Antibody Drug Conjugates for HER2 Negative Breast Cancer: A Revolution in Chemotherapy for Breast Cancer

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Antibody Drug Conjugates for HER2 Negative Breast Cancer

- HER2 directed ADCs for HER2 low and HER2 ultra-low metastatic breast cancer
  - Destiny Breast 04
  - Destiny Breast 06

- Trop2 directed ADCs for HR+ metastatic breast cancer
  - Tropics 02
  - Tropion Breast 01

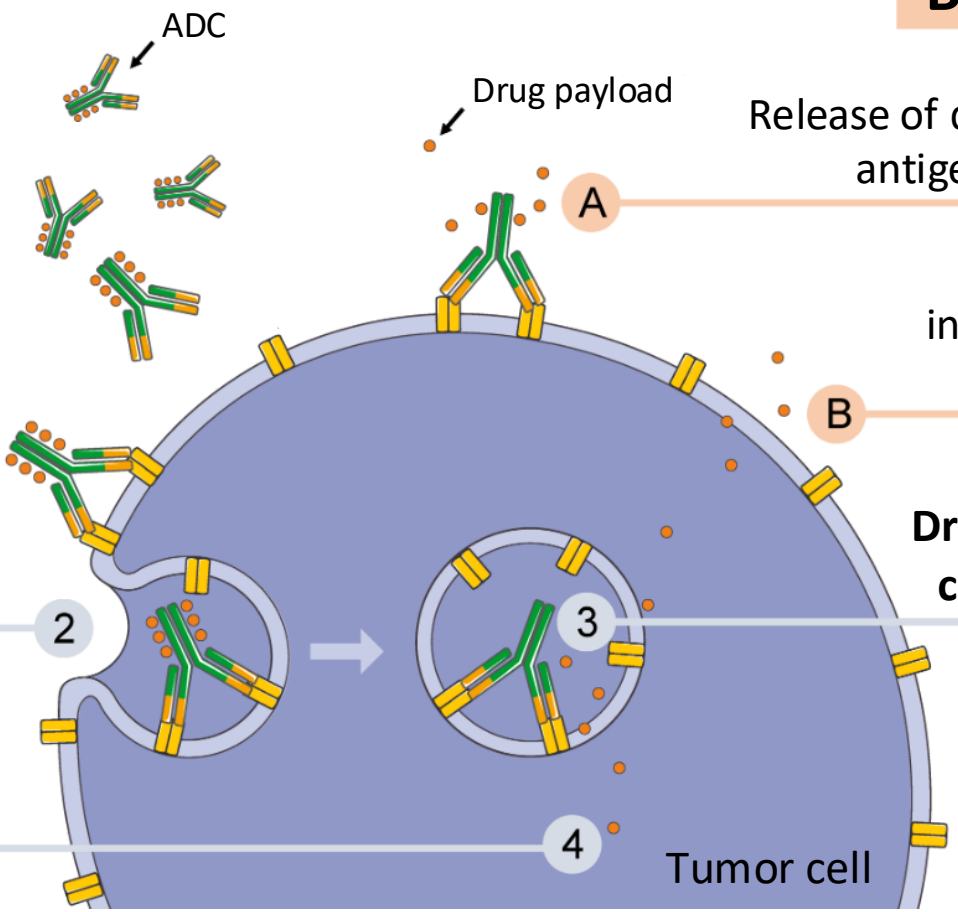
Antibody Drug Conjugate: Mechanism of Action

Classical ADC Mode of Action

ADC binding to receptor (1)

Internalization by endocytosis (2)

Cytotoxic effect induced by drug payload (4)



Bystander Killing Effect

Release of drug payload from antibody after antigen binding, before internalization (A)

Release of drug payload into intercellular space because of high drug membrane permeability (B)

Drug payload release after linker cleavage by lysosomal enzymes (3)

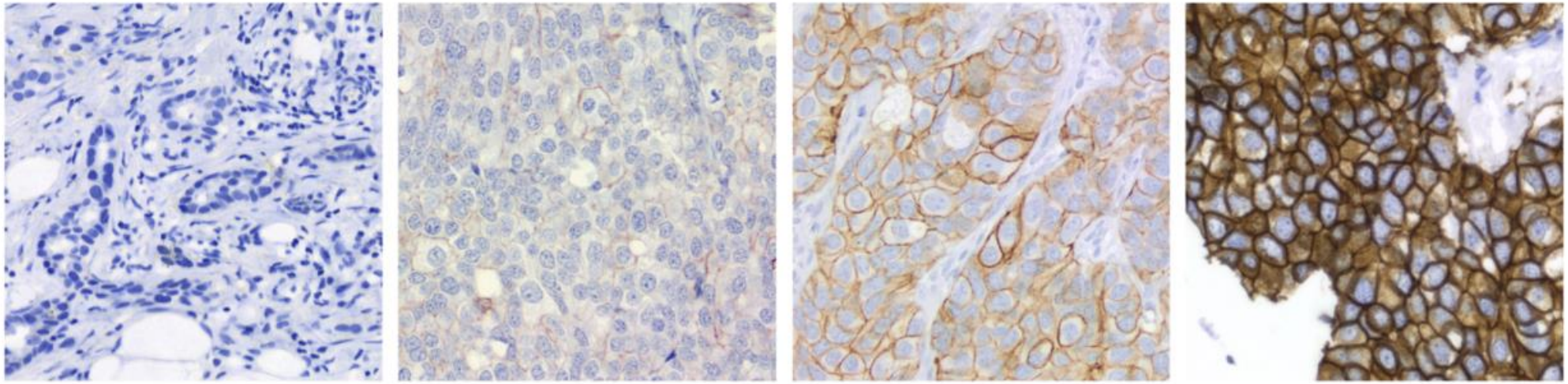
A high drug-to-antibody ratio increases antitumoral efficacy despite low antigen density on tumor cells

- Some ADCs require internalization for payload cleavage, but others can be hydrolyzed extracellularly

ADC, antibody-drug conjugate.

HER2 Directed ADC: Trastuzumab Deruxtecan

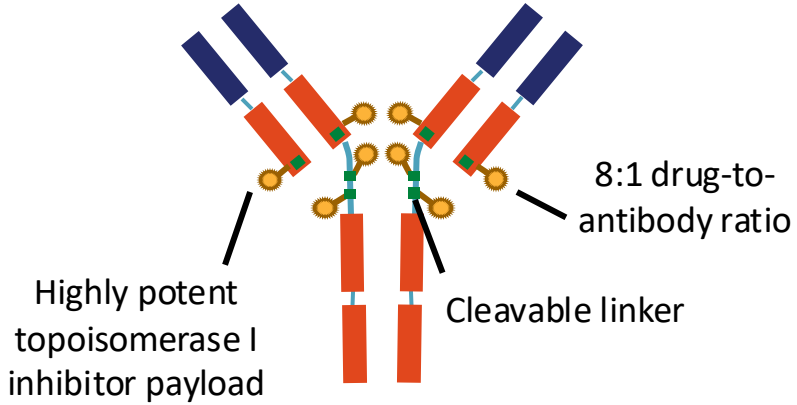
Categories of HER2 Expression



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

Image adapted from Marchiò C, et al. *Semin Cancer Biol.* 2021;72:123-135.

Trastuzumab Deruxtecan (T-DXd): Newer-Generation HER2-Targeted ADC



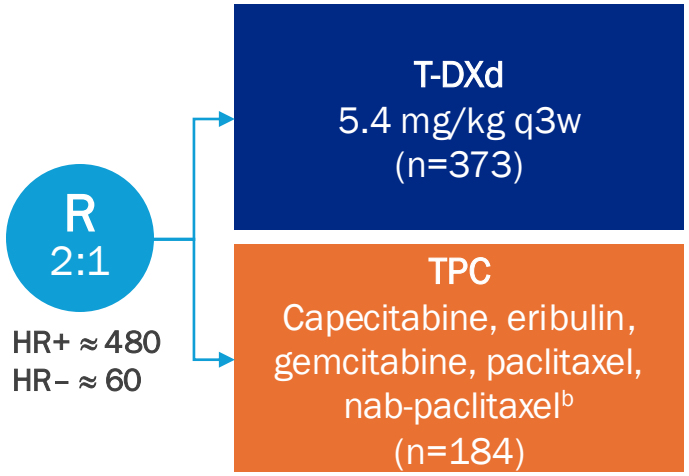
Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer.

DESTINY-Breast04:
Phase 3 Trial of T-DXd vs TPC in HER2-Low MBC

Key Eligibility Criteria[a]

- HER2-low (IHC1+ or IHC2+/ISH–), unresectable, and/or MBC treated with 1-2 prior lines of CT in the metastatic setting
- HR+ disease considered endocrine refractory



Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[c]

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

Stratification factors

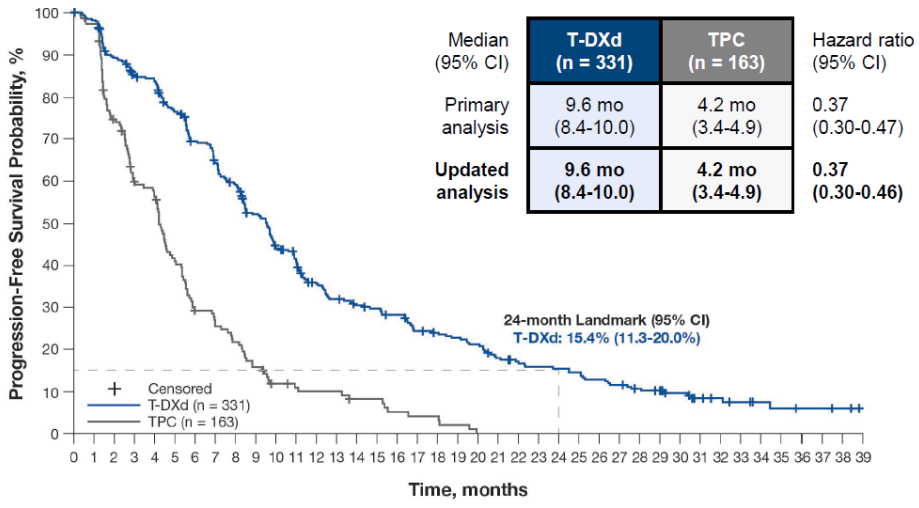
- Centrally assessed HER2 status[d] (IHC1+ vs IHC2+/ISH–)
- 1 vs 2 prior lines of CT
- HR+ (with vs without prior treatment with CDK4/6i) vs HR–

