Antibody Drug Conjugates: Expanding a Targeted Assault on all Breast Cancer Subtypes

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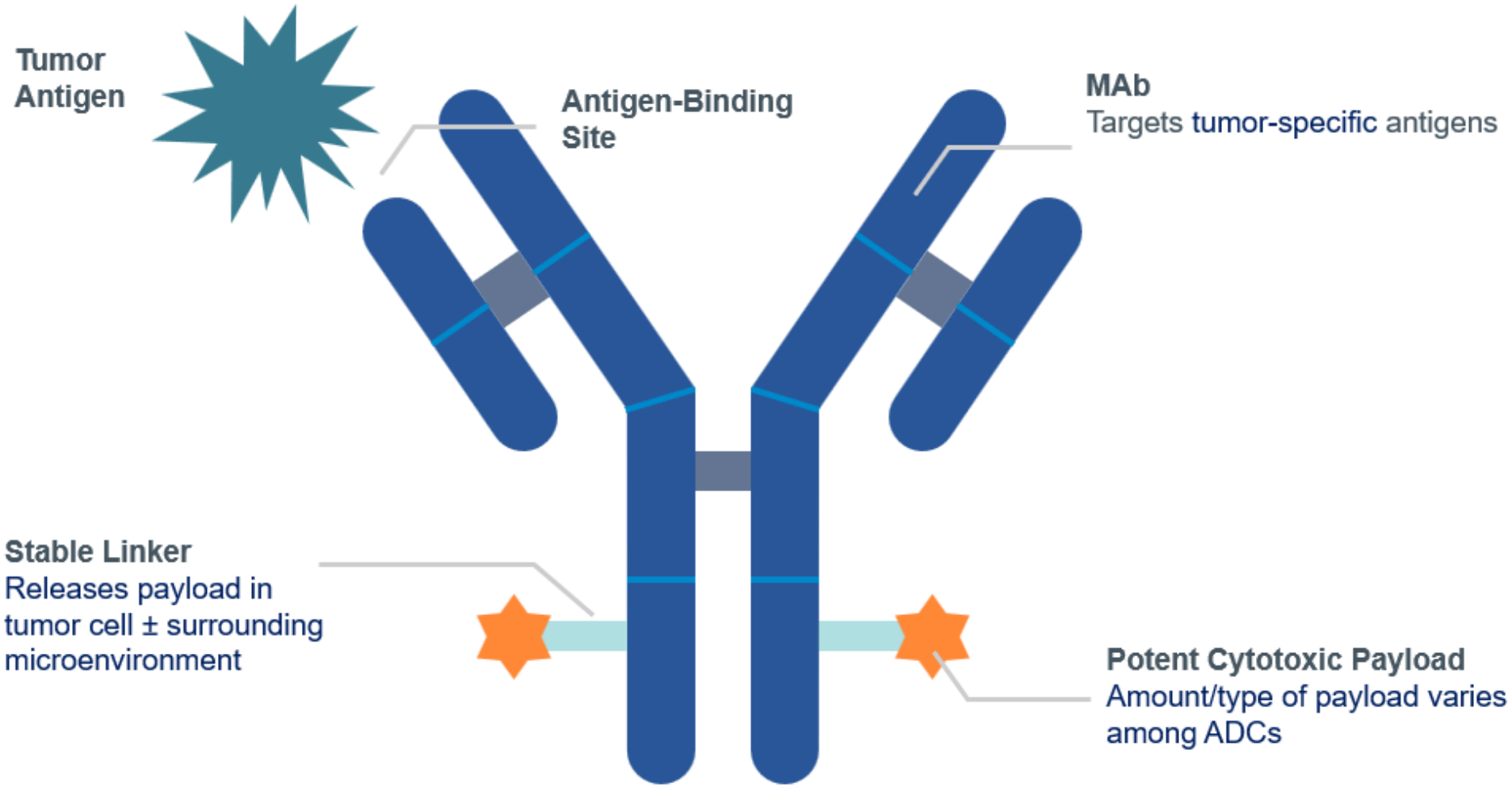
Basic Structure of Antibody–Drug Conjugate

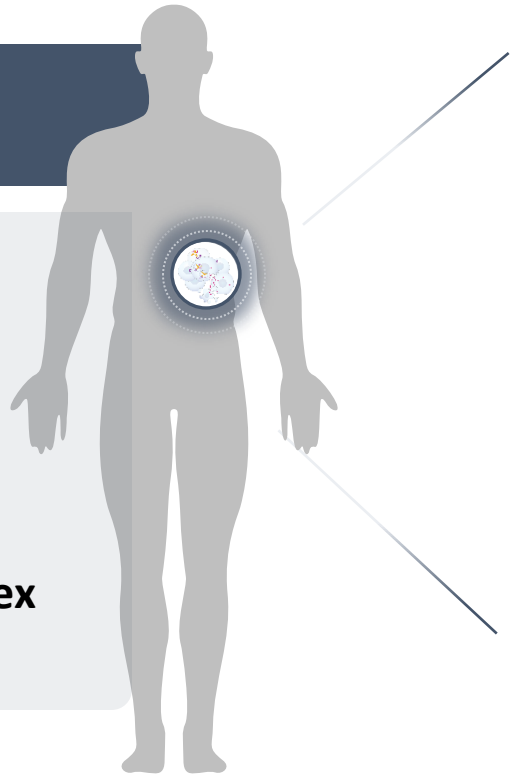


The promise of ADCs: improve the therapeutic index of systemic chemotherapy

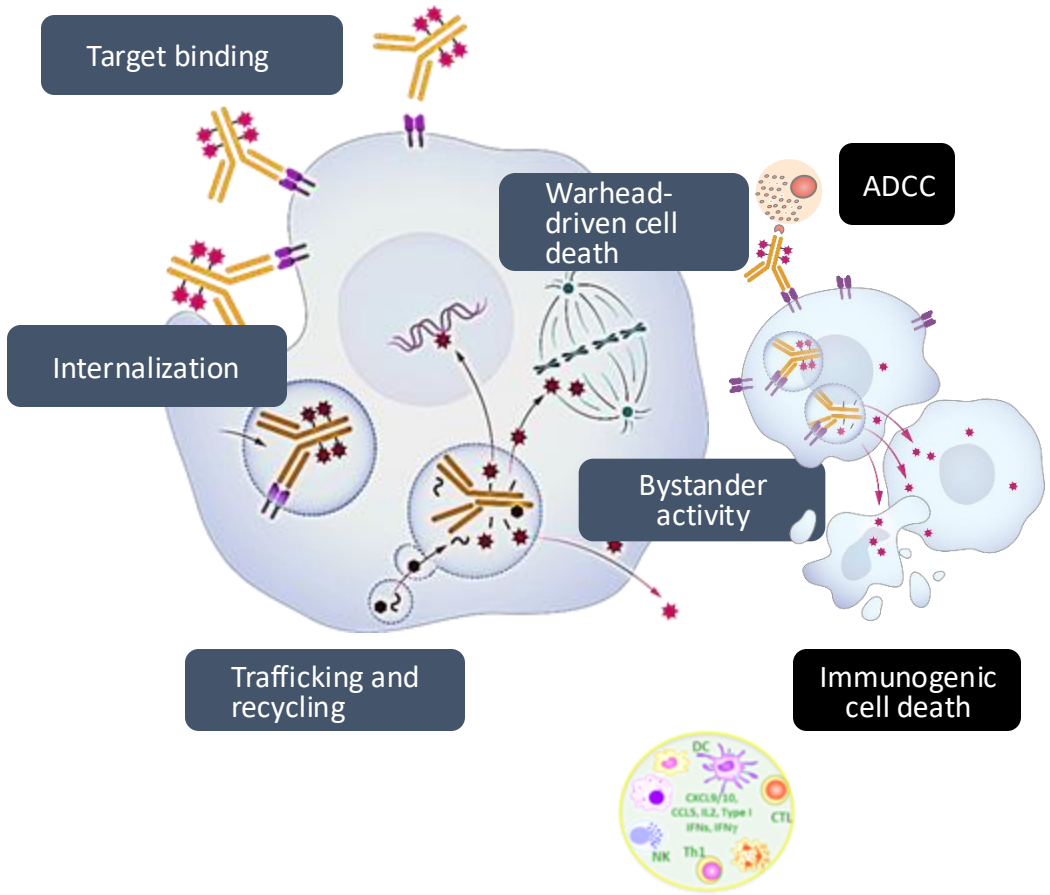
Most patients receive chemotherapy; however, significant toxicities remain.

ADCs TO REPLACE CHEMOTHERAPY

- Targeted delivery to cancer cell
- Improved efficacy
- Decreased toxicity
- Increased therapeutic index



Optimized ADC technology and biology must align to build successful ADC.



Courtesy of Reshma Mahtani, DO.

First ADCs Approved for Heme and Solid Tumors

2000: 1st FDA Approved ADC

Gemtuzumab ozogamicin* for CD33+ AML CD33 antibody ADC with calicheamicin payload

MYLOTARG™ (gemtuzumab ozogamicin) for injection, for intravenous use
Initial U.S. Approval: 2000

MYLOTARG is a CD33-directed antibody-drug conjugate indicated for:

- treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults (1.1).
- treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older (1.2).

2013: 1st FDA Approved ADC for Solid Tumors

Trastuzumab emtansine for HER2+ MBC HER2 antibody (IgG1) conjugated to DM1 via non cleavable linker

February 22, 2013 at 9:29 AM EST

WALTHAM, Mass.–(BUSINESS WIRE)– ImmunoGen, Inc. (Nasdaq: IMGN), a biotechnology company that develops anticancer therapeutics using its TAP technology, today announced that Roche has reported that the U.S. Food and Drug Administration (FDA) has granted marketing approval to Kadcyla for the treatment of people with HER2-positive metastatic breast cancer who have received prior treatment with Herceptin® (trastuzumab) and a taxane chemotherapy.

Pharmacodynamic Biomarkers for ADC Development

Solid tumors: **8 ADCs** are approved today for **15 solid tumor indications.**

Targets: HER2, TROP-2, nectin-4, tissue factor, Folate receptor α

First ADC approved for the treatment of a solid tumor.
Trastuzumab emtansine is approved for HER2+ ABC.

Trastuzumab deruxtecan is approved for HER2+ ABC.

Enfortumab vedotin is approved for mUC.

Trastuzumab emtansine approval is expanded to HER2+ EBC.

Sacituzumab govitecan is approved for pretreated mTNBC.

Cetuximab saratolacan approved for head and neck cancer by Japanese government

Trastuzumab deruxtecan is approved for mGC.

Sacituzumab govitecan is approved for mUC.

Tisotumab vedotin is approved for cervical cancer.

Distamab vedotin is approved for mGC in China.

Mirvetuximab soravtansine-gynx is approved for ovarian cancer.

Trastuzumab deruxtecan approved for HER2-low ABC and for mNSCLC with HER2-mutation.

Enfortumab vedotin + Pembrolizumab approved for mUC not eligible for cisplatin.

Sacituzumab govitecan approval expanded to HR+/HER2- ABC.

