with OVC,[a] 8 CA-125 responses[b] were observed



Data cutoff: February 25, 2022.

CA-125, cancer antigen 125; CR, complete response; GCIG, Gynecologic Cancer InterGroup; NA, not available; OVC, ovarian cancer; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Patients with baseline CA-125 value and ≥1 postbaseline CA-125 value were included.

[b] According to the GCIG criteria, patients can be evaluated for response only if they have a baseline sample that is ≥2 × the upper limit of normal obtained within 2 weeks prior to starting treatment. CA-125 response is defined as a ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for ≥28 days.

Conclusions

- DS-6000a was generally well tolerated, and the recommended dose for expansion (RDE) was declared 8.0 mg/kg
- DS-6000a demonstrated early clinical signals (RECIST and CA-125 responses) in heavily pretreated patients with advanced platinum-resistant OVC and RCC
- Expansion cohorts (part B) opened at 8.0 mg/kg are enrolling patients with OVC and RCC

Our DXd-ADC Pipeline

	Project (Target)	Target indications	Discovery	Pre-Clinical	Ph1	Ph2	Ph3	Filed	Launched
1	ENHERTU® (HER2)	Breast, Gastric, NSCLC, CRC, etc.							
2	Dato-DXd (TROP2)	NSCLC, Breast, etc.							
3	HER3-DXd (HER3)	NSCLC, Breast							
4	DS-7300 (B7-H3)	ESCC, CRPC, sq-NSCLC, SCLC, etc.							
5	DS-6000 (CDH6)	Renal, Ovarian							
6	DS-3939 (TA-MUC1)	Solid tumors							
7	DS-XXXX (Undisclosed)	Undisclosed							

Timeline indicates the most advanced stage of each project

CRC: colorectal cancer, CRPC: castration-resistant prostate cancer, ESCC: esophageal squamous cell carcinoma, GIST: gastrointestinal stromal tumor, NSCLC: non small cell lung cancer,. SCLC: small cell lung cancer

Expanding to further unmet needs with validated DXd-ADC platform

Agenda

1. Introduction
2. Shift the paradigm for HER2-low BC
3. Build trust in HER2+ Breast Cancer
4. Addressing further needs in BC
5. Rising Stars
6. **Future news flow**

FY2022 Future News Flow

As of Jun 2022

Daiichi-Sankyo

Planned publications

Coming Soon

Results of QuANTUM-First* will be presented at "Presidential Symposium" on Jun 11 at EHA 2022 congress

***Phase 3 study of quizartinib in newly diagnosed FLT3-ITD (+) AML**

AML: acute myeloid leukemia, EHA: European Hematology Association

FY2022 Future News Flow

As of Jun 2022

Regulatory decisions

ENHERTU®	DESTINY-Breast03: HER2 positive BC, 2L, Ph3 • EU: FY2022 H1, JP: FY2022 H2 DESTINY-Breast04: HER2-low BC, post chemo, Ph3 • US: FY2022 H2 DESTINY-Gastric02: HER2 positive GC, 2L, Ph2 • EU: FY2022 H2 DESTINY-Lung01: HER2 mutated NSCLC, 2L, Ph2 • US: FY2022 H1
Quizartinib	QuANTUM-First: AML, 1L, Ph3 • JP/US: FY2022 H2
Valemetostat	Registrational Ph2: R/R ATL/L • JP: FY2022 H1

Key data readouts

ENHERTU®	DESTINY-Breast02: HER2 positive BC, 3L, Ph3 • FY2022 H1
Dato-DXd	TROPION-Lung01: NSCLC, 2/3L, Ph3 • FY2022 H2
DS-5670	Ph1/2/3: COVID-19 mRNA vaccine, booster • FY2022 H2