Patient Characteristics	HR+ Cohort		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=373)	TPC (n=184)
Median age (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
ECOG PS 0	187 (56)	95 (58)	200 (54)	105 (57)
ECOG PS 1	144 (44)	68 (42)	173 (46)	79 (43)
HER2 IHC1+	193 (58)	95 (58)	215 (58)	106 (58)
HER2 IHC2+/ISH–	138 (42)	68 (42)	158 (42)	78 (42)
HR+	328 (99)	162 (99)	333 (89)	166 (90)
HR–	3 (1)	1 (1)	40 (11)	18 (10)
Brain mets at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver mets at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Median prior lines of CT in the metastatic setting (range), n	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Median prior lines of ET in the metastatic setting (range), n	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Prior CDK4/6i, n (%)	233 (70)	115 (71)	239 (64)	119 (65)

[a] HR status is based on data collected using the interactive web/voice response system at the time of randomization, which includes mis-stratified patients.
[b] TPC was administered accordingly to the label. [c] Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; [d] Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only Assay system.
efficacy in the HR– cohort was an exploratory endpoint.
Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

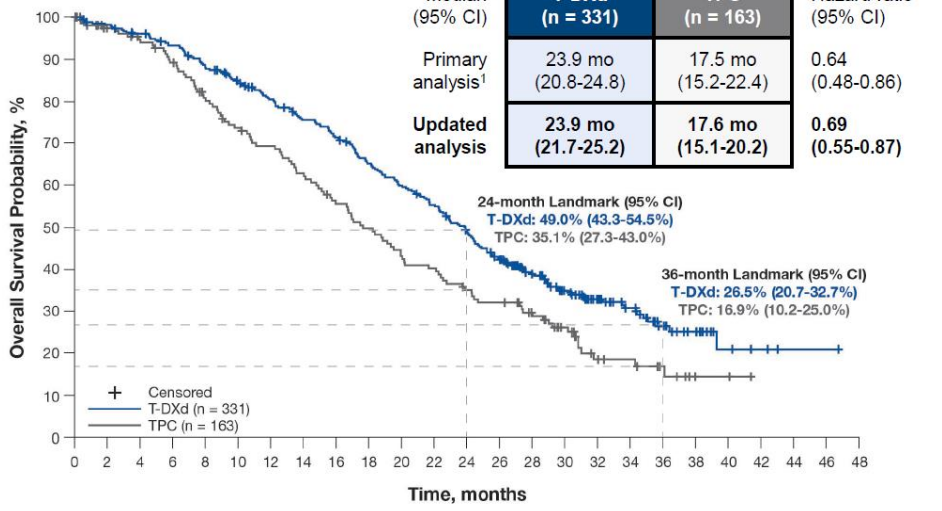
DESTINY-Breast04: Updated PFS and OS[1,2]

PFS in HR+ Cohort (by Investigator Review[a])



Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

OS in HR+ Cohort



Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**

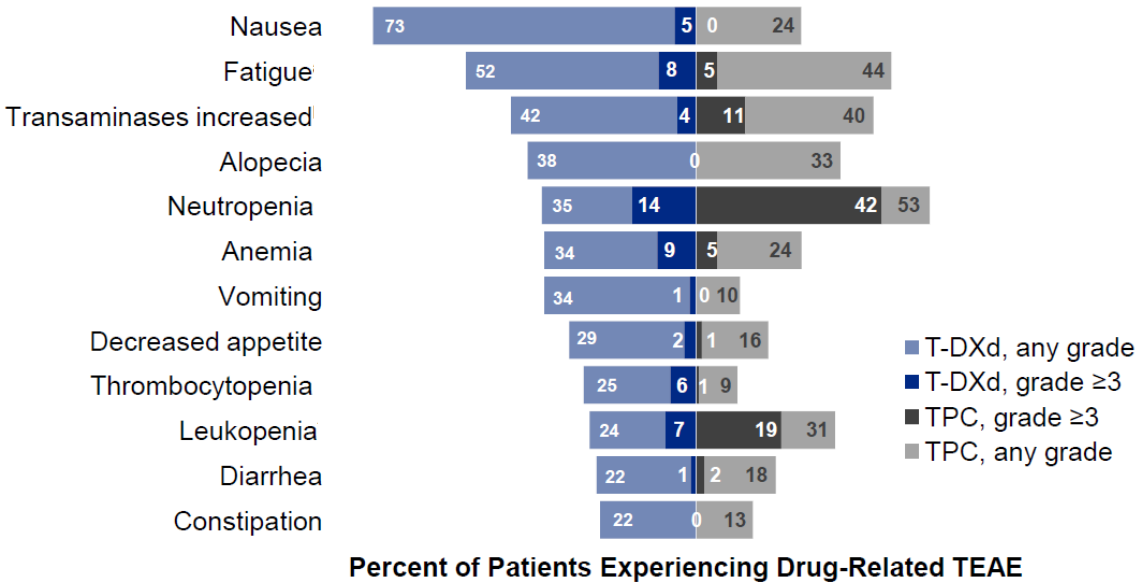
- Median follow-up was 32.0 mo (95%CI, 31.0–32.8)
- In updated survival analyses, T-DXd demonstrated a survival benefit over TPC, consistent with results from the primary analyses[1,2]
  - T-DXd reduced the risk of disease progression or death by 63% in the HR+ cohort and 64% in all patients vs TPC[2]
  - T-DXd reduced the risk of death by 31% in both the HR+ cohort and all patients vs TPC[2]

[a] PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 months and 5.4 months for T-DXd and TPC, respectively (HR=0.51). For all patients, the PFS by BICR was 9.9 months and 5.1 months for T-DXd and TPC, respectively (HR=0.50). The updated analysis is based on PFS by investigator.

1. Modi S, et al. *N Engl J Med*. 2022;387(1):9-20. **2.** Modi S, et al. ESMO 2023. Abstract 376O.

DESTINY-Breast04: Updated Safety

Drug-Related TEAEs in ≥20% of Patients



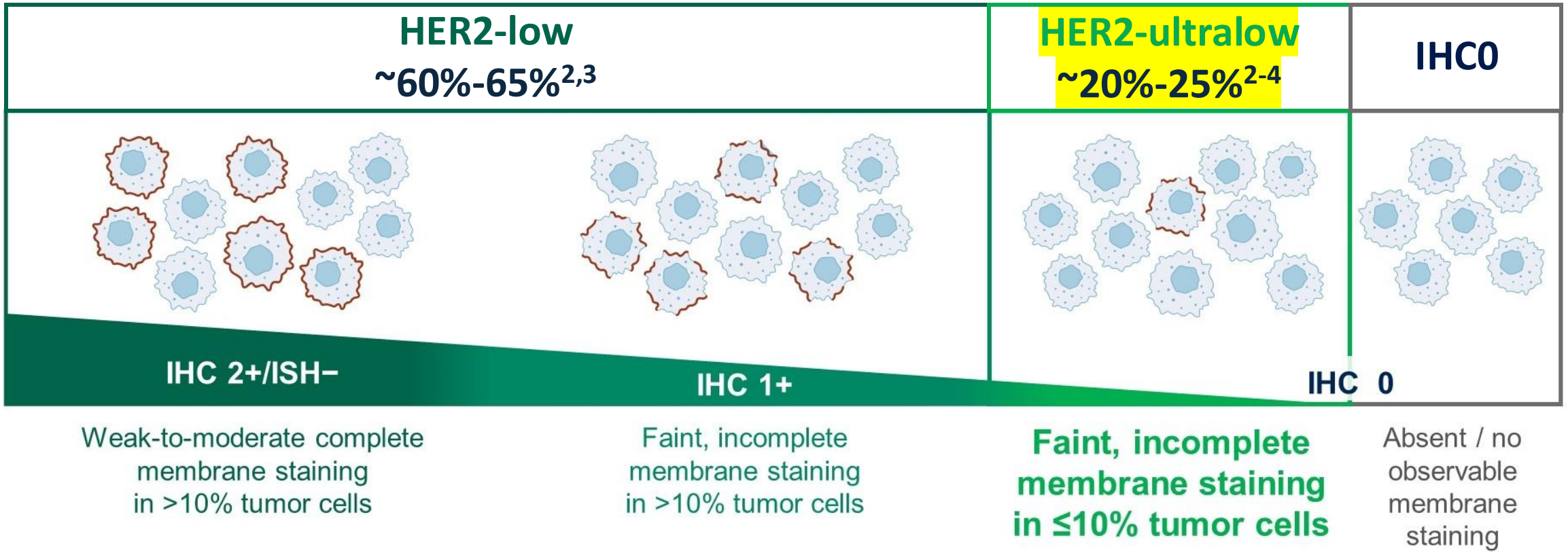
Safety Summary[a]		T-DXd (n=371)	TPC (n=172)
Median treatment duration (range), mo		8.2 (0.2-39.1)	3.5 (0.3-19.7)
TEAEs		369 (99.5)	169 (98.3)
Grade ≥3		202 (54.4)	116 (67.4)
Serious TEAEs, n (%)		108 (29.1)	44 (25.6)
TEAEs associated with, n (%)	**Dose discontinuations**	62 (16.7)	14 (8.1)
	Dose interruptions	155 (41.8)	73 (42.4)
	Dose reductions	89 (24.0)	65 (37.8)
	Deaths	15 (4.0)	5 (2.9)
Total on-treatment deaths[b]		14 (3.8)	8 (4.7)

- Most common TEAEs associated with treatment discontinuation
  - T-DXd: 10.2%, ILD/pneumonitis
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAEs associated with dose reduction
  - T-DXd: 4.6%, nausea; 3.0%, decreased platelet count
  - TPC: 10.5%, neutropenia; 5.2% PPE syndrome

Updated OS analysis data cutoff date: March 1, 2023; median follow-up was 32.0 months.
[a] Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b] On-treatment death is defined as death that occurred any time from date of first dose through 47 days after the last dose of the study treatment.
Modi S, et al. ESMO 2023. Abstract 376O.

HER2-Ultralow Categorization

Potential to expand the patient population that can receive HER-2–directed therapies[1]



HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization.