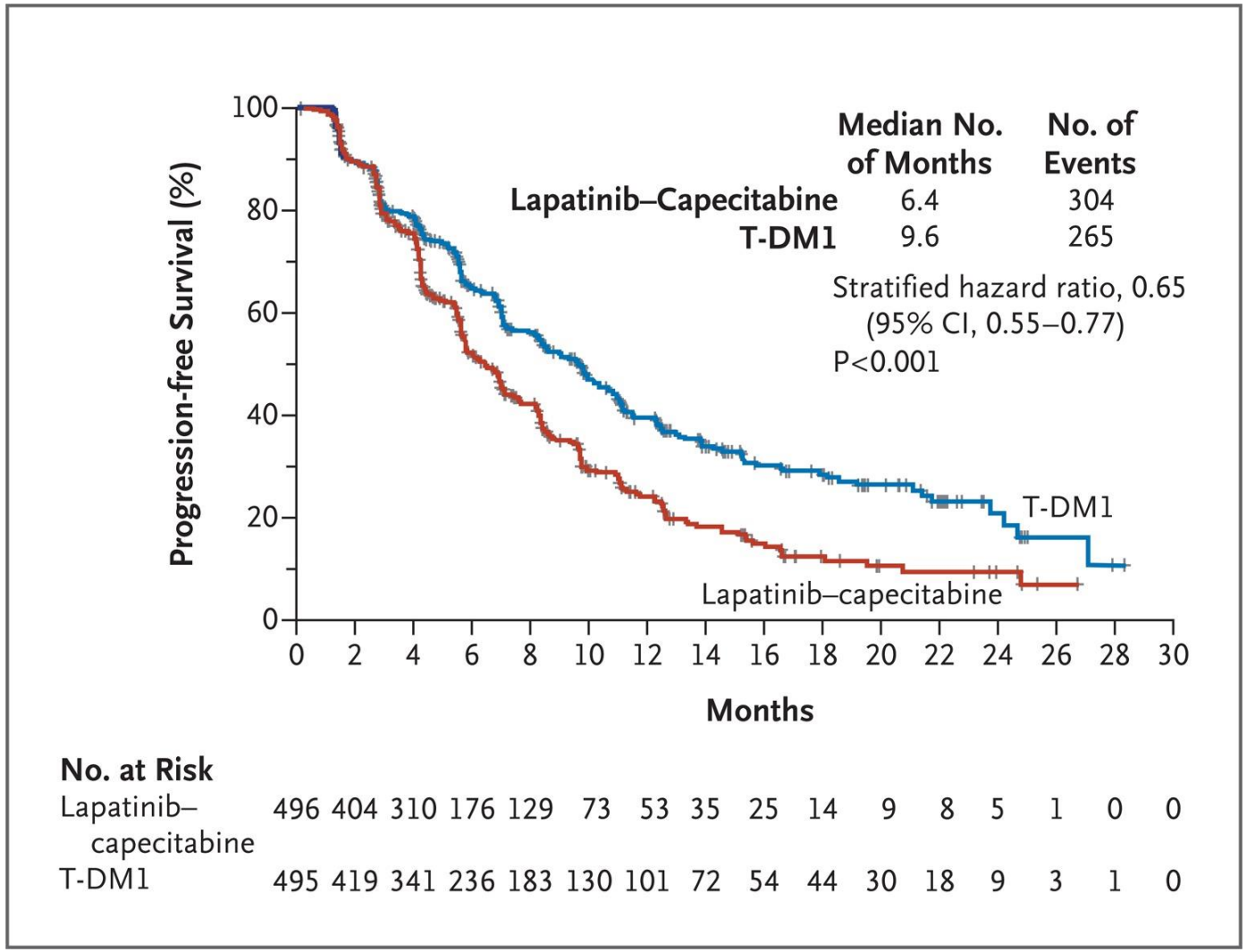
ABC = advanced breast cancer; AML = acute myeloid leukemia; EBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; mGC = metastatic gastric cancer; mTNBC = metastatic triple-negative breast cancer; mUC = metastatic urothelial cancer; R/R = relapsed and/or refractory.

Adapted from Tarantino P, et al. *CA Cancer J Clin*. 2022;72:165-182. Gogia P, et al. *Cancers (Basel)*. 2023;15:3886.

Trastuzumab Emtansine (T-DM1): Late Stage

EMILIA TRIAL

- T-DM1 was first approved in 2013, after showing to improve PFS and OS in **HER2+** breast cancer in the **EMILIA trial**
- Toxicity profile → improved compared with capecitabine and lapatinib

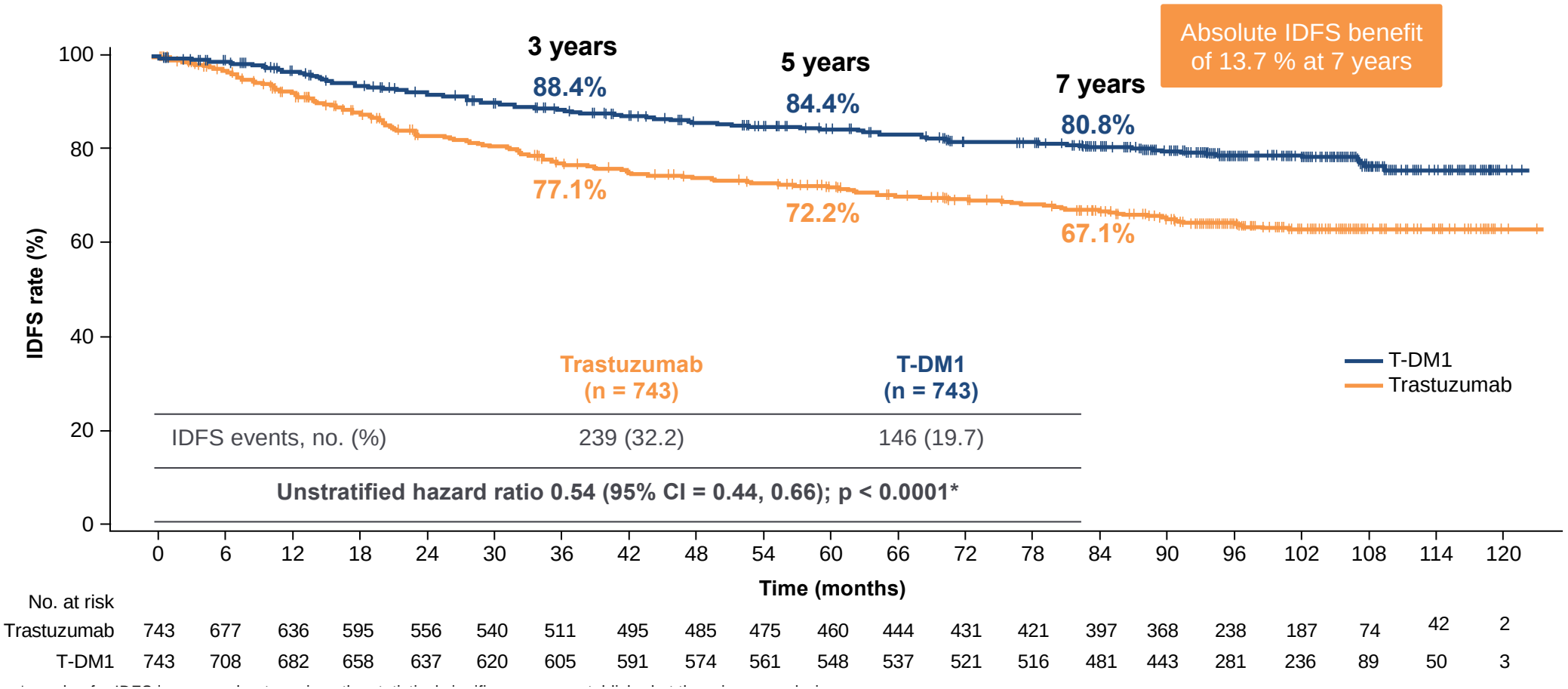


Verma S, et al. NEJM 2012

Trastuzumab Emtansine (T-DM1): Early Stage

KATHERINE TRIAL

KATHERINE IDFS final analysis; median follow-up 8.4 years

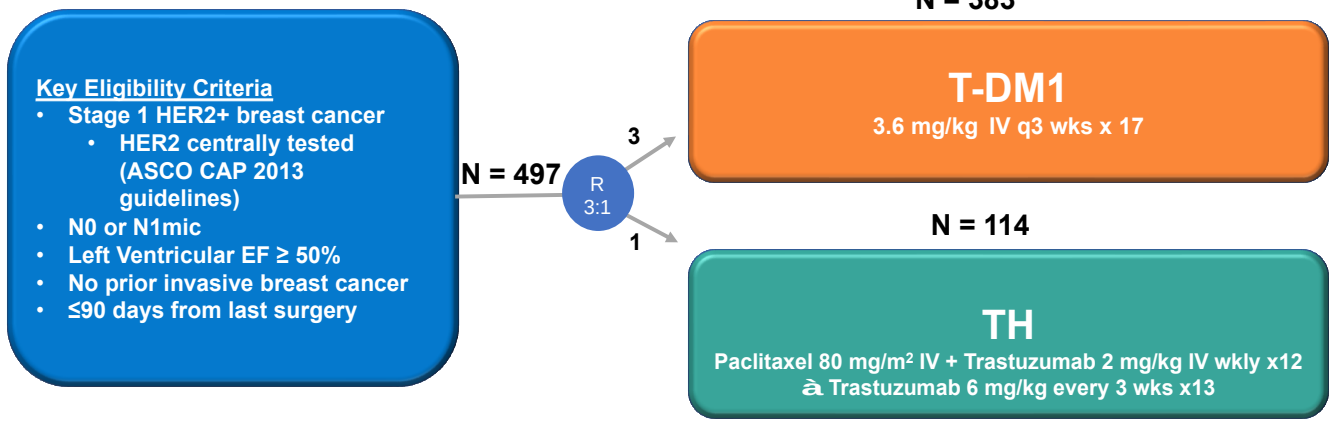


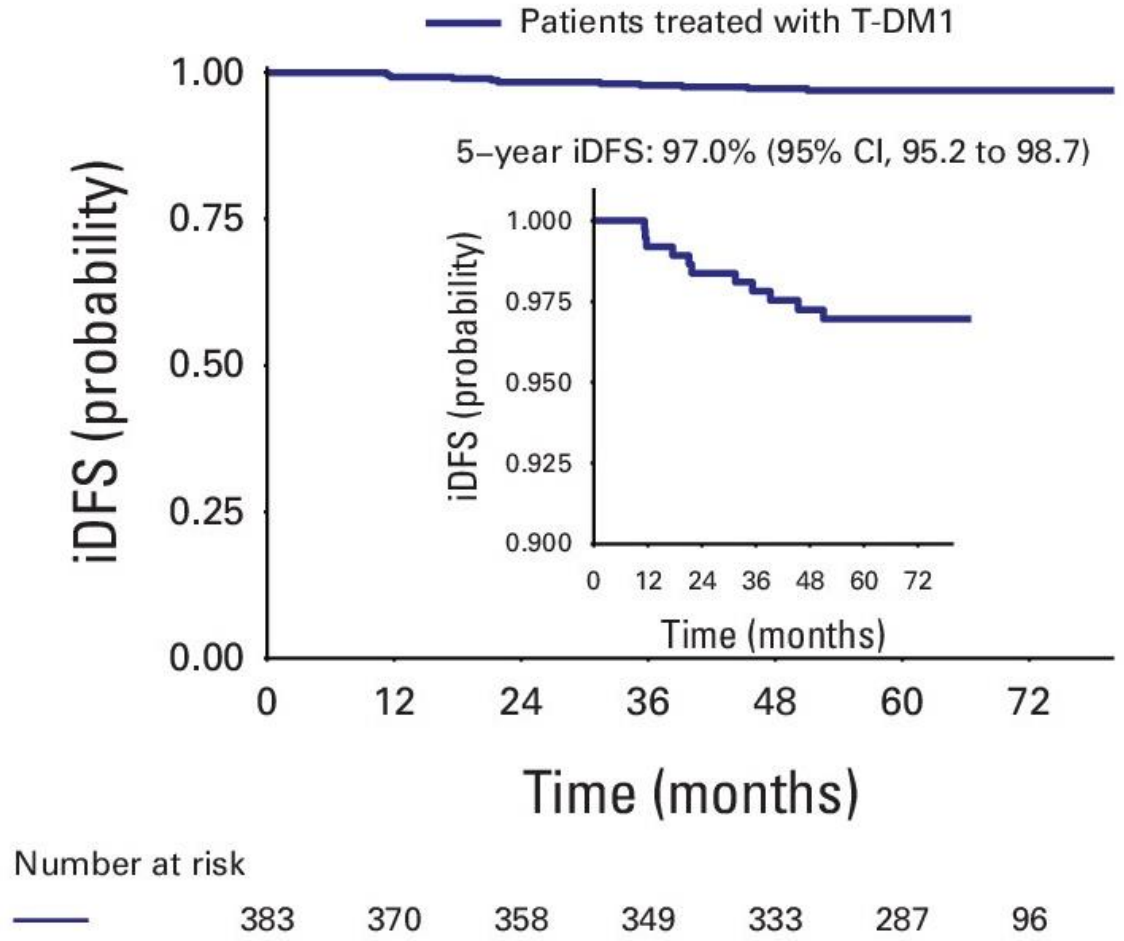
Loibyl et al SABCS 2023

Trastuzumab Emtansine (T-DM1): Early Stage

ATEMPT TRIAL

An option in the **ADJUVANT** setting for patients with stage I HER2+ breast cancer, with the ATEMPT phase 2 trial showing **outstanding 5-year iDFS (97%)** and **improved QoL** compared with TH