Planned regulatory submissions

ENHERTU®	DESTINY-Breast04: HER2-low BC, post chemo, Ph3 • JP/US/EU/CN: FY2022 H1
Quizartinib	QuANTUM-First: AML, 1L, Ph3 • JP/US/EU: FY2022 H1
DS-5670	Ph1/2/3: COVID-19 mRNA vaccine, booster • JP: FY2022 H2

Planned pivotal study initiation

Dato-DXd	TROPION-Breast02: TNBC, 1L, Ph3 • FY2022 H1
HER3-DXd	HERTHENA-Lung02: EGFR mutated NSCLC, 2L, Ph3 • FY2022 H1

AML: acute myeloid leukemia, ATL/L: adult T-cell leukemia/lymphoma, BC: breast cancer, GC: gastric cancer, NSCLC: non small cell lung cancer, R/R: relapsed/refractory

Timeline indicated is based on the current forecast and subject to change.

Appendix

ENHERTU®: Clinical Development Plan | Breast cancer

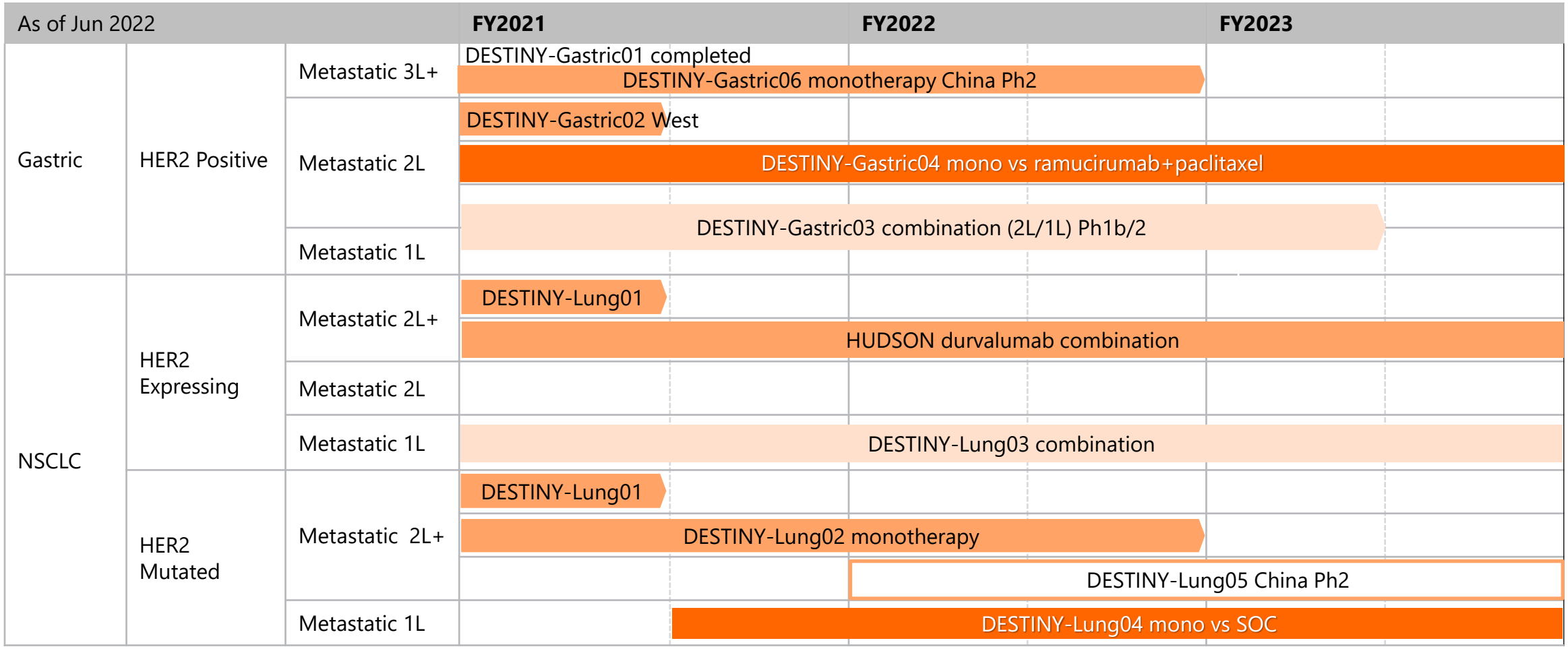
As of Jun 2022			FY2021	FY2022	FY2023
HER2 Positive		Metastatic 3L+	DESTINY-Breast01 completed		
			DESTINY-Breast02 monotherapy vs PC		
		Metastatic 2L	DESTINY-Breast03		
			DESTINY-Breast07 combination (2L/1L) Ph1b/2		
		Metastatic 1L			
			DESTINY-Breast09 T-DXd ± pertuzumab vs THP		
		Post-neoadjuvant	DESTINY-Breast05 monotherapy vs T-DM1		
		Neoadjuvant	DESTINY-Breast11 T-DXd vs T-DXd / THP vs AC / THP		
		Adjuvant			
HER2-low	HR+ HR-	Metastatic Post Chemo	DESTINY-Breast04 mono vs PC		
			DESTINY-Breast08 combination		
		Post-neoadjuvant			
	HR+	Metastatic Chemo Naive	DESTINY-Breast06 monotherapy vs PC		
	HR-	Metastatic 1L	BEGONIA durvalumab combination Ph1b/2 (Arm 6)		
		Neoadjuvant			