1. Wolff AC, et al. *J Clin Oncol*. 2023;41:3867-3872. 2. Denkert C, et al. *Lancet Oncol*. 2021;22:1151-1161. 3. Chen Z, et al. *Breast Cancer Res Treat*. 2023;202:313-323. 4. Mehta S, et al. ASCO 2024. Abstract e13156.

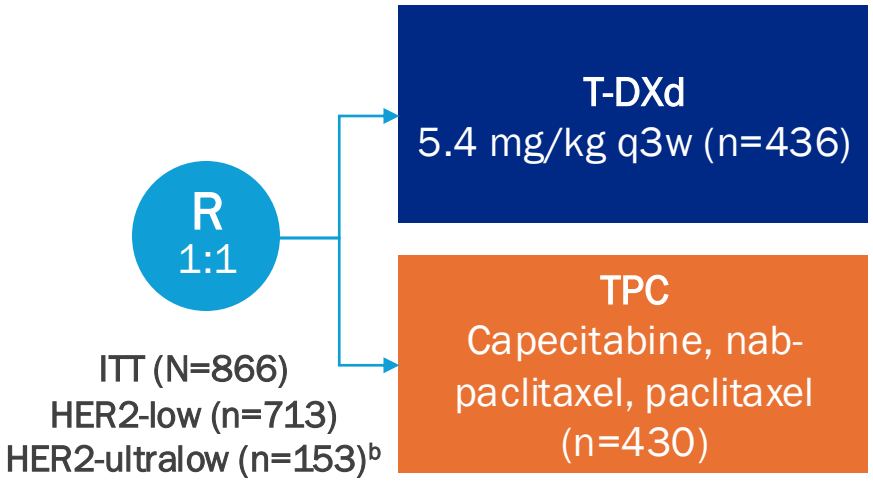
DESTINY-Breast06: Phase 3 Trial of T-DXd vs TPC in HR+/HER2-Low or HR+/HER2-Ultralow MBC

Key Eligibility Criteria

- HR+/HER2-low (HER2 IHC 1+ or IHC 2+/ISH–) or HR+/HER2-ultralow (HER2 IHC 0 with membrane staining) MBC[a]
- Chemo-naive in the MBC setting

Prior lines of therapy

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



Primary endpoint:

- PFS (BICR) in HER2-low

Key secondary endpoints:

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

Stratification Factors

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

[a] HER2 status was determined based on most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+). [b] HER2-ultralow status as determined per interactive response technology data (efficacy analyses in the HER2-ultralow subgroup were based on n=152 per central laboratory testing data).
Curigliano G, et al. ASCO 2024. Abstract LBA1000.

DESTINY-Breast06: Patient Demographics and Key Baseline Characteristics

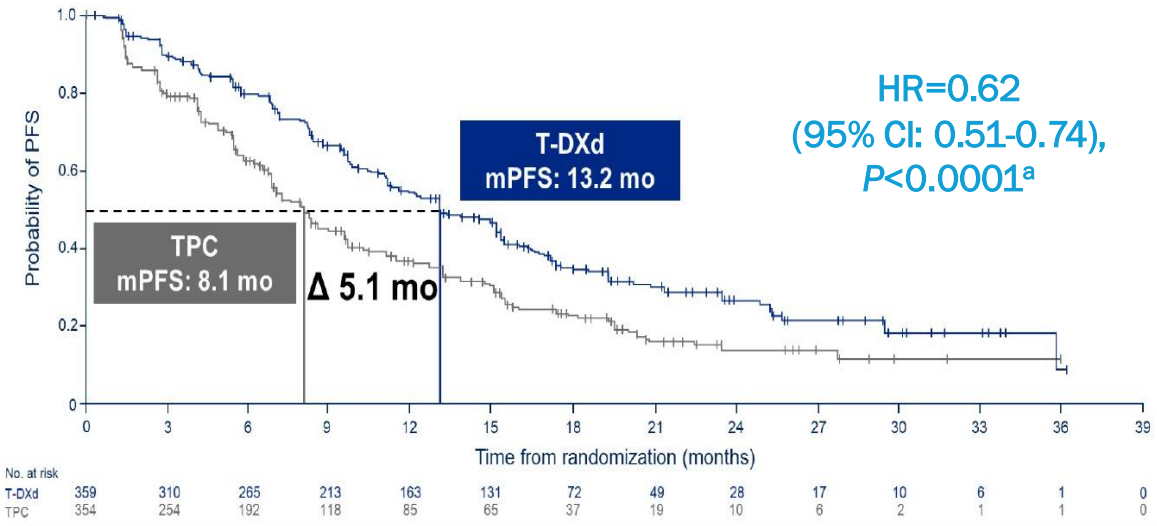
Patient Characteristics		HER2-low[a]		ITT		HER2-ultralow	
		T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Median age (range), years		58 (28-87)	57 (32- 83)	58 (28-87)	57 (32-83)	58.0 (33-85)	57.5 (34-82)
ECOG PS, n (%)[b]	1	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)	44 (57.9)	39 (51.3)
	2	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)	30 (39.5)	35 (46.1)
HER2 status, n (%)[c]	HER2-ultralow[d]	—	—	76 (17.4)	76 (17.7)	76 (100)	76(100)
	IHC 1+ (HER2-low)	238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)	—	—
	IHC 2+/ISH– (HER2-low)	117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)	—	—
Primary endocrine resistance, n (%)[e]		105 (29.2)	116 (32.8)	128 (29.4)	140 (32.6)	23 (30.3)	24 (31 .6)
ET in MBC setting, n (%)	Median lines (range)	2 (1-4)	2 (1-5)	2 (1-4)	2 (1-5)	2.0 (1-4)	2.0 (1 - 5)
	ET monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
	ET + CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
	ET + other targeted therapy[f]	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)

- Median follow-up was 18.2 mo in the ITT population and 18.6 mo in the HER2-low population

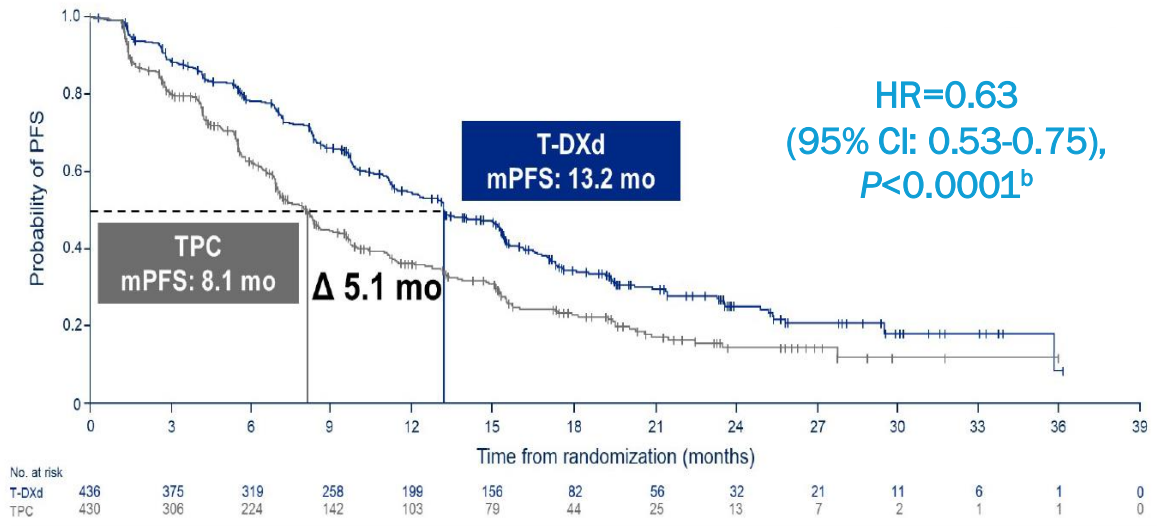
[a] HER2-low status defined at randomization per interactive response technology data. [b] n=14 patients had missing ECOG PS status at baseline. [c] n=2 patients in the ITT population (1 per treatment group) were found to have HER2 IHC 0 with absent membrane staining per central lab testing. [d] Defined as IHC 0 with membrane staining. [e] Defined as relapse while on the first 2 years of adjuvant ET, or progression within the first 6 mo of 1L ET for MBC. [f] mTORi (23.8%), PI3Ki (4.2%), or PARPi (0.9%) in the ITT population.
Curigliano G, et al. ASCO 2024. Abstract LBA1000.

DESTINY-Breast06: PFS

PFS by BICR in HER2-Low (Primary Endpoint)



PFS by BICR in ITT (HER2-Low + HER2-Ultralow)

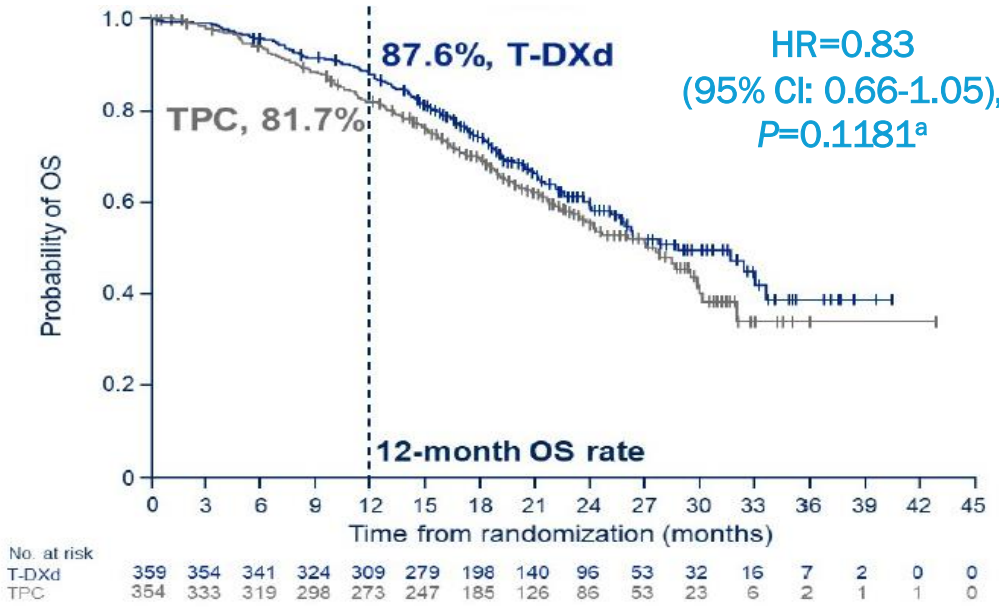


- PFS benefit with T-DXd vs TPC was generally consistent across predefined subgroups in the HER2-low population, including patients aged ≥65 years, those with prior CDK4/6i or taxane use, and those with primary endocrine resistance
- In a prespecified exploratory analysis, PFS benefit with T-DXd vs TPC in the HER2-ultralow population (median of 13.2 vs 8.3 mo; HR, 0.78 [95% CI, 0.50-1.21]) was consistent with that of the HER2-low population