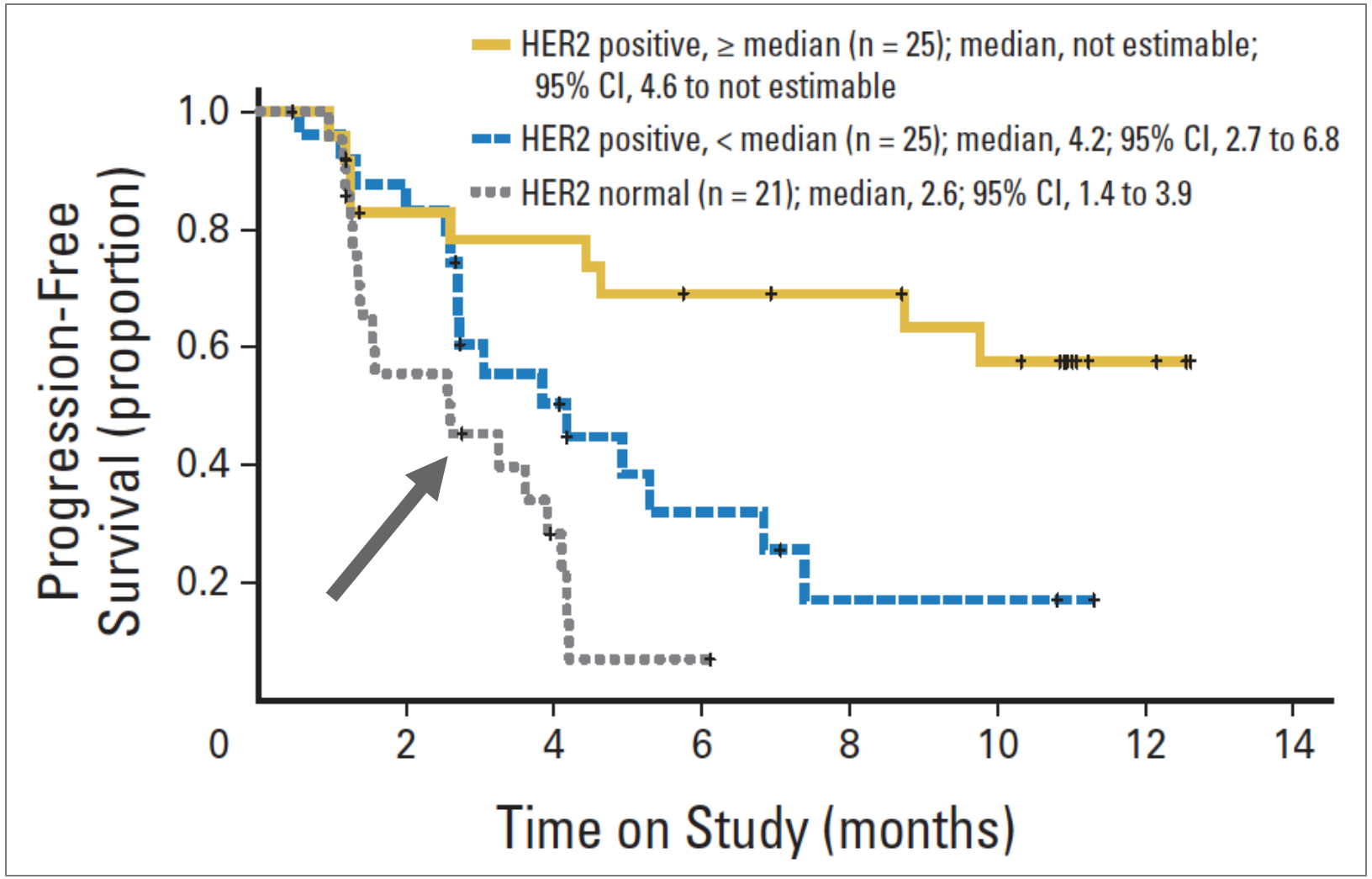


Tarantino P, et al. J Clin Onc 2024

Little activity of T-DM1 in HER2-negative breast cancer

ACTIVITY IN HER2-NEGATIVE BREAST CANCER

- Less activity of T-DM1 in **HER2-negative** breast cancer
- Among 21 HER2-negative MBC patients receiving T-DM1, **ORR was 4.8%** and the **median PFS was 2.6 months**



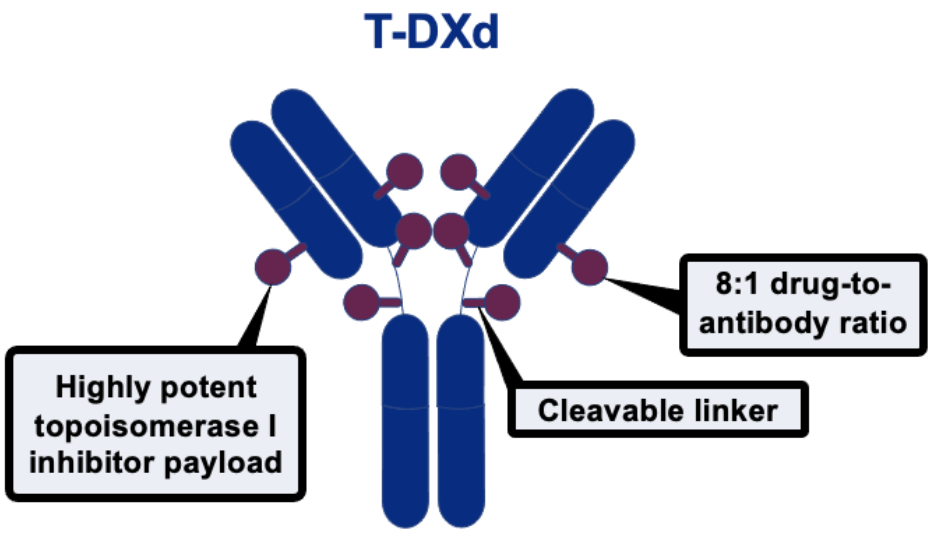
Burris HA, et al. J Clin Oncol. 2011

Evolution of ADC Technology

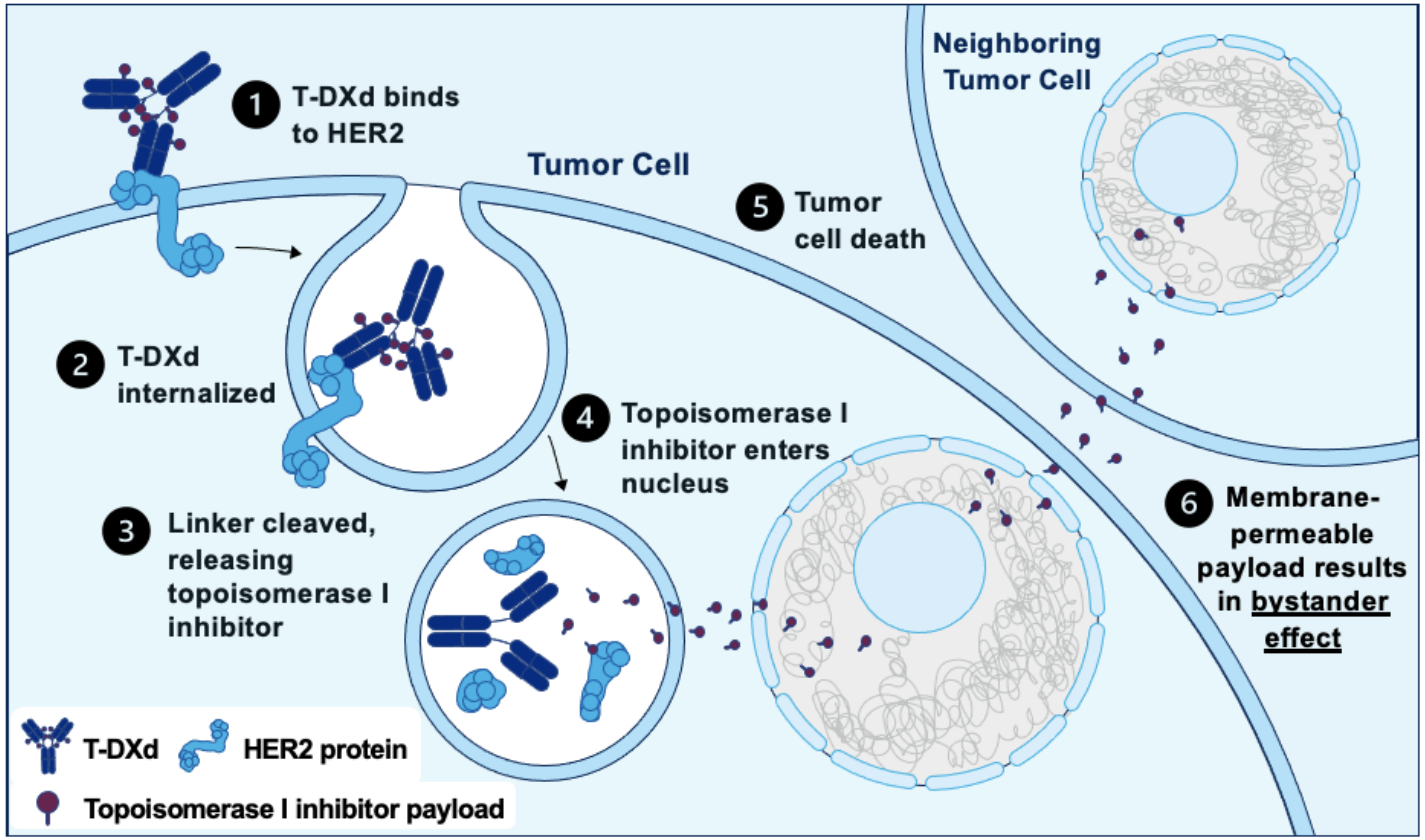
	Trastuzumab emtansine	Sacituzumab govitecan	Trastuzumab deruxtecan	Datopotamab deruxtecan
Target	HER2	TROP2	HER2	TROP2
Antibody	Trastuzumab	hRS7 IgG1κ	Humanized HER2 antibody with same sequence as trastuzumab	anti-TROP2 IgG1
DAR	~3.5:1	~7.6:1	7-8:1	4:1
Linker	Thioether	Hydrolysable	Tetrapeptide-based	Tetrapeptide-based
Cleavable Linker?	No	Yes	Yes	Yes
Payload	Emtansine	SN-38	DXd	DXd
Payload MoA	Anti-microtubule	Topoisomerase I inhibitor	**Topoisomerase I inhibitor**	**Topoisomerase I inhibitor**
Target overexpression essential for activity	Overexpression	No	Low/Ultra-Low expression	No
Approved Indication	HER2+ MBC, HER2+ EBC	**metastatic TNBC;** HR+/HER2- MBC and metastatic urothelial carcinoma	HER2+ and HR+/HER2 low MBC; HER2+ gastric cancer; HER2 mutated NSCLC, HER2-overexpressing solid tumors	Awaited

Trastuzumab Deruxtecan (T-DXd)

STRUCTURE AND MECHANISM OF ACTION



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

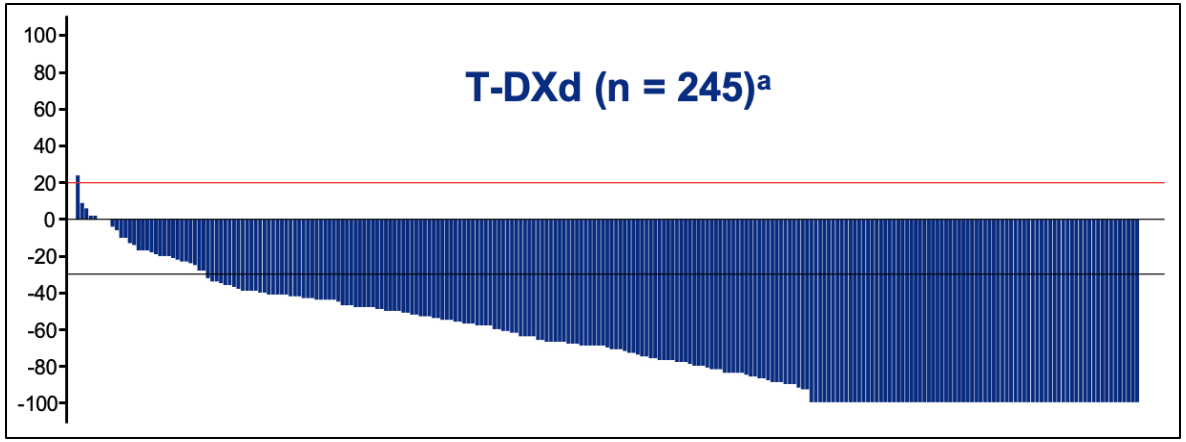


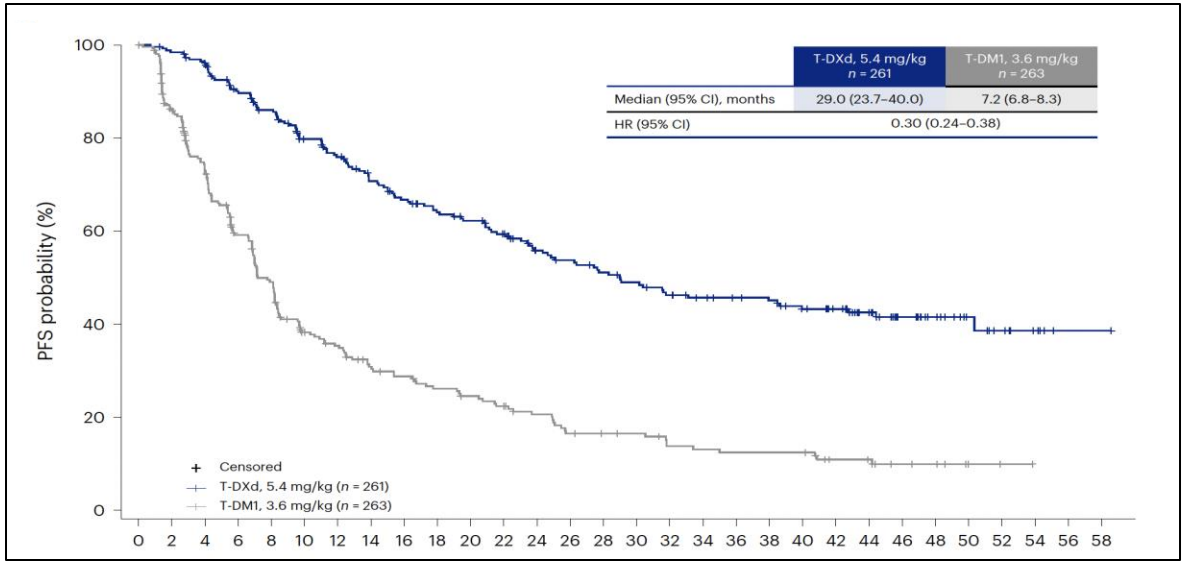
Modi S, et al. ASCO Annual Meeting 2022

T-DXd vs T-DM1 (DESTINY Breast 03 phase 3 trial)