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

AC: adriamycin + cyclophosphamide, THP: taxane + Herceptin + pertuzumab, PC: physician's choice

ENHERTU®: Clinical Development Plan | GC & NSCLC



Study initiation & end points are all shown as either beginning of 1H or 2H

GC: gastric cancer, NSCLC: non-small cell lung cancer, SOC: standard of care

ENHERTU®: Clinical Development Plan | CRC & other tumors

As of Jun 2022			FY2021	FY2022	FY2023
CRC	HER2 Expressing	Metastatic 3L	DESTINY-CRC01 completed	DESTINY-CRC02 monotherapy	
Other Tumors/ multiple tumors	HER2 Expressing	Metastatic 2L	Nivolumab combo (breast, bladder)		
			Pembrolizumab combination (breast, NSCLC)		
			DESTINY-PanTumor02		
	HER2 Mutated	Metastatic 2L	DESTINY-PanTumor01		

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

CRC: colorectal cancer, NSCLC: non small cell lung cancer

Dato-DXd: Clinical Development Plan | NSCLC

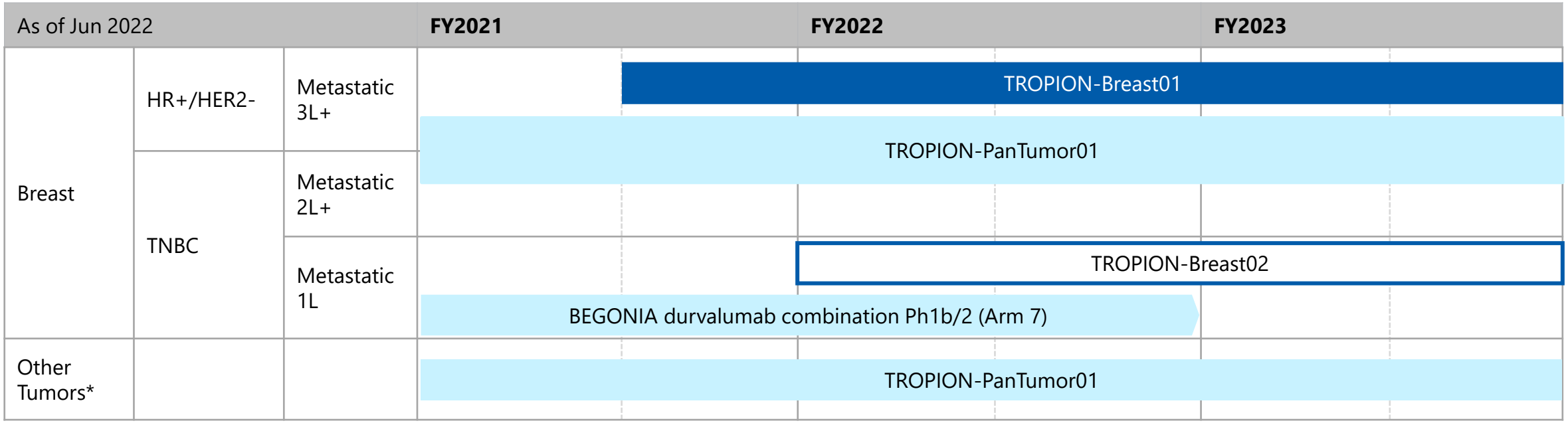
As of Jun 2022			FY2021	FY2022	FY2023
NSCLC	All comers	Metastatic 2L/3L	TROPION-Lung01 monotherapy		