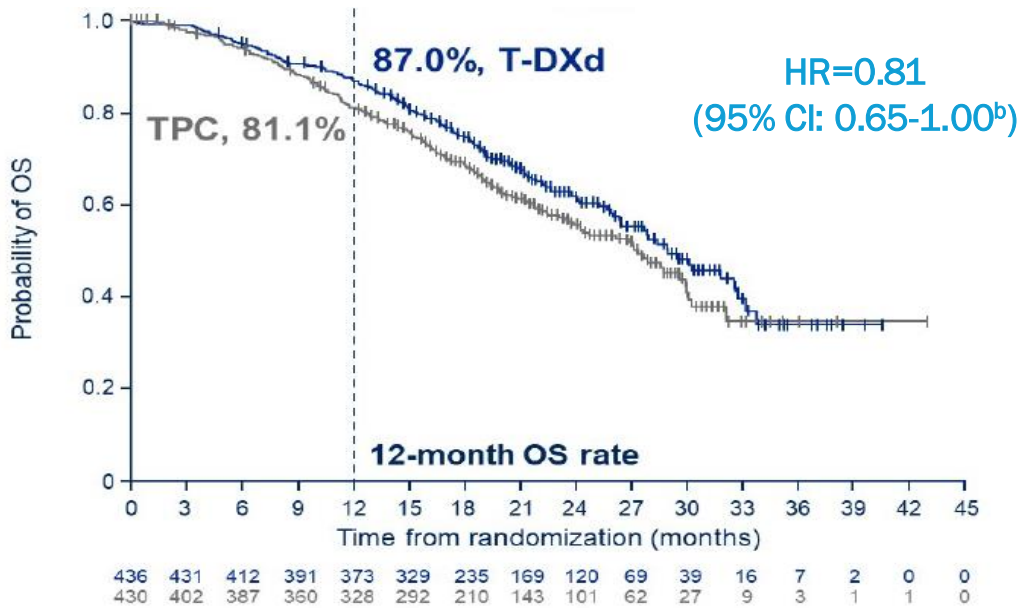
[a] *P* value of <0.05 required for statistical significance. [b] *P* value of <0.015 required for statistical significance.
Curigliano G, et al. ASCO 2024. Abstract LBA1000.

DESTINY-Breast06: OS in HER2-Low and ITT

OS in HER2-Low



OS in ITT (HER2-Low + HER2-Ultralow)



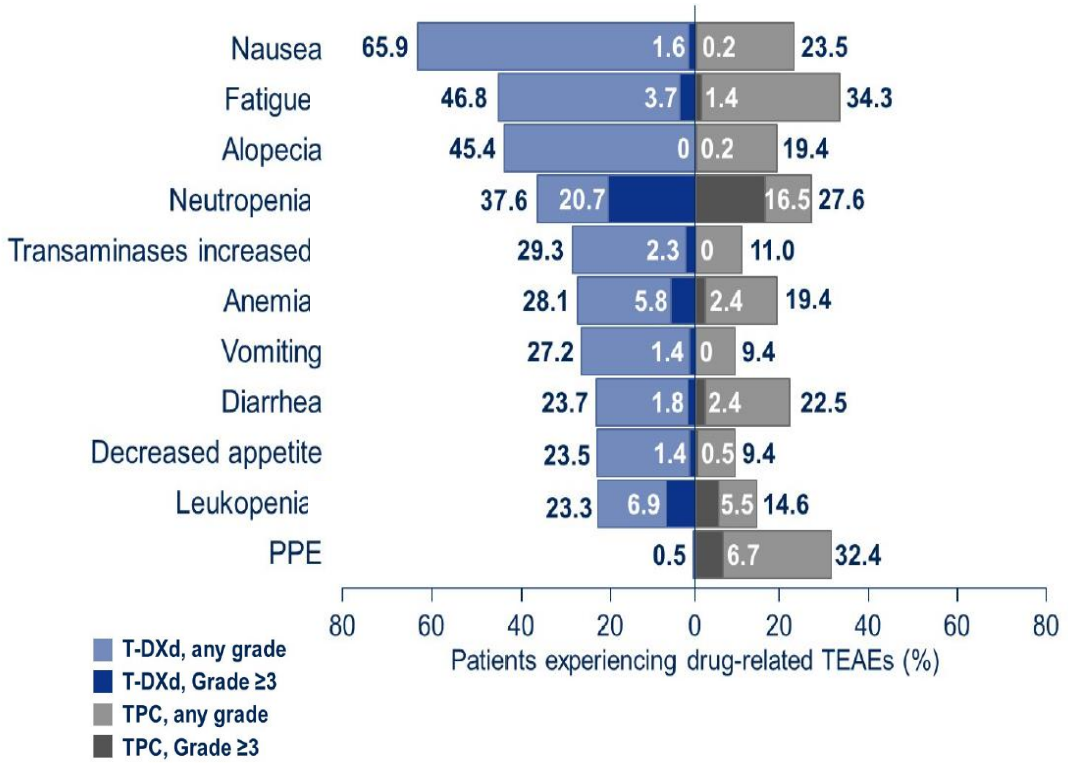
- 39.6% maturity (of total N for the HER2-low population) at this first interim analysis of OS

[a] *P* value of <O.0046 required for statistical significance. [b] No test of significance was performed in line with the multiple testing procedure.

Curigliano G, et al. ASCO 2024. Abstract LBA1000.

DESTINY-Breast06: Safety

Drug-Related TEAEs in ≥20% of Patients in Either Treatment Group



AESI Adjudicated as Drug-Related ILD/Pneumonitis[a]

n (%)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n=434)	49 (11.3)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)
TPC (n=417)	1 (0.2)	0	1 (0.2)	0	0	0

- 14.3% vs 9.4% of patients in the T-DXd vs TPC arms discontinued treatment due to TEAEs
- The most common TEAE associated with treatment d/c was pneumonitis (5.3%) in the T-DXd arm[b] and peripheral sensory neuropathy (1.4%) in the TPC arm
- The most common TEAE associated with dose reduction was nausea (4.4%) in the T-DXd arm and palmar-plantar erythrodysesthesia (16.5%) in the TPC arm
- 5 patients (1.2%) in the T-DXd arm[c] and none in the TPC arm experienced TRAEs leading to death

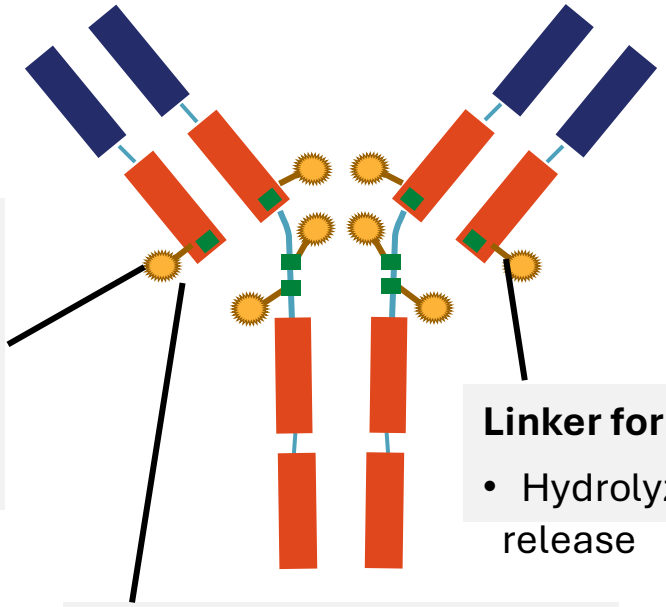
[a] Grouped term. Median time to first onset of ILD/pneumonitis for patients with T-DXd was 141 days (range, 37-835). No pending cases of drug-related ILD/pneumonitis to be adjudicated. One ILD-related death per investigator assessment was upheld by the adjudication committee. An additional 2 deaths were adjudicated as ILD-related by the adjudication committee. [a] In the T-DXd group, 3.5% of patients discontinued due to ILD. [b] Reasons were ILD (n=2), sepsis (n =1), neutropenic sepsis (n=1), and general physical health deterioration (n=1).
Curigliano G, et al. ASCO 2024. Abstract LBA1000.

Trop2 Directed ADC: Sacituzumab govitecan

Sacituzumab govitecan: Anti-TROP2 Monoclonal Antibody

SN-38 Payload

- Metabolite of Topo-1 inhibitor, irinotecan
- SN-38 more potent than parent compound



Linker for SN-38

- Hydrolyzable linker for payload release

7.6:1 drug-to-antibody ratio

Internalization of sacitzumab govitecan leads to release of the SN-38 payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect

Topo-I, topoisomerase I; TROP-2, trophoblast cell surface antigen-2.

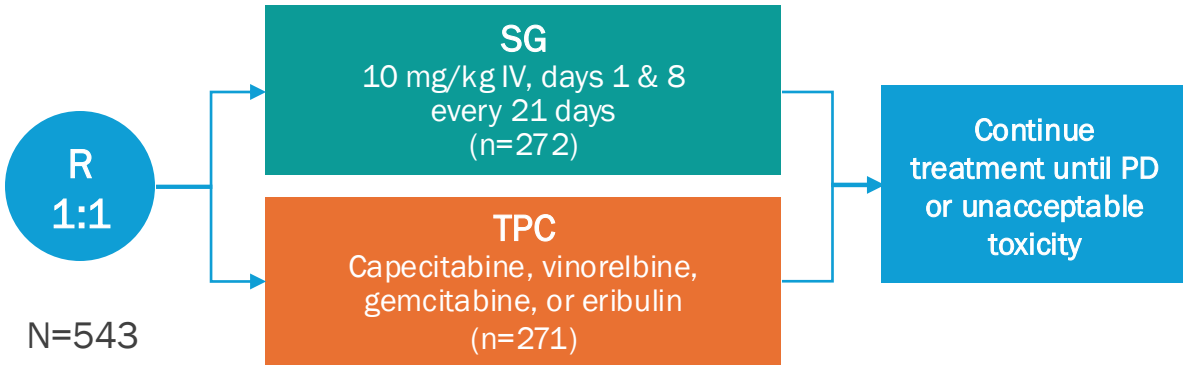
Rugo H, et al. *J Clin Oncol*. 2022;40:3365-3376.