ACTIVITY IN HER2+ BREAST CANCER – SECOND LINE

Approved for **second line** treatment of **HER2+** metastatic breast cancer, after outperforming T-DM1 in DESTINY-Breast03 phase 3 trial

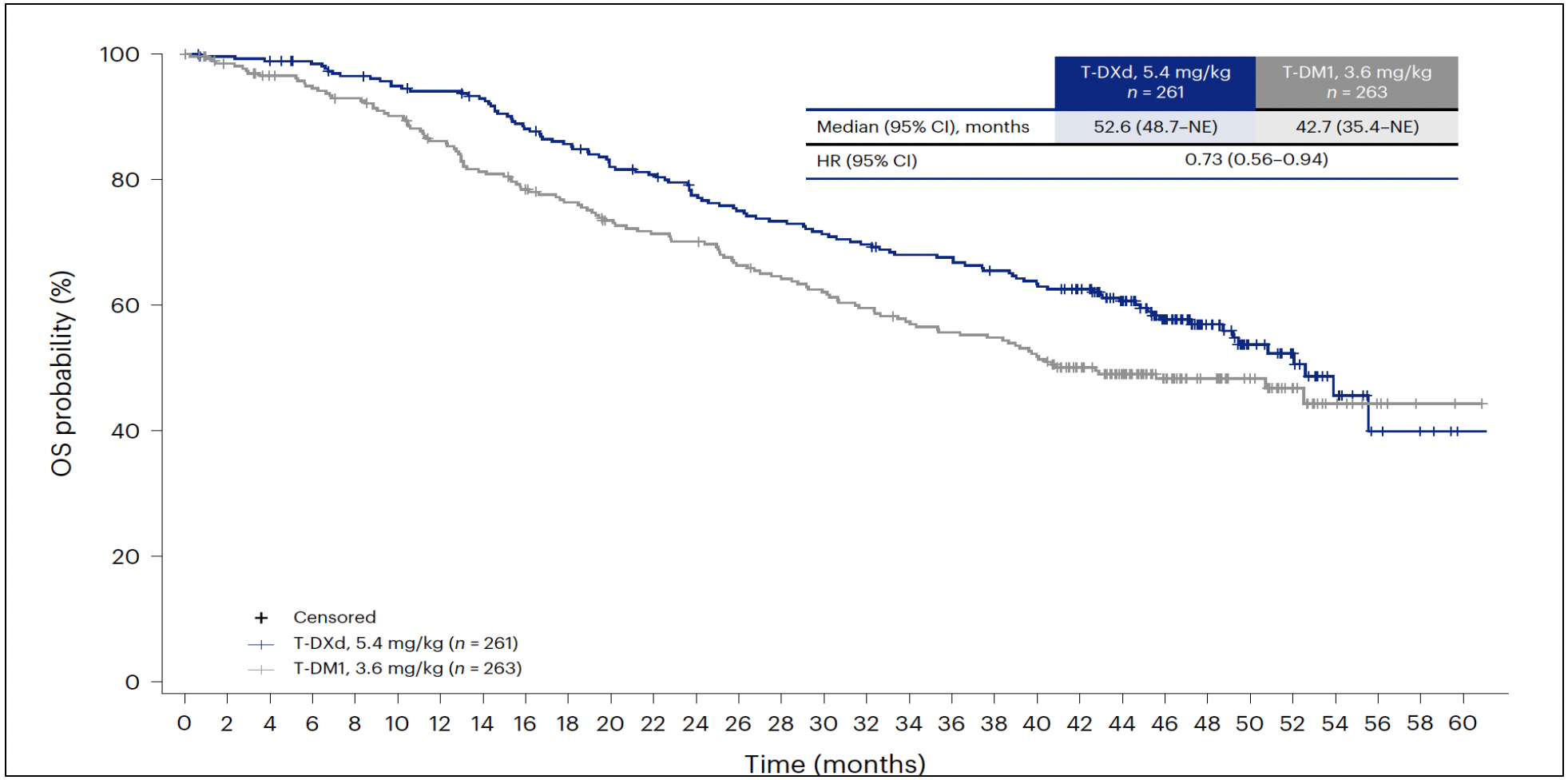




Cortes J., et al. Nature Med 2024

T-DXd vs T-DM1 (DESTINY Breast 03 phase 3 trial)

10-month improvement in OS with 2L T-DXd (vs. T-DM1) in DESTINY-Breast03

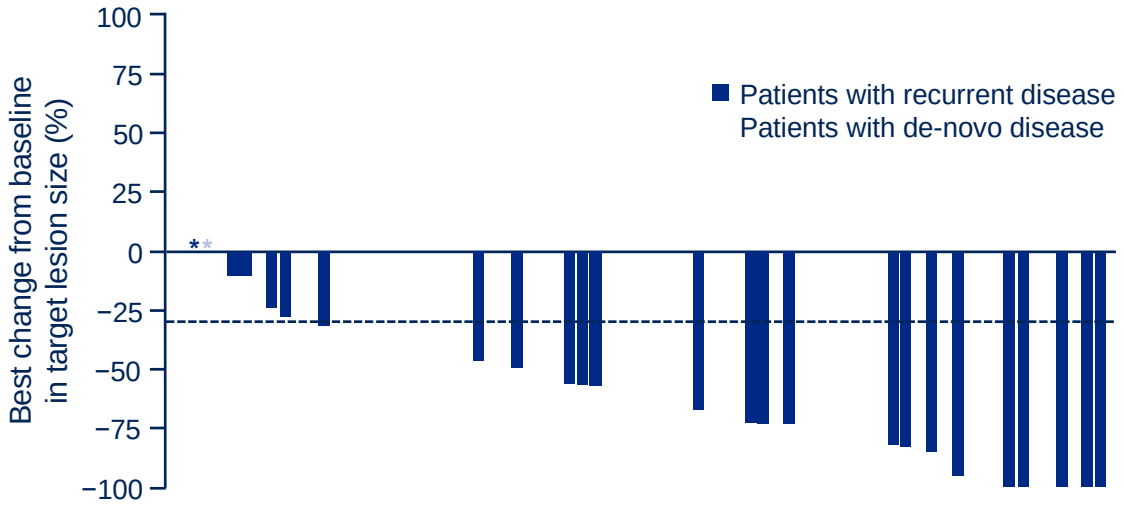


Cortes J., et al. Nature Med 2024

DESTINY-Breast07 phase 1b/2 trial

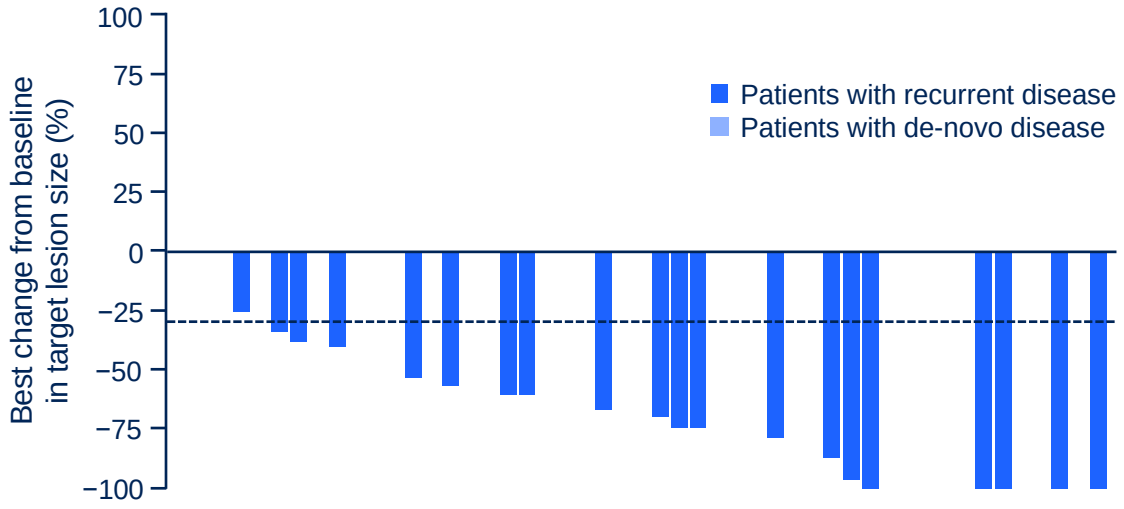
PFS at 1 year with 1L T-DXd: 89.4% with T-DXd/pertuzumab, 80.8% with T-DXd mono

T-DXd monotherapy (n=75)



Confirmed ORR, % (80% CI)	76.0 (68.5–82.4)
Complete response, n (%)	6 (8.0)
Partial response, n (%)	51 (68.0)
Median DOR, months (range)	NE (2.1–28.5)

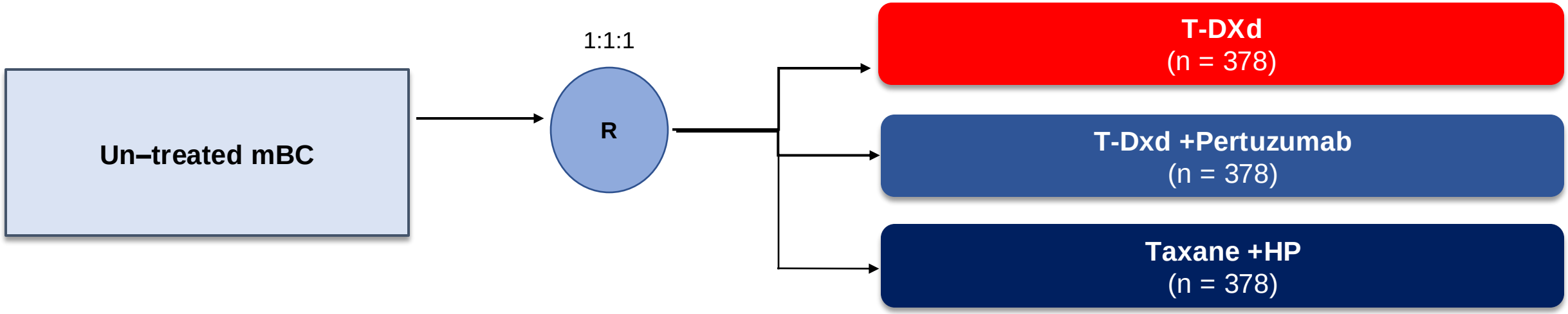
T-DXd + pertuzumab (n=50)



Confirmed ORR, % (80% CI)	84.0 (75.3–90.5)
Complete response, n (%)	10 (20.0)
Partial response, n (%)	32 (64.0)
Median DOR, months (range)	NE (4.5–28.3)