	ICI combination Without actionable mutations	Metastatic 1L/2L	TROPION-Lung02 pembrolizumab combination		
			TROPION-Lung04 durvalumab combination		
		Metastatic 1L		TROPION-Lung08 pembrolizumab combination	
	With actionable mutations	Metastatic 2L+	TROPION-Lung05 monotherapy		

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

ICI: immune checkpoint inhibitor, NSCLC: non small cell lung cancer

Dato-DXd: Clinical Development Plan | Breast & other tumors



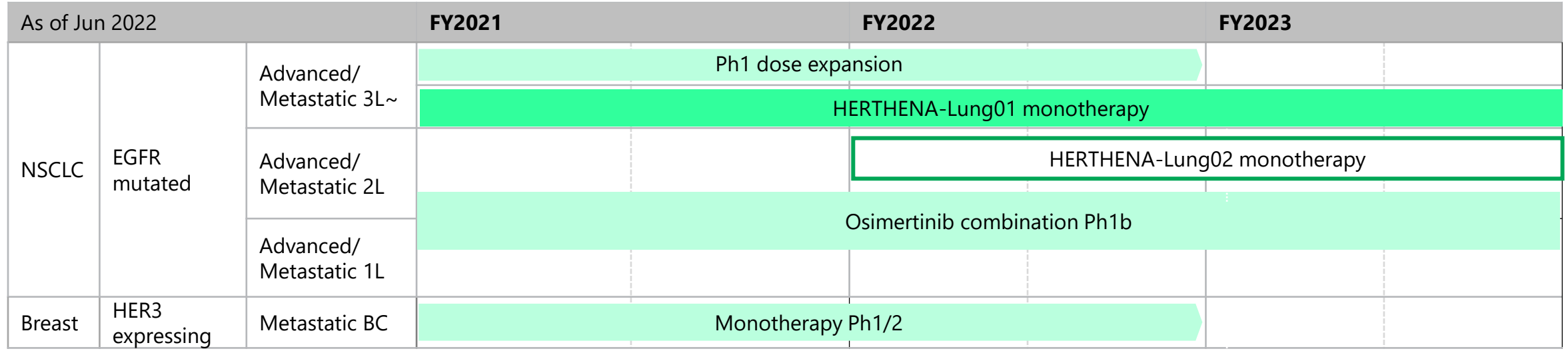
*Other tumors are gastric, esophageal, urothelial, and SCLC. Inclusion of these tumors is based upon TROP2 expression as well as preclinical and other evidence that Dato-DXd may be effective.

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

SCLC: small cell lung cancer, TNBC: triple negative breast cancer

HER3-DXd: Clinical Development Plan | NSCLC & other tumors



Study initiation & end points are all shown as either beginning of 1H or 2H

BC: breast cancer, NSCLC: non small cell lung cancer

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