TROPiCS-02: Phase 3 Trial of SG vs TPC in HR+/HER2– MBC

Includes HER2-low

Key Eligibility Criteria

- HR+/HER2– (HER2 IHC0, IHC1+, or IHC2+/ISH–) locally recurrent inoperable or MBC with PD after:
  - ≥1 ET, taxane, and CDK4/6i in any setting
  - ≥2 to ≤4 lines of CT for metastatic disease
  - Measurable disease by RECIST v1:1



Primary endpoint

- PFS by BICR

Secondary endpoints

- OS, ORR, DOR, CBR by LIR and BICR, PRO, safety

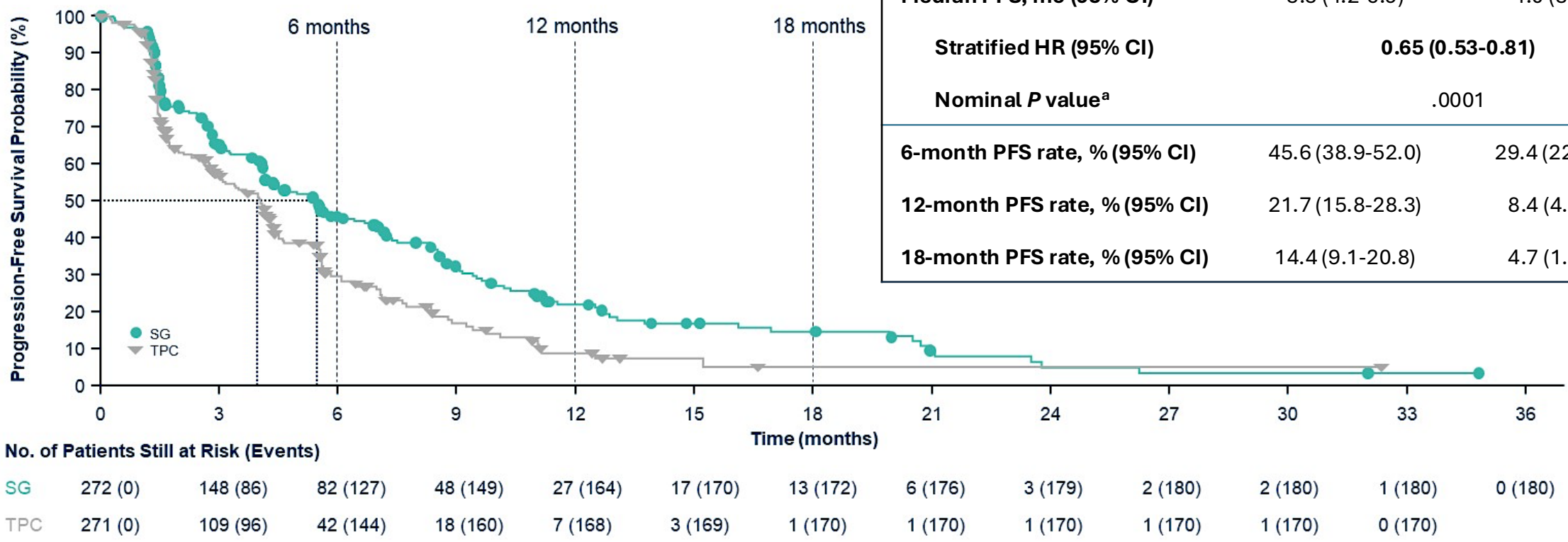
Patient Characteristics		SG (n=272)	TPC (n=271)
Median age (range), years		57 (29-86)	55 (27-78)
ECOG PS, n (%)	0	116 (43)	126 (46)
	1	156 (57)	145 (54)
Visceral mets at baseline, n (%)		259 (95)	258 (95)
Liver mets,[a] n (%)		229 (84)	237 (87)
Median time from initial MBC diagnosis to randomization (range), months		48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior CT in (neo)adjuvant setting, n (%)		173 (64)	184 (68)
Prior ET use in the metastatic setting ≥6 months, n (%)		235 (86)	234 (86)
Prior CDK4/6i, n (%)	≤12 months	161 (59)	166 (61)
	>12 months	106 (39)	102 (38)
	Unknown	5 (2)	3 (1)
Median prior CT regimens in the metastatic setting (range), n[b]		3 (0-8)[b]	3 (1-5)[b]

[a] Presence of baseline target/nontarget liver lesion per RECIST v1.1 by local investigator review. [b] The reported number of prior therapies was miscounted at screening for some patients. Nine patients had fewer or more prior CT regimens in the metastatic setting than the specified inclusion criteria and were included in the ITT population.

Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376.

PRIMARY ENDPOINT(S)

TROPiCS-02: Progression-Free Survival



BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65 (0.53-0.81)**	
Nominal *P* value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

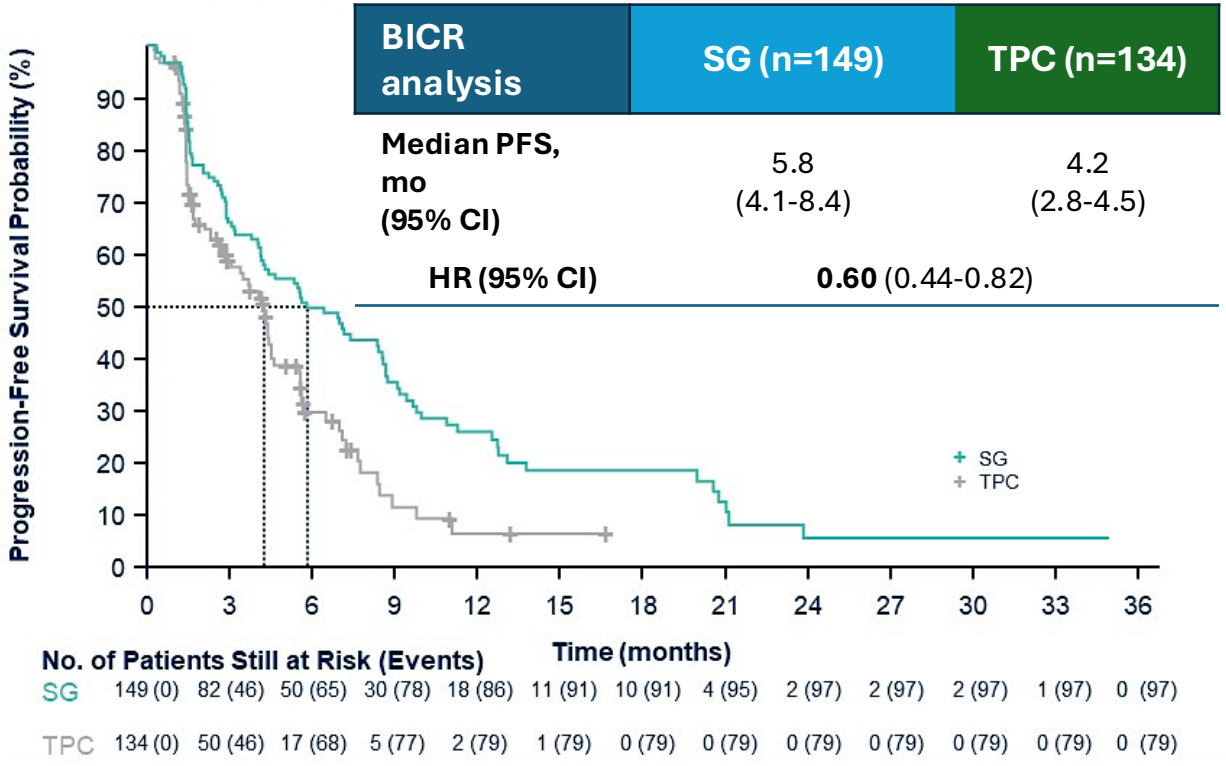
BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free-survival; SG, sacituzumab govitecan; TPC, physician's choice of chemotherapy.

Tolaney SM, et al. ASCO 2023; Presentation 1003.

PRIMARY ENDPOINT(S)

TROPiCS-02: Progression-Free Survival by HER2 Status

HER2-Low (IHC1+, IHC2+/ISH-)