Andre' F…Jhaveri K et al. ASCO 2024

DESTINY Breast-09 Trial : 1st Line HER2+ MBC

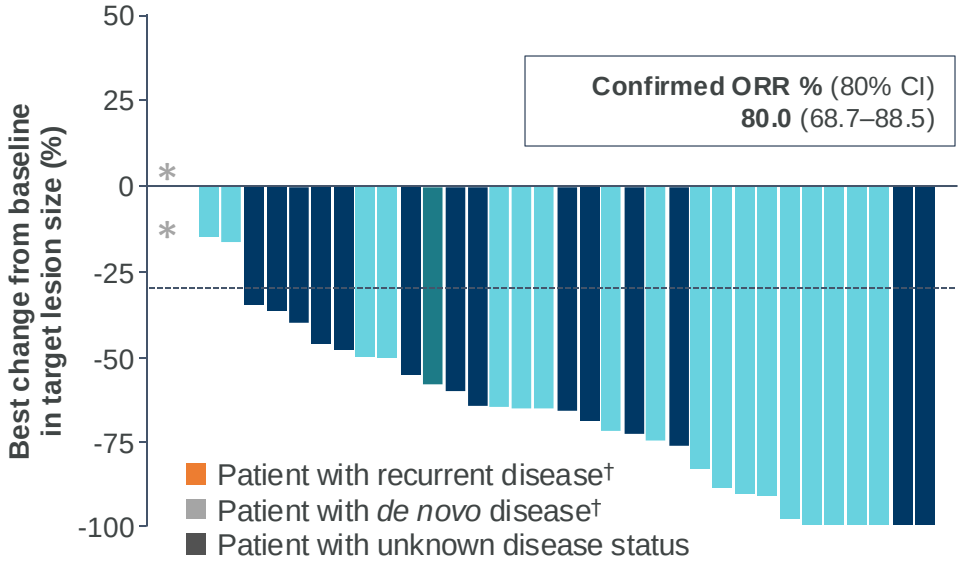


Primary endpoint: PFS

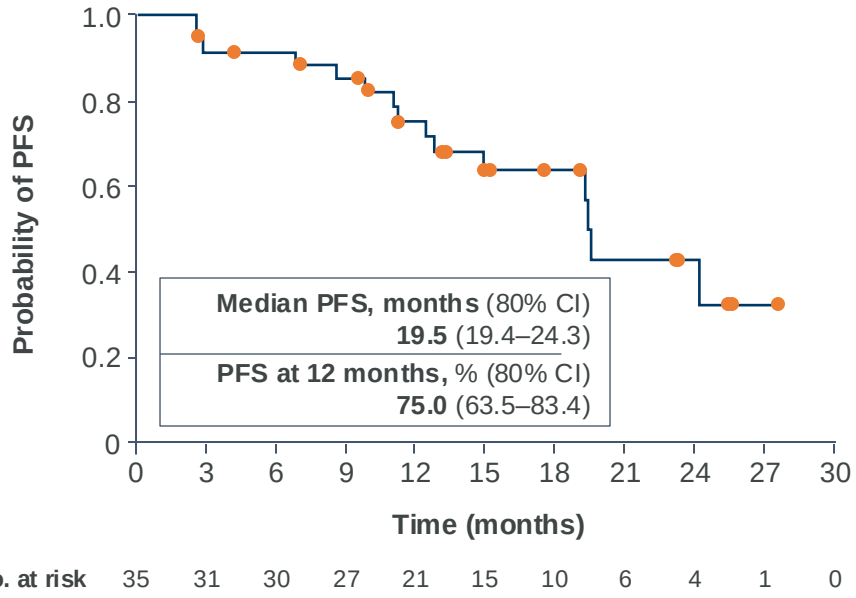
NCT04784715

Interim analysis of DESTINY-Breast07 assessed the safety, tolerability, and antitumour activity of T-DXd in patients with active BM in the 1/2L setting

Best percentage change in target lesion size with T-DXd monotherapy in patients with active BM per RECIST 1.1



PFS per RECIST 1.1



- Median DoR per RECIST 1.1 **18.1 months,** median IC DoR per RANO-BM **14.2 months**
- By RANO-BM criteria confirmed **IC ORR** was reported in **60.0%** of patients (n=21)
- **Median IC PFS** per RANO-BM criteria was **15.4 months** (80% CI, 13.6–NC)

Dashed reference line at −30% from indicates the threshold for partial response

*Patients had 0% change from baseline; †disease status at original diagnosis.

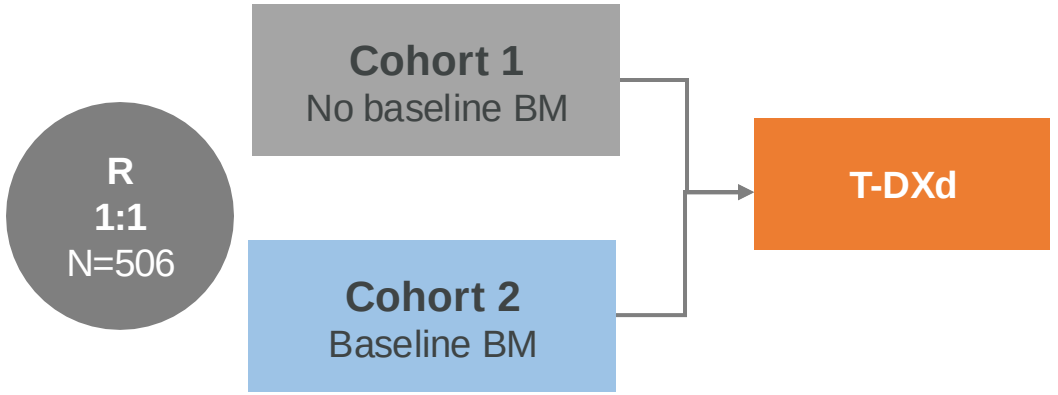
1/2L=first-/second-line; BM=brain metastases; CI=confidence interval; DoR=duration of response; IC=intracranial; NC=not calculable; ORR=objective response rate; PFS=progression-free survival; RANO-BM=Response Assessment in Neuro-oncology Brain Metastases; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; T-DXd=trastuzumab deruxtecan.

Anders C, et al. Presented at ESMO Breast 2024, May 15–17. Berlin, Germany. Poster 185P.

DESTINY-Breast12 is a Phase IIIb/IV trial investigating T-DXd in patients with HER2-positive mBC, with or without BM[1,2]

Eligibility criteria

- Unresectable/advanced or mBC
- Confirmed HER2-positive status as determined to ASCO/CAP guidelines evaluated at a local laboratory
- Patient received and progressed on trastuzumab, pertuzumab, or T-DM1. Prior treatment with tucatinib is not permitted
- No more than 2 lines/regimens of therapy in the metastatic setting
- ECOG PS 0–1
- Patients with no evidence of BM or untreated BM not needing immediate local therapy or previously treated stable or progressing BM



Primary endpoint

- ORR by RECIST 1.1 (Cohort 1)
- PFS by RECIST 1.1 (Cohort 2)

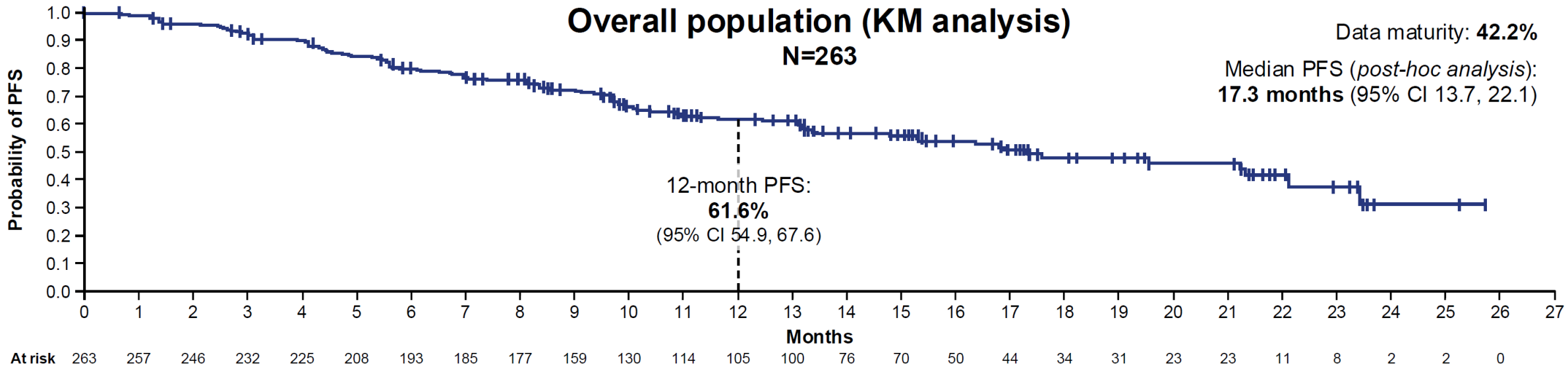
Secondary endpoints

- OS
- DoR
- Time to progression
- DoT on subsequent lines of therapy
- PFS2
- Incidence of new symptomatic CNS metastasis during treatment in patients without BM at baseline (Cohort 1)
- Site of next progression
- ORR in patients with BM at baseline (Cohort 2)
- CNS PFS in patients with BM at baseline (Cohort 2)
- Safety

BM=brain metastases; CNS=central nervous system; DoR=duration of response; DoT=duration of treatment; ECOG PS=Eastern Cooperative Oncology Group performance status; HER2=human epidermal growth factor receptor 2; mBC=metastatic breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PFS2=time to second progression or death; PFS=progression-free survival; R=randomisation; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan.

1. National Institute of Health (NIH). NCT0473961 (DESTINY-Breast12). Available at: https://clinicaltrials.gov/study/NCT04739761 (Accessed July 2024); 2. AstraZeneca. Protocol D9673C00007 Amendment 1. 02 April 2021.

DESTINY-Breast 12: Baseline BM: Primary Endpoint (PFS)

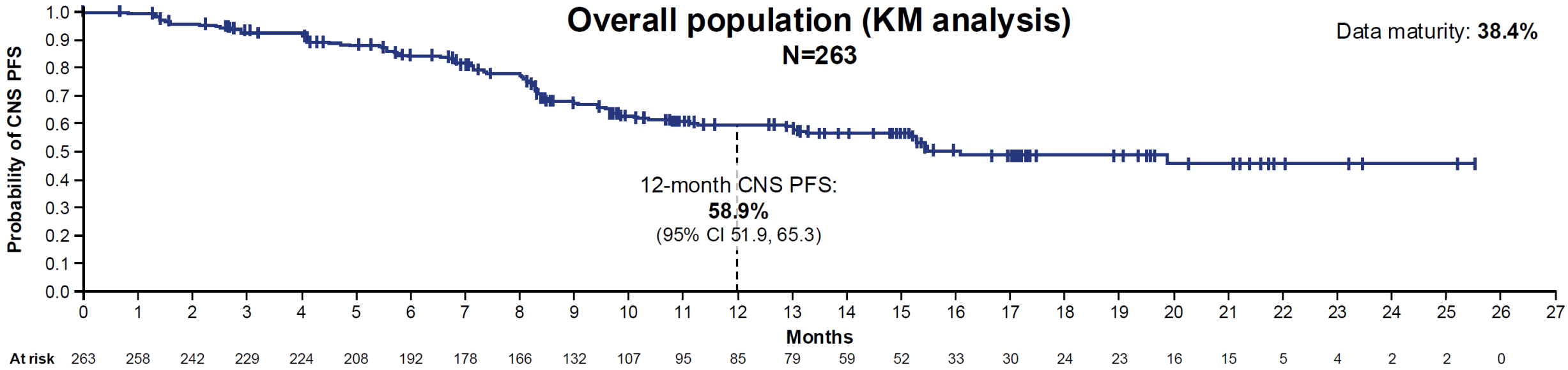


	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	Active BM subgroups: Untreated (n=39) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=67) *Post-hoc analysis*
Overall no. events	**111**	64	47	20	27
12-month PFS, % (95% CI)	**61.6 (54.9, 67.6)**	62.9 (54.0, 70.5)	59.6 (49.0, 68.7)	47.0 (29.6, 62.7)	66.7 (53.4, 76.9)

T-DXd showed consistent 12-month PFS in patients with stable and active BMs

PFS assessed by ICR per RECIST 1.1
BM, brain metastasis; CI, confidence interval; ICR, independent central review; KM, Kaplan-Meier; no., number of; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

DESTINY-Breast 12: Baseline BM: CNS PFS



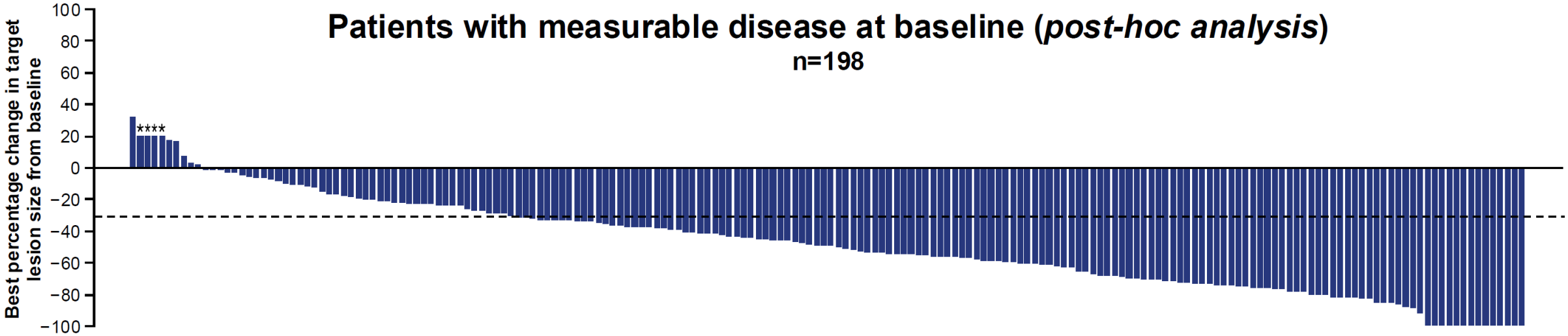
	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)
Overall no. events	**101**	61	40
12-month CNS PFS, % (95% CI)	**58.9 (51.9, 65.3)**	57.8 (48.2, 66.1)	60.1 (49.2, 69.4)