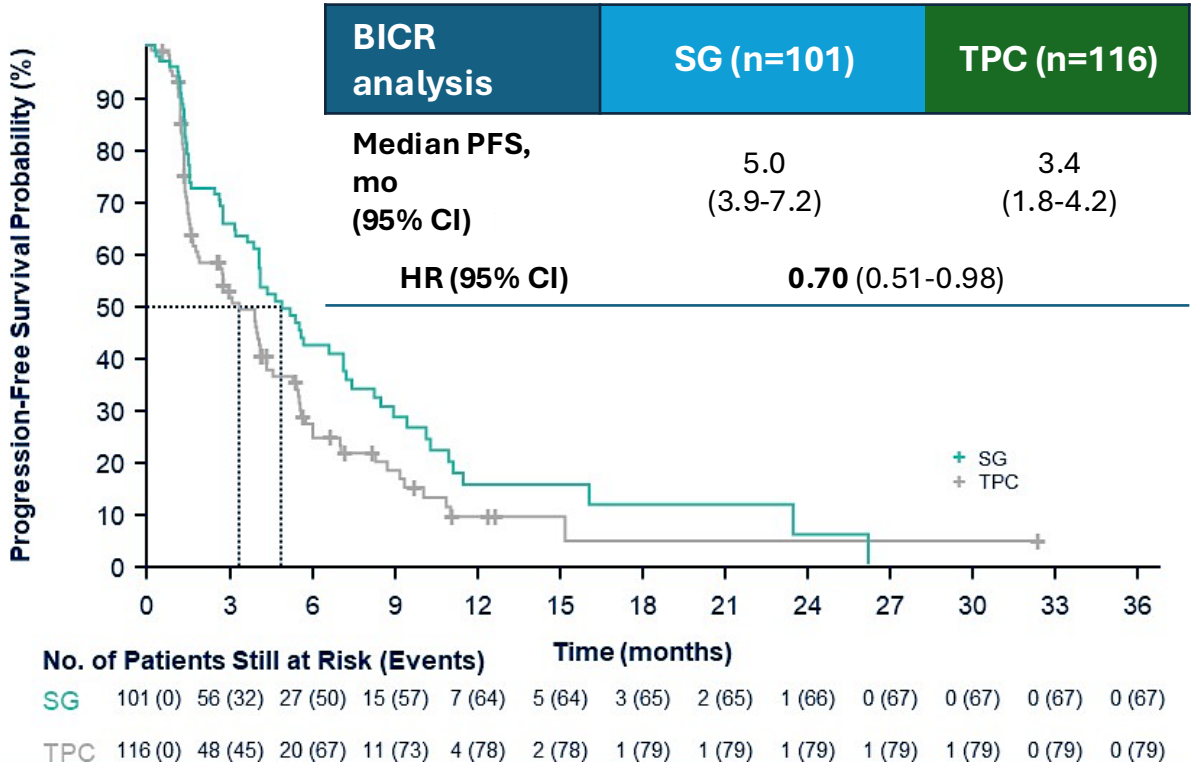


BICR analysis	SG (n=149)	TPC (n=134)
Median PFS, mo (95% CI)	5.8 (4.1-8.4)	4.2 (2.8-4.5)
HR (95% CI)	**0.60** (0.44-0.82)	

No. of Patients Still at Risk (Events)

SG	149 (0)	82 (46)	50 (65)	30 (78)	18 (86)	11 (91)	10 (91)	4 (95)	2 (97)	2 (97)	2 (97)	1 (97)	0 (97)
TPC	134 (0)	50 (46)	17 (68)	5 (77)	2 (79)	1 (79)	0 (79)	0 (79)	0 (79)	0 (79)	0 (79)	0 (79)	0 (79)

HER2 IHC0



BICR analysis	SG (n=101)	TPC (n=116)
Median PFS, mo (95% CI)	5.0 (3.9-7.2)	3.4 (1.8-4.2)
HR (95% CI)	**0.70** (0.51-0.98)	

No. of Patients Still at Risk (Events)

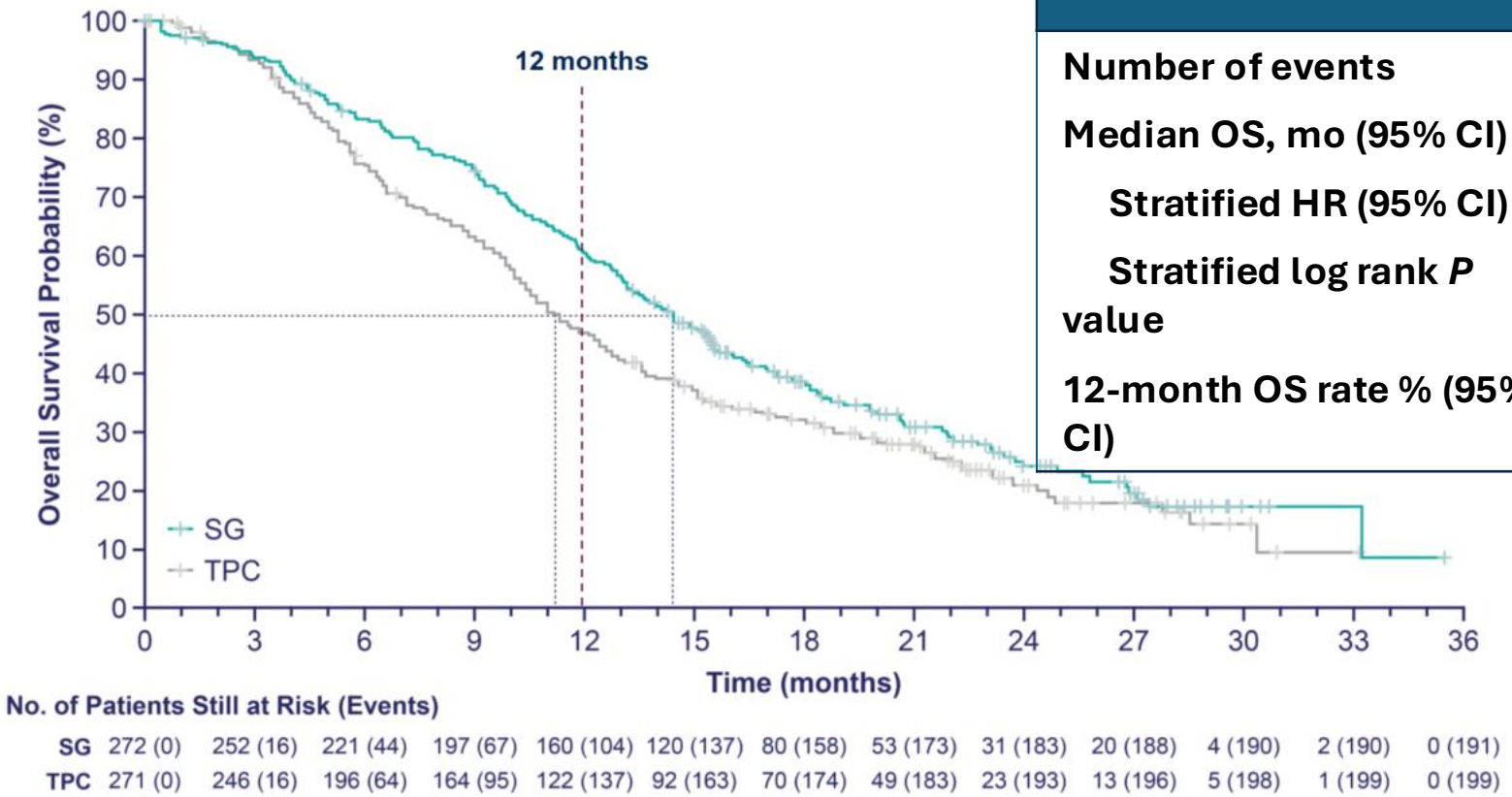
SG	101 (0)	56 (32)	27 (50)	15 (57)	7 (64)	5 (64)	3 (65)	2 (65)	1 (66)	0 (67)	0 (67)	0 (67)	0 (67)
TPC	116 (0)	48 (45)	20 (67)	11 (73)	4 (78)	2 (78)	1 (79)	1 (79)	1 (79)	1 (79)	1 (79)	0 (79)	0 (79)

BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free-survival; SG, sacituzumab govitecan; TPC, physician's choice of chemotherapy.

Tolaney SM, et al. ASCO 2023; Presentation 1003.

SECONDARY ENDPOINT(S)

TROPiCS-02: Overall Survival



	SG (n=272)	TPC (n=271)
Number of events	191	199
Median OS, mo (95% CI)	14.4 (13.0-15.7)	11.2 (10.1-12.7)
Stratified HR (95% CI)	**0.79** (0.65-0.96)	
Stratified log rank *P* value	.020	
12-month OS rate % (95% CI)	61 (55-66)	47 (41-53)

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, physician's choice of chemotherapy.

Rugo HS, et al. *Lancet*. 2023;402:1423-1433.

SAFETY

TROPiCS-02: Safety

Treatment-related AE[a]	SG (n=268)		Chemotherapy (n=249)	
	All grades	Grade ≥3	All grades	Grade ≥3
Hematologic, n (%)				
Neutropenia[b]	188 (70)	136 (51)	134 (54)	94 (38)
Anemia[c]	91 (34)	17 (6)	62 (25)	8 (3)
Leukopenia[d]	37 (14)	23 (9)	23 (9)	13 (5)
Lymphopenia[e]	31 (12)	10 (4)	25 (10)	8 (3)
Febrile neutropenia	14 (5)	14 (5)	11 (4)	11 (4)
Gastrointestinal, n (%)				
Diarrhea	152 (57)	25 (9)	41 (16)	3 (1)
Nausea	148 (55)	3 (1)	77 (31)	7 (3)
Vomiting	50 (19)	1 (<1)	30 (12)	4 (2)
Constipation	49 (18)	0	36 (14)	0
Abdominal pain	34 (13)	2 (1)	17 (7)	0
Others, n (%)				
Alopecia	123 (46)	0	41 (16)	0
Fatigue	100 (37)	15 (6)	73 (29)	6 (2)
Asthenia	53 (20)	5 (2)	37 (15)	2 (1)
Decreased appetite	41 (15)	1 (<1)	34 (14)	1 (<1)
Neuropathy[f]	23 (9)	3 (1)	38 (15)	6 (2)

[a] Patients may report more than one event per preferred term. AEs were coded using Medical Dictionary for Regulatory Activitiesv24.0, and AE severity was graded per NCI CTCAE v5.0. [b] Combined preferred terms of neutropenia and neutrophil count decreased. [c] Combined preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased. [d] Combined preferred terms of leukopenia and WBC count decreased. [e] Combined preferred terms of lymphopenia and lymphocyte count decreased. [f] Combined preferred terms of gait disturbance, hypoesthesia, muscular weakness, neuropathy peripheral, paresthesia, and peripheral sensory neuropathy.

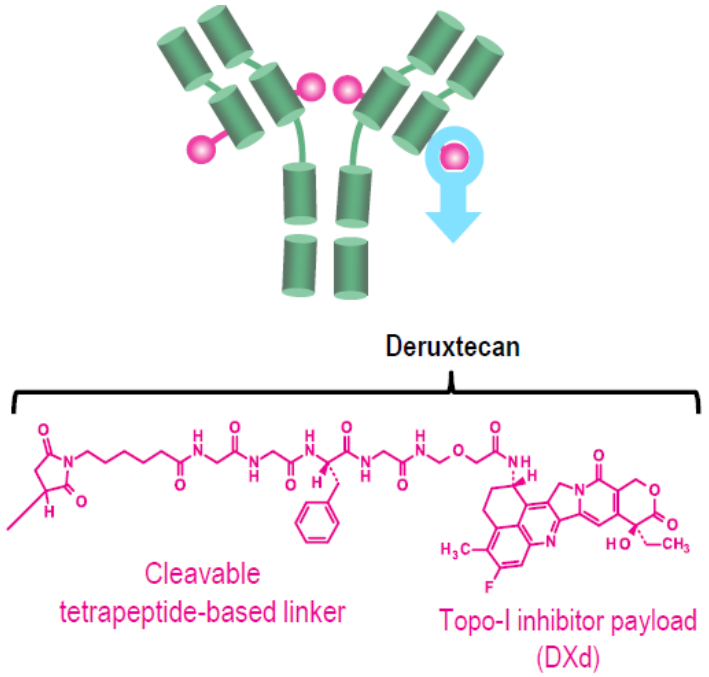
AE, adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; WBC, white blood cell.