T-DXd showed consistent 12-month CNS PFS in patients with stable and active BMs

Patients who had systemic progression, but no CNS progression, were censored at the time of the progression assessment; the analysis did not account for systemic progression as a competing event. CNS PFS assessed by ICR per RECIST 1.1

BM, brain metastasis; CI, confidence interval; CNS, central nervous system; ICR, independent central review; KM, Kaplan-Meier; no., number of; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

DESTINY-Breast 12: Baseline BM: ORR

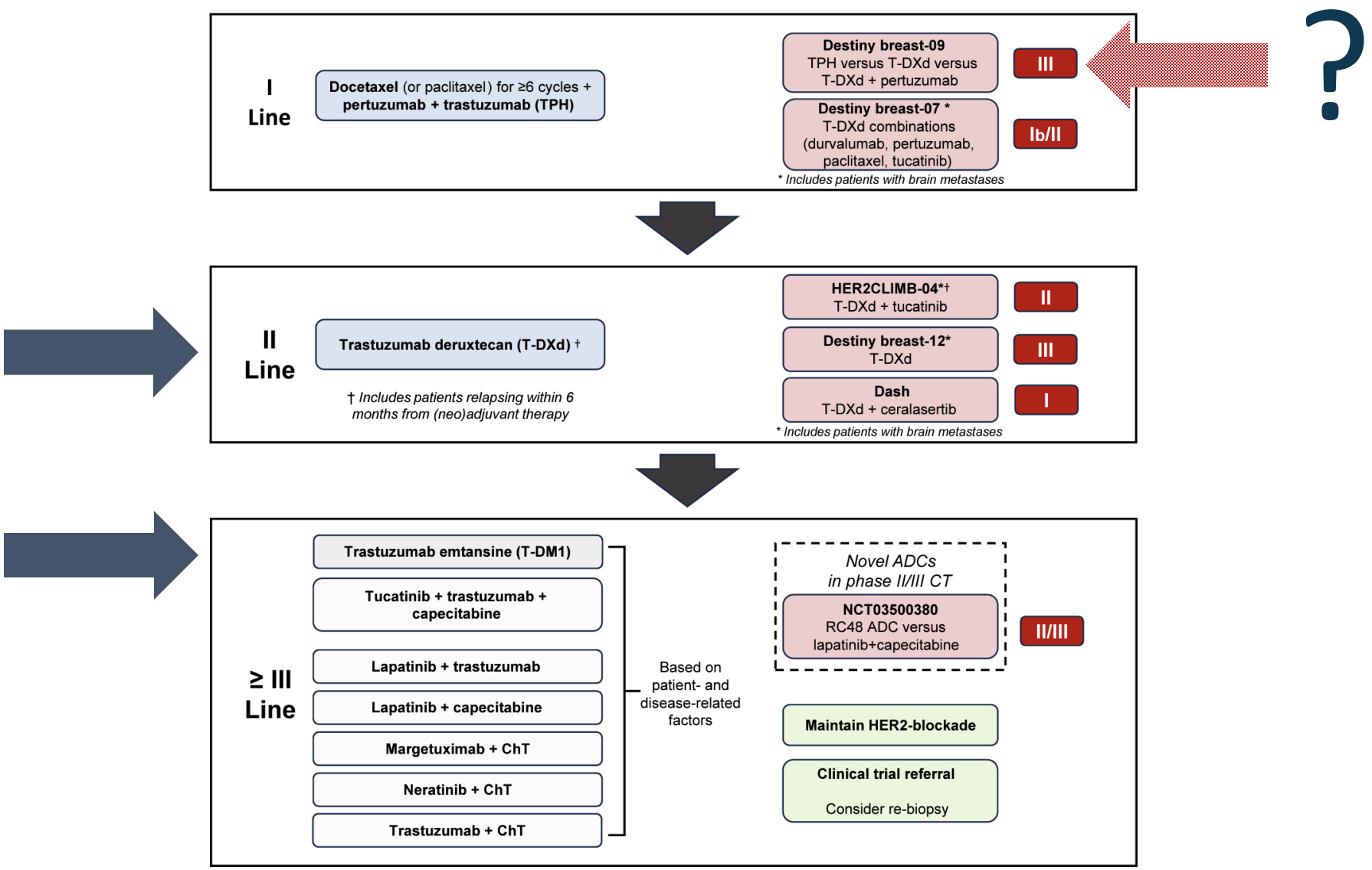


	Full analysis set†			Measurable disease at baseline (*post-hoc analysis*)		
	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	All patients (n=198)	Stable BMs (n=109)	Active BMs (n=89)
Confirmed ORR, % (95% CI)	**51.7 (45.7, 57.8)**	49.7 (41.9, 57.5)	54.7 (45.2, 64.2)	**64.1 (57.5, 70.8)**	67.0 (58.1, 75.8)	60.7 (50.5, 70.8)
CR, n (%)	11 (4.2)	–	–	2 (1.0)	–	–
PR, n (%)	125 (47.5)	–	–	125 (63.1)	–	–

T-DXd showed substantial responses in the overall BMs population, including patients with stable and active BMs

Median duration of response in the overall population was not calculated. Dashed line indicates a 30% decrease in target tumor size (PR). Response obtained by assessing target lesions, non-target lesions, and new lesions (extracranial and CNS)
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD; †includes 65 patients with no measurable disease at baseline
BM, brain metastasis; CI, confidence interval; CNS, central nervous system; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

Treatment algorithm for HER2+ MBC

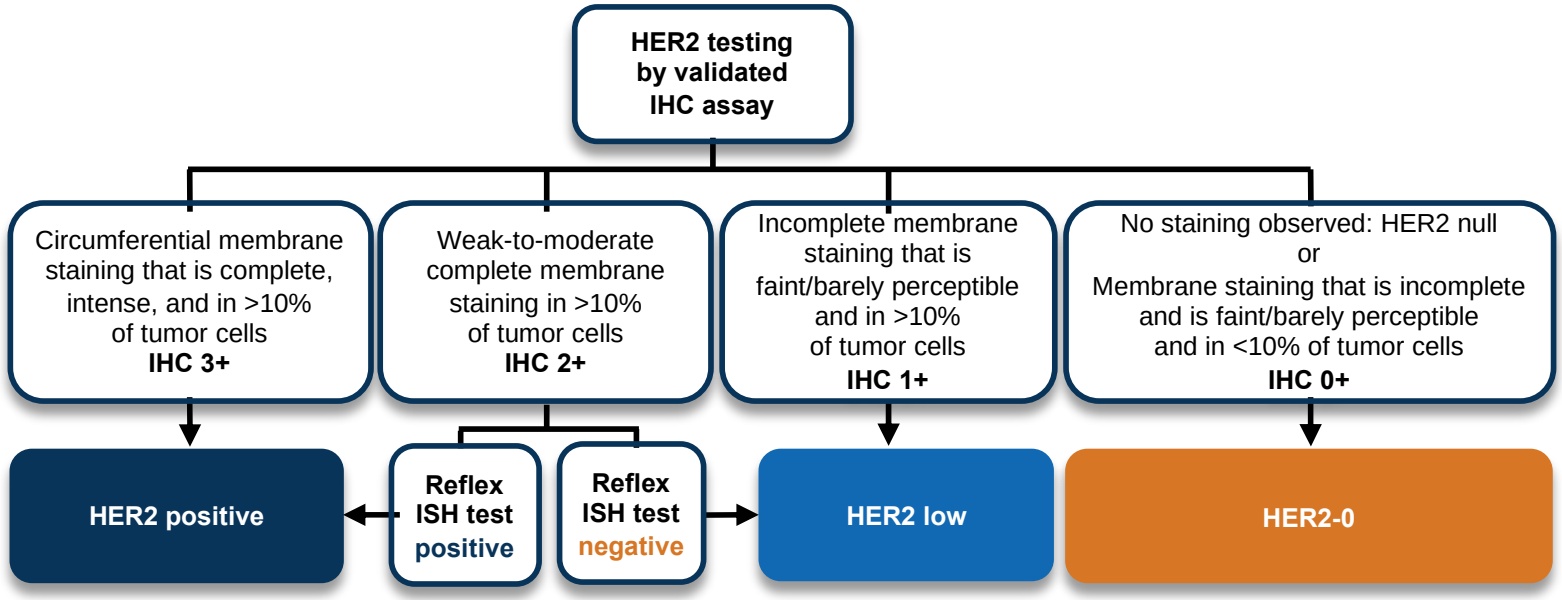


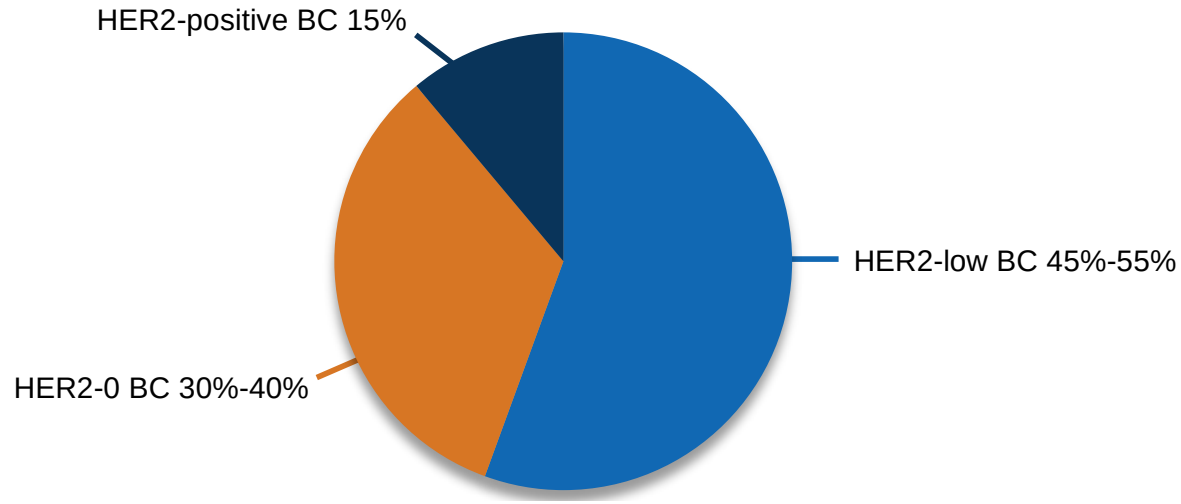
Antonarelli G et al. ESMO Open 2023

Select Trials in Progress with T-DXd: HER2+

- **Early stage**
  - Destiny Breast05 (NSABP B-60)
    - T-DM1 vs T-DXd as post neoadjuvant therapy (n=1600)
      - Question: Safety of concurrent radiation therapy?
        - Katherine trial: radiation pneumonitis 1.5 vs 0.7%, no difference in radiation skin injury
  - Destiny Breast 11
    - Neoadjuvant T-DXd x 8 v T-DXd x 4/THP vs AC/THP (n=624)

Expanding the use of HER2 ADCs to HER2-low breast cancer

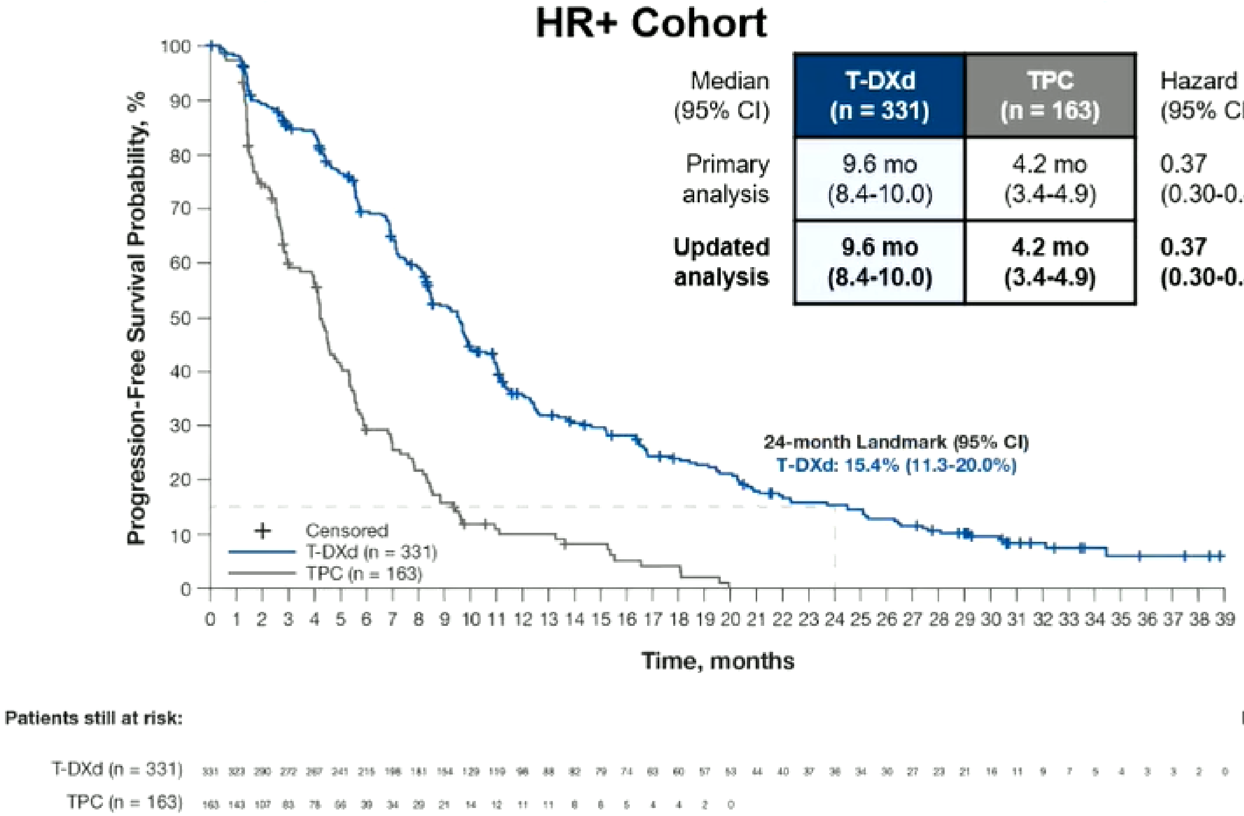


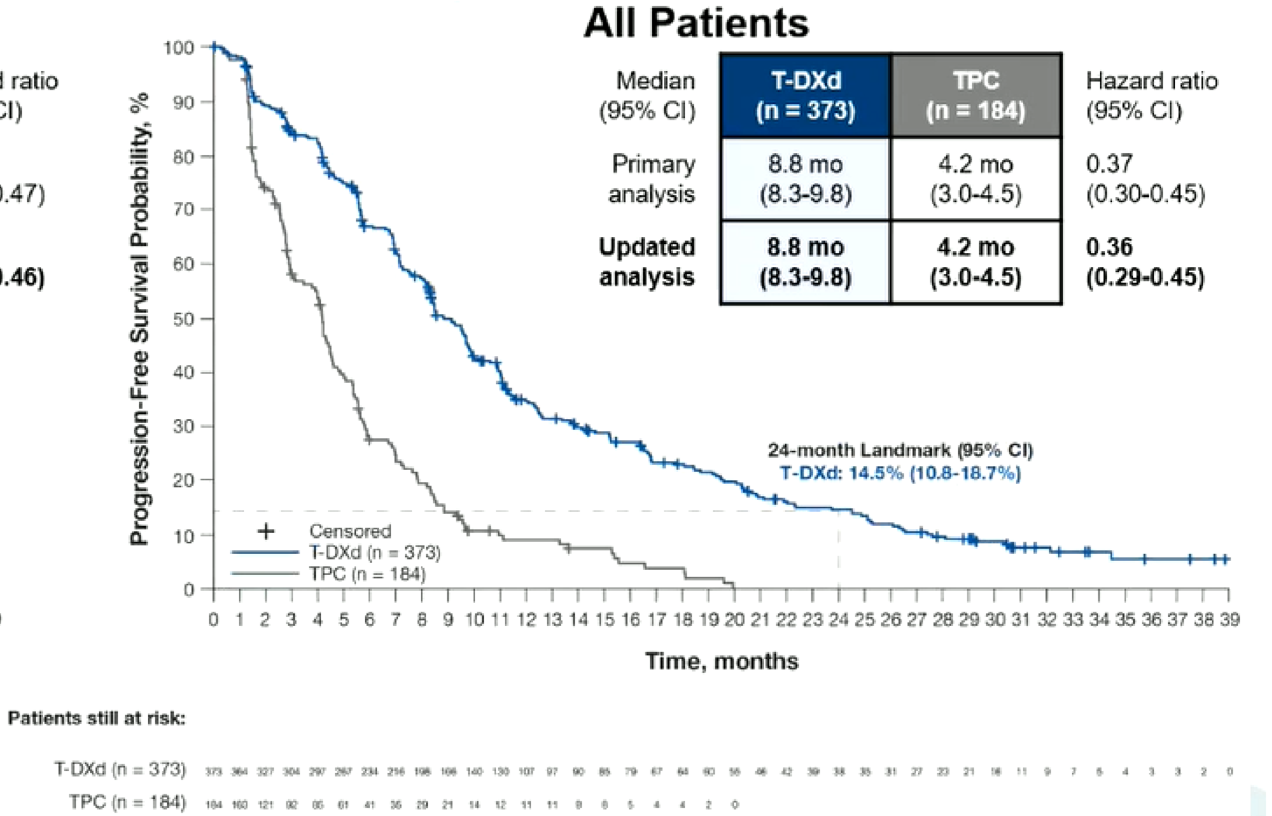


Tarantino P et al. *J Clin Oncol.* 2020;38:1951.

DESTINY- Breast 04: Updated PFS analysis

Median of 2 prior lines of ET and **1 prior line of chemo**



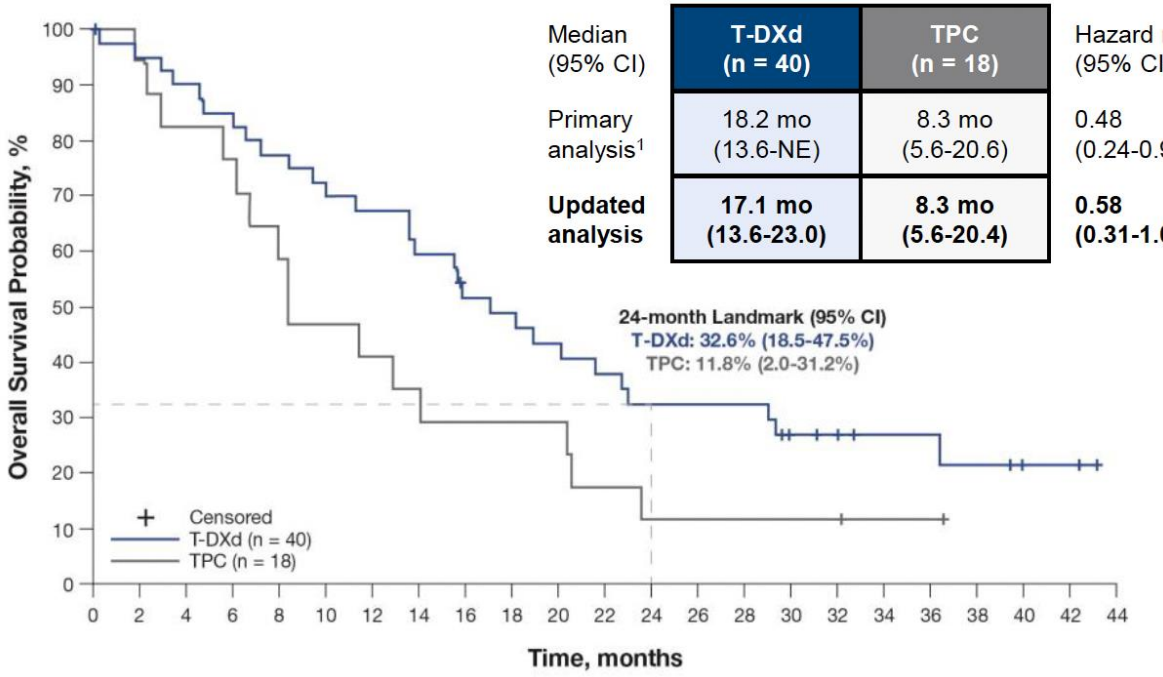


Modi S. et al. Presented at ESMO 2023

DESTINY-Breast04 phase 3 trial: activity in TNBC (i.e. HR-/HER2-low)

Overall Survival

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**



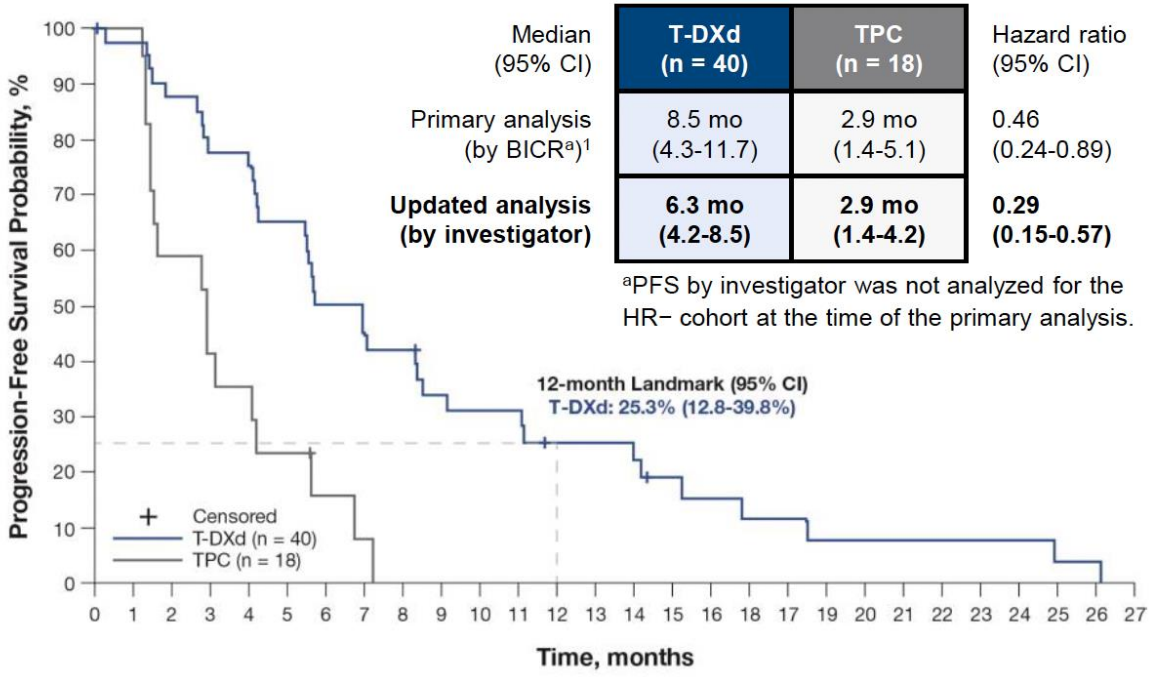
Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.