Rugo HS, et al. *J Clin Oncol*. 2022;40:3365-3376.

Trop2 Directed ADC: Datopotomab deruxtecan

Dato-DXd: Anti-TROP2 IgG1 Monoclonal Antibody

- Dato-DXd is a TROP2-directed ADC, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells, and has several unique properties[a]:
  - Optimized drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumor-selective cleavable linker
  - Bystander antitumor effect



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

ADC, antibody drug conjugate; Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; Topo-I, topoisomerase I; TROP-2, trophoblast cell surface antigen-2.

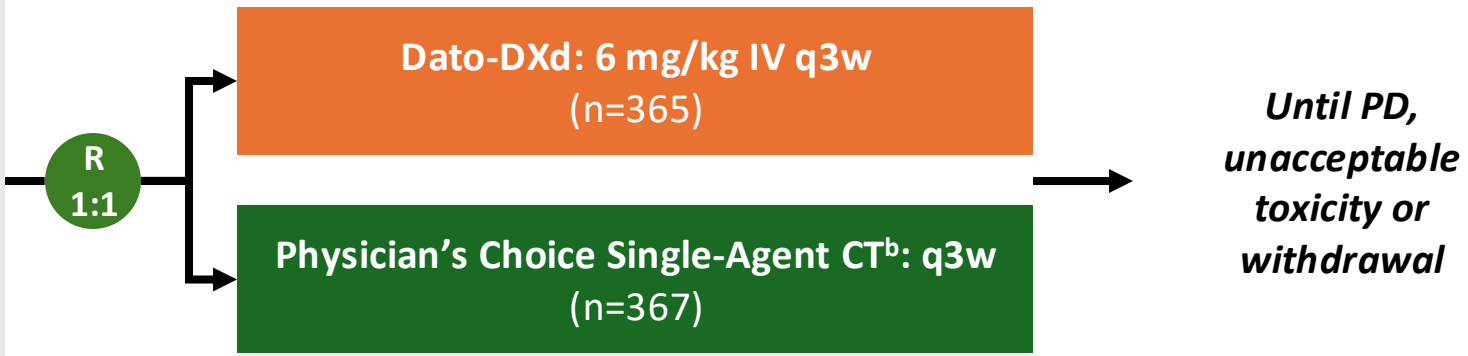
Bardia A, et al. ESMO 2023. Presentation LBA11.

STUDY DESIGN

TROPION-Breast01: Phase 3[1,2]

N=732

- Patients with unresectable or metastatic HR+/HER2- (IHC 0/1+/2+; ISH-) BC
- Previous treatment with 1-2 lines of CT[a]
- Progressive disease on endocrine therapy or unsuitable for endocrine therapy
- ECOG performance status 0/1



Stratified by lines of CT[a] (1 vs 2), geographic location (US/Canada/Europe vs rest of world), Prior CDK4/6 inhibitor (yes vs no)

- **Dual primary endpoints:** PFS (by BICR) per RECIST v1.1, OS
- **Secondary endpoints:** ORR, PFS (by investigator), DOR, DCR, safety

[a] In inoperable/metastatic setting.[1] [b] CT options: eribulin mesylate 1.4 mg/m^2 IV Days 1, 8; capecitabine 1000 mg/m^2 or 1250 mg/m^2 po bid Days 1-14; vinorelbine 25 mg/m^2 IV Days 1, 8; or gemcitabine 1000 mg/m^2 IV Days [1]

BC, breast cancer; BICR, blinded independent central review; CDK, cyclin-dependent kinase; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Bardia A, et al. ESMO 2023. Presentation LBA11. 2. Bardia A, et al. *Future Oncol*. 2024;20:423-436.

BASELINE CHARACTERISTICS

TROPION-Breast01: Patient Characteristics

Characteristic[1,2]	Dato-DXd (n=365)	ICC (n=367)
Age, median (range), years	56 (29-86)	54 (28-86)
Female, n (%)	360 (99)	363 (99)
Race, Black or African American / Asian / White / Other,[a] %	1 / 40 / 49 / 10	2 / 41 / 46 / 10
Ethnicity, Hispanic or Latino / Not Hispanic or Latino,[b] %	11 / 88	12 / 87
Prior lines of chemotherapy,[c] 1 / 2, %	63 / 37	61 / 38
Prior CDK4/6 inhibitor, n (%)	299 (82)	286 (78)
Prior taxane and/or anthracycline, n (%)	330 (90)	339 (92)
No prior taxane nor anthracycline, n (%)	35 (10)	28 (8)

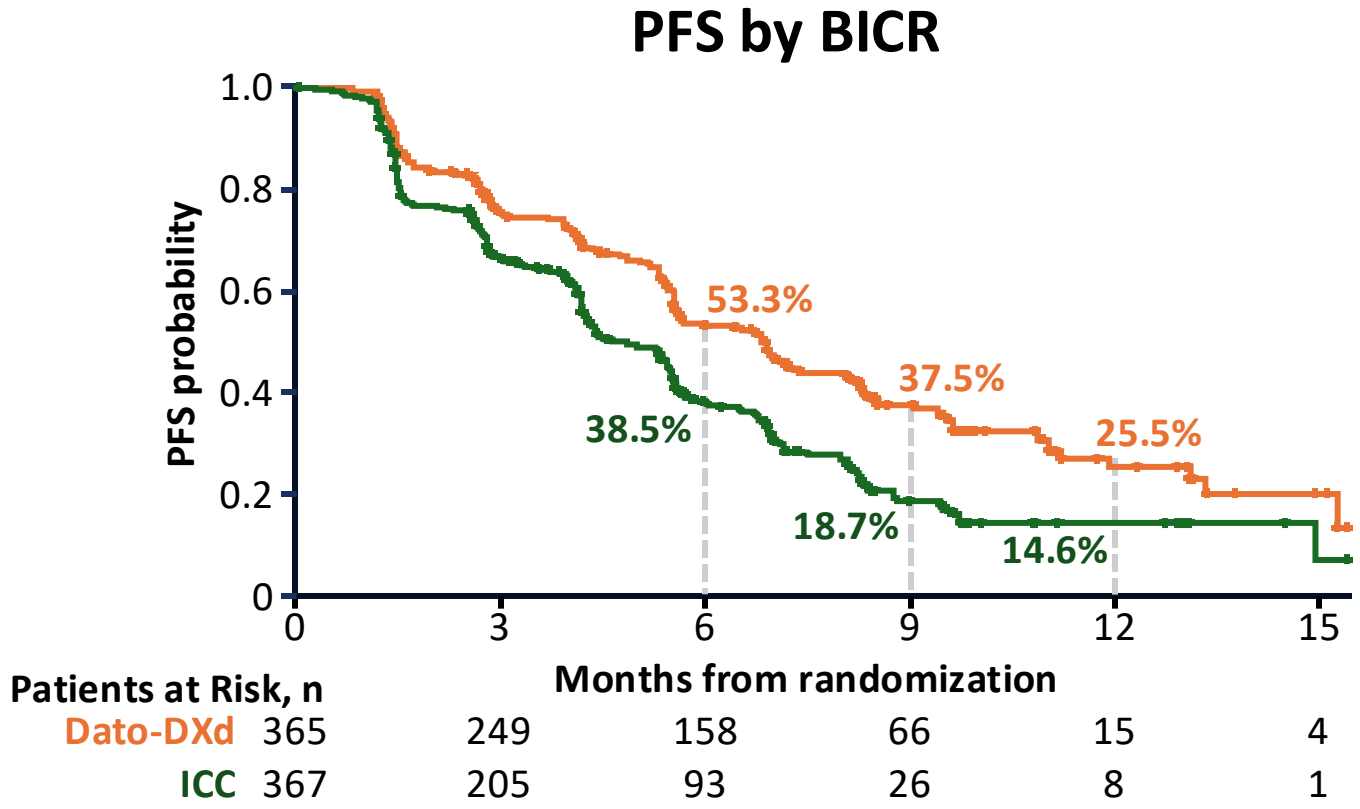
[a] Including not reported. [b] Ethnicity missing: 3 patients in Dato-DXd group; 6 patients in ICC group. [c] In the inoperable/metastatic setting; one patient in the Dato-DXd group had 3 prior lines of chemotherapy; one patient in the ICC group had 4 prior lines.

CDK, cyclin-dependent kinase; Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice of chemotherapy.

Bardia A, et al. ESMO 2023. Presentation LBA11.

PRIMARY ENDPOINT(S)

TROPION-Breast01: Progression-Free Survival by BICR (Updated)



	Dato-DXd (n=365)	ICC (n=367)
mPFS, mo (95% CI)	**6.9** (5.7-7.4)	**4.9** (4.2-5.5)
HR (95% CI)	**0.63 (0.52-0.76)**	
P value	*P*< .0001	

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

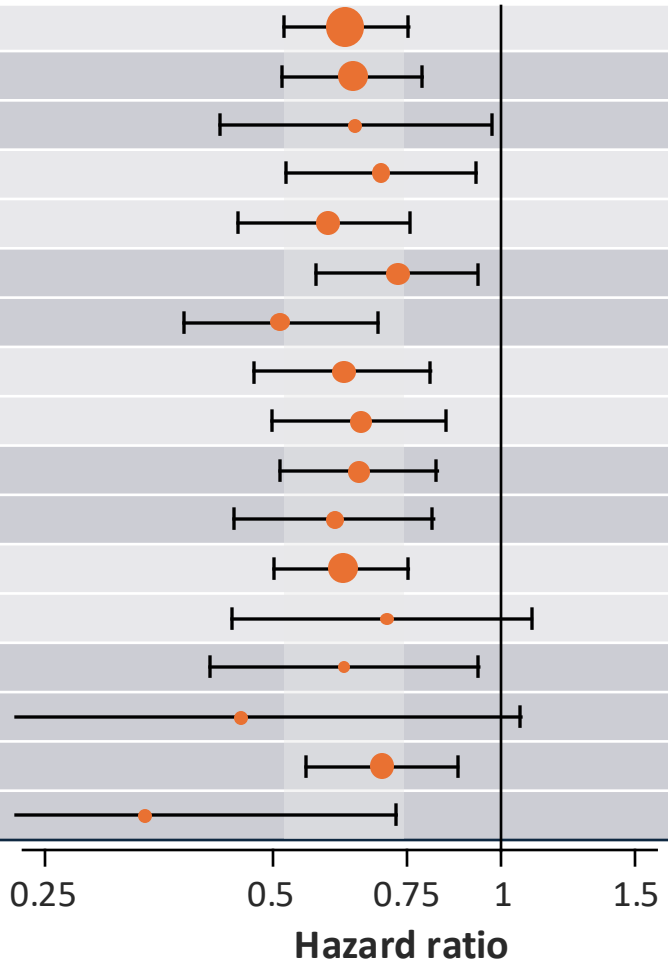
BICR, blinded independent central review; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ICC, investigator's choice of chemotherapy; mPFS, median progression-free survival; PFS, progression-free survival.

Bardia A, et al. ESMO 2023. Presentation LBA11.

PRIMARY ENDPOINT(S)

TROPION-Breast01: Progression-Free Subgroups

		Events/n		Hazard ratio
		Dato-DXd	ICC	
All patients		212/365	235/367	0.63
Age at randomization	<65 years	163/274	190/295	0.64
	≥65 years	49/91	45/72	0.65
Race	Asian	88/146	101/152	0.70
	Non-Asian	109/187	119/183	0.59
ECOG performance status	0	119/197	136/220	0.73
	1	91/165	98/145	0.52
Geographic region	US, Canada, Europe	110/186	112/182	0.62
	Rest of world[a]	102/179	123/185	0.66
Number of previous lines of chemotherapy	1	128/229	145/225	0.65
	2	84/135	90/141	0.60
Prior use of CDK4/6 inhibitor	Yes	177/299	190/286	0.62
	No	35/66	45/81	0.70
Prior use of taxane and/or anthracycline	Taxane alone	48/80	47/71	0.62
	Anthracycline alone	9/14	16/21	0.46
	Both taxane and anthracycline	141/236	155/247	0.70
	Neither taxane nor anthracycline	14/35	17/28	0.34



Size of circle is proportional to the number of events across both treatment groups.

[a] Three patients from Canada were incorrectly stratified to Rest of World.

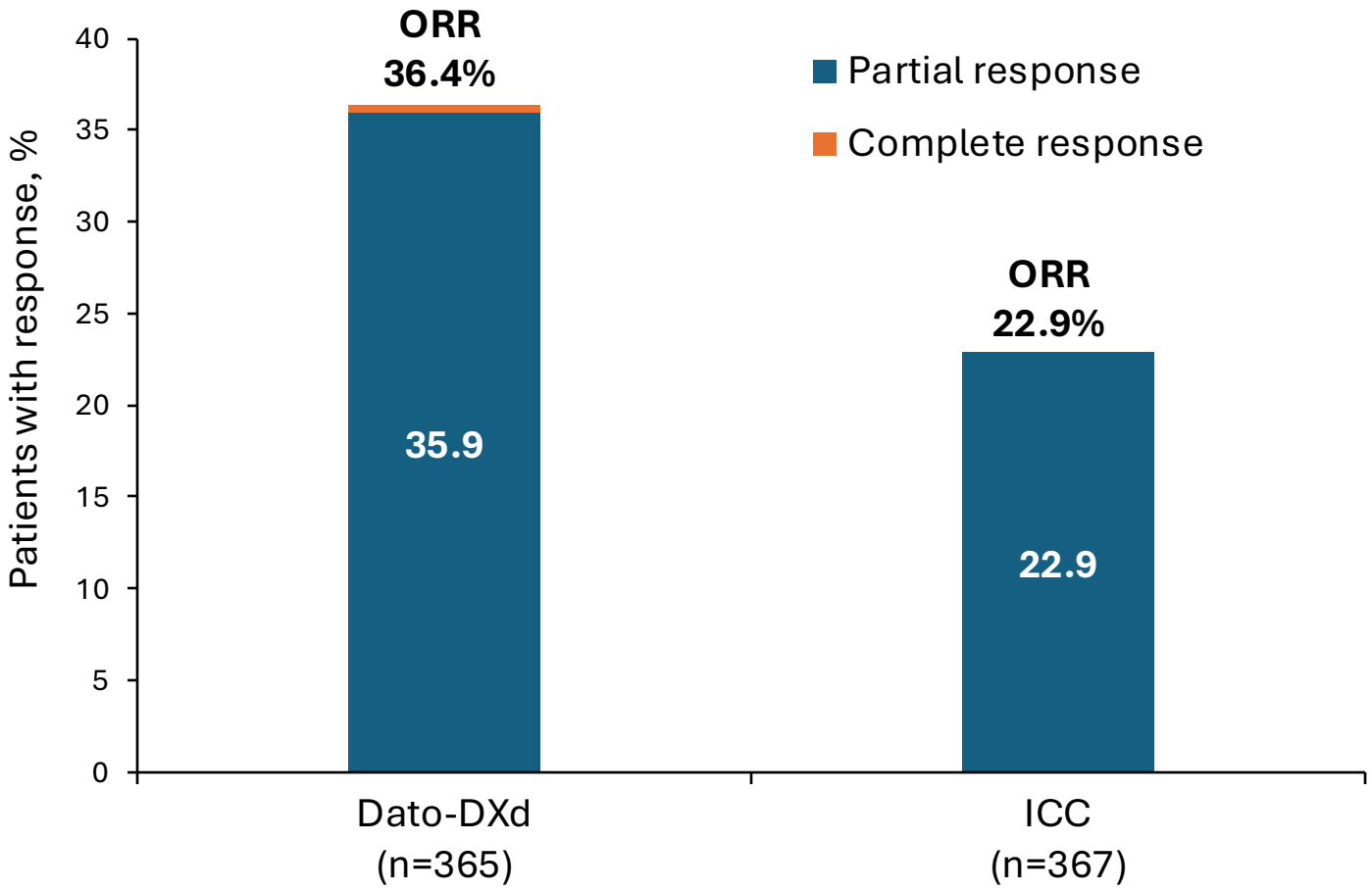
CDK, cyclin-dependent kinase; Dato-DXd, datopotamab deruxtecan; ECOG, Eastern Cooperative Oncology Group; ICC, investigator's choice of chemotherapy.

Bardia A, et al. ESMO 2023. Presentation LBA11.

PRIMARY ENDPOINT(S)

TROPION-Breast01: Response Rate and OS

Confirmed objective response rate[1]



OS[2]

	Dato-DXd (n=365)	ICC (n=367)
Number of events (%)	223 (61)	213 (58)
mOS, months (95% CI)	**18.6** (17.3-20.1)	**18.3** (17.3-20.5)
HR (95% CI)	**1.01 (0.83-1.22)**	
P value	NS	

Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ICC, investigator's choice of chemotherapy; NS, not statistically significant; ORR, objective response rate; OS, overall survival.

1. Bardia A, et al. ESMO 2023. Presentation LBA11. 2. Datroway. Prescribing information. Daiichi Sankyo, Inc.; 2025.

SAFETY

TROPION-Breast01: Safety

Event, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system				
Anemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

- Oral mucositis/stomatitis led to Tx discontinuation in 1 patient in the Dato-DXd group
- Ocular events were mostly dry eye; 1 patient discontinued Tx in the Dato-DXd group
- Adjudicated drug-related ILD (Dato-DXd arm only):
  - All grades: 3% (n=9)
  - Grade ≥3: 1% (n=2)

Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice chemotherapy; ILD, interstitial lung disease; Tx, treatment.

Bardia A, et al. ESMO 2023. Abstract LBA11.

Utilization of ADCs in Clinical Practice

Antibody Drug Conjugate	Current FDA Approvals in HER2 negative Metastatic Breast Cancer
Trastuzumab deruxtecan	• August 5, 2022: FDA approved trastuzumab deruxtecan (T-DXd) for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy. • January 27, 2025: FDA granted trastuzumab deruxtecan (T-DXd) approval for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer who have progressed on ≥1 endocrine-based therapies in the metastatic setting.
Sacituzumab govitecan	• February 3, 2023: FDA approved sacituzumab govitecan-hziy for patients with unresectable locally advanced or metastatic HR positive, HER2 negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.
Datopotomab deruxtecan	• January 17, 2025: FDA granted Dato-DXd approval for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Invasive Breast Cancer

SYSTEMIC THERAPY FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
See BINV-Q (1) for Considerations for Systemic Therapy.		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b] and/or IHC HER2 0+, 1+, or 2+/ISH negative[d]	Systemic chemotherapy[e] (category 1, preferred) BINV-Q (5), or fam-trastuzumab deruxtecan-nxki[e,f] (other recommended regimen)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 0+, 1+, or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[f] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan-nxki	Sacituzumab govitecan[g] (Category 1, preferred)
		Systemic chemotherapy BINV-Q (5)
		Targeted therapy BINV-Q (6) and BINV-Q (7)
		For HER2 IHC 0, 1+, or 2+/ISH negative:[d] Datopotamab deruxtecan-dlnk[h] (other recommended regimen)
Third Line and beyond	Any	Systemic chemotherapy BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents and emerging biomarker options BINV-Q (6), BINV-Q (7), and BINV-Q (8)

Sequencing of ADCs – Paucity of Data

- Is resistance driven by resistance to the antibody or to the payload
- Abelman et al, SABCS 2023: Cross-resistance to ADC2 can be driven by either antibody target or payload
- Huppert et al, SABCS 2023:
  - Efficacy outcomes were generally better for ADC1 vs ADC2, regardless of HR+ status and which ADC was used first
    - However, there was a subset of patients with more durable responses with ADC2
  - There was no significant difference in the rwPFS of ADC2 in patients who received intervening therapy between ADCs vs those who did not