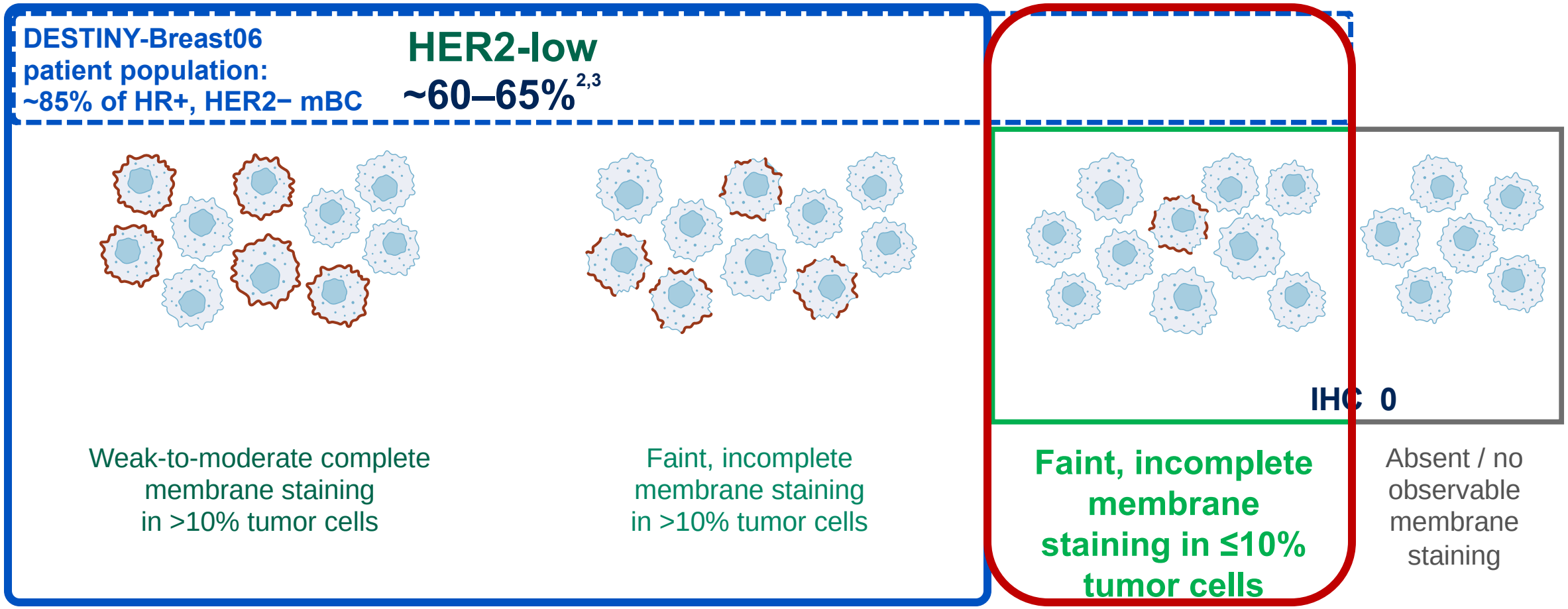
Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Modi S. et al ESMO 2023

Expanding the targetability to HER2 IHC 0 “ultra-low”

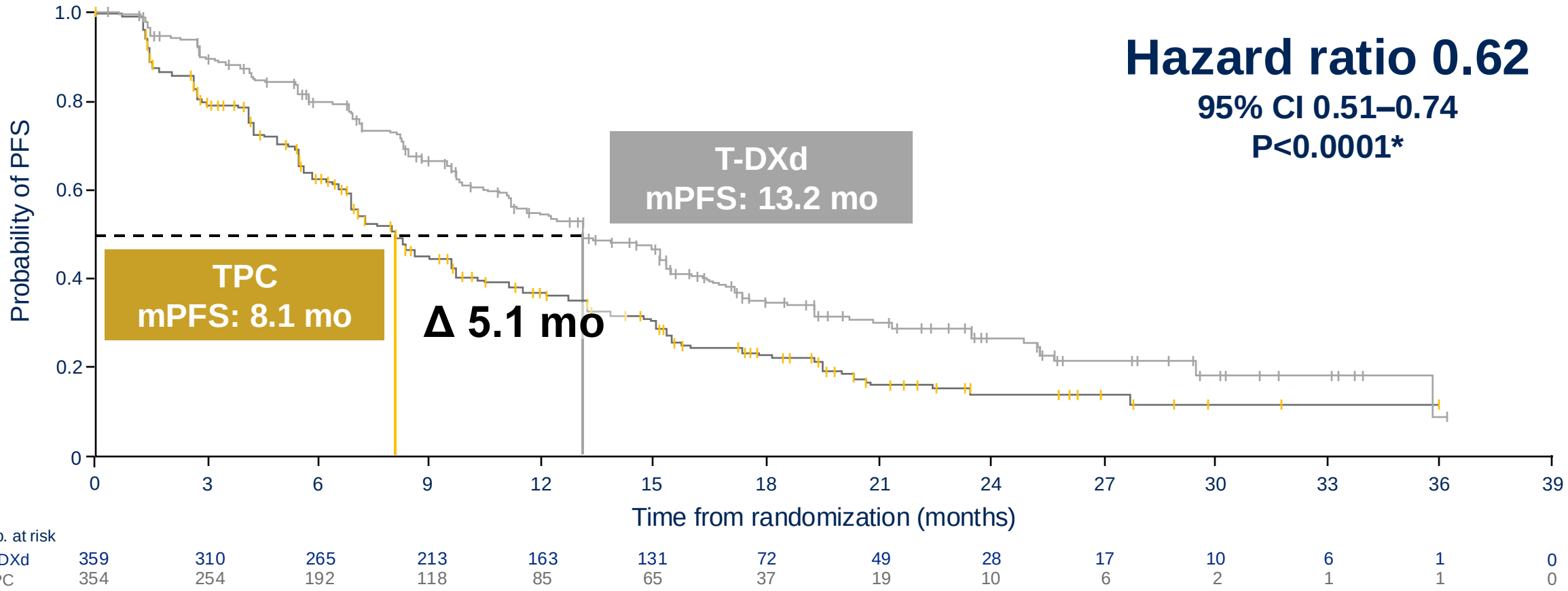
HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])



Curigliano G et al. *ASCO 2024*

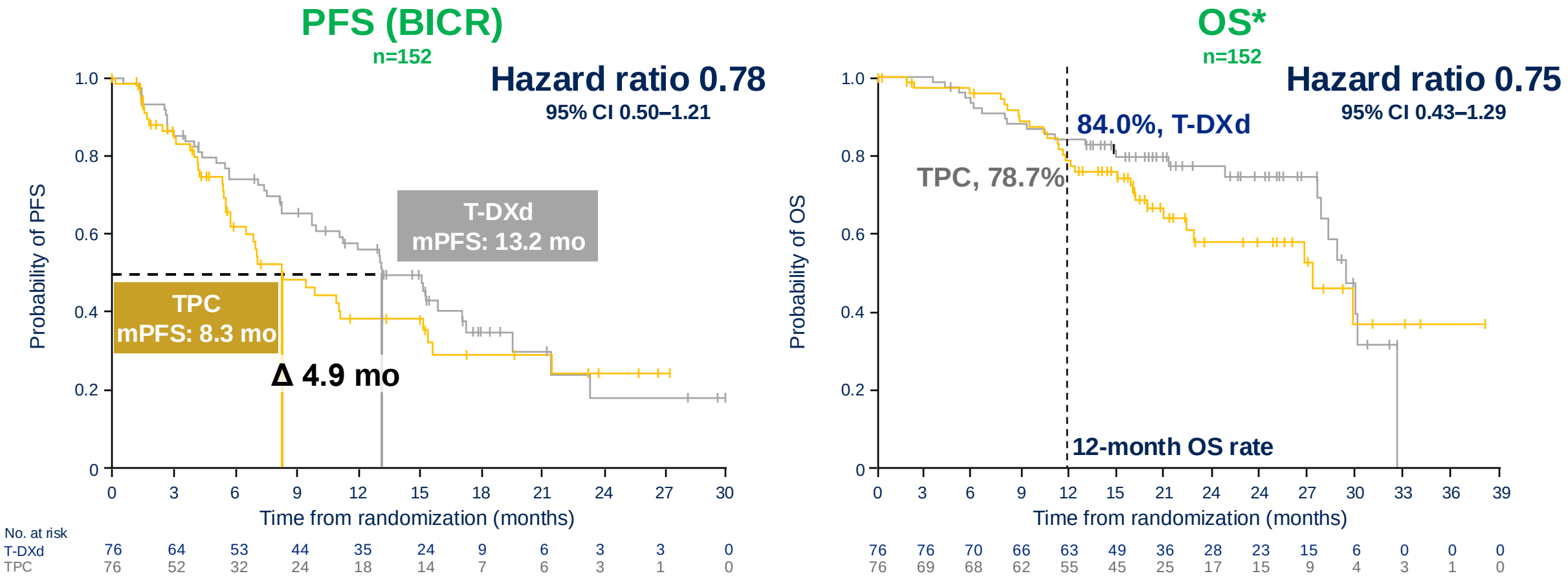
DESTINY- Breast 06: PFS (BICR) in HER2-low: primary endpoint

Median of 2 prior lines of ET, 90% with prior CDK4/6i, **no prior chemo**, 85% had visceral disease, 70% relapsed



Curigliano G et al. ASCO 2024; Bardia et al NEJM 2024

PFS and OS in HER2-ultra-low: prespecified exploratory analyses



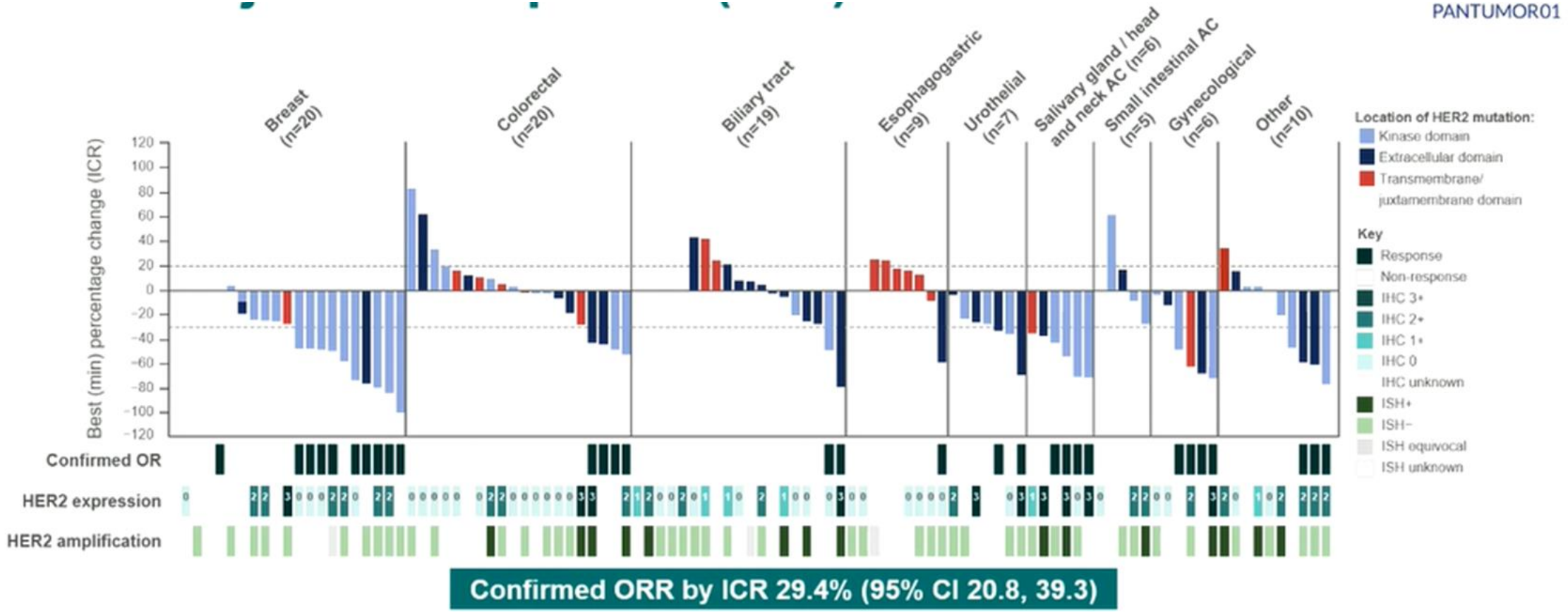
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano G et al. ASCO 2024; Bardia et al NEJM 2024

DESTINY-PanTumor01 : Role of T-DXd in *ERBB2* mutant solid tumors

HER2 mutations occur in 2-12% of solid tumor
DESTINY-Lung 02: T-DXd in *HER2* mutant Lung cancer (N=91)
ORR: 55%; Median PFS 8.2 months (95% CI, 6.0-11.9); Median OS: 17.8 months (95% CI, 13.8-22.1)
Accelerated approval in *HER2 mutant NSCLC*
8% ER+ MBC; Up to 15% in metastatic ILC



NCT04639219

Li et al NEJM 2022;Cerami et al. Cancer Discovery 2012; Razavi et al Cancer Cell 2018; Jhaveri et al SABCS 2021; Jhaveri ESMO 2022; Li et al ESMO 2023

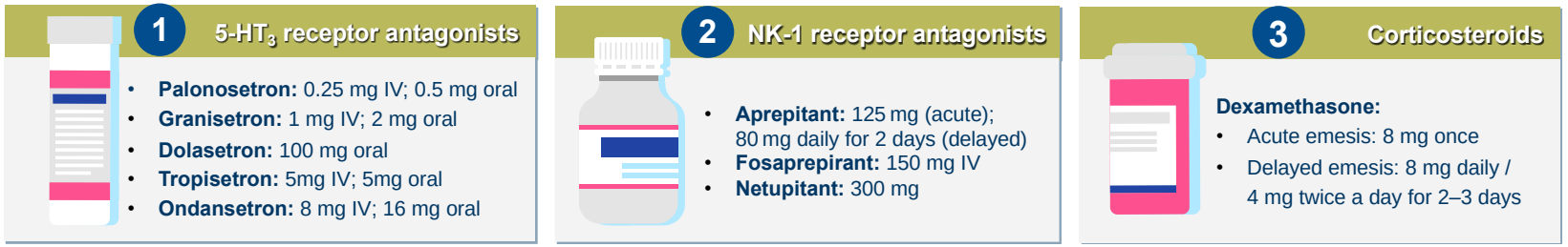
DB04: Nausea and Vomiting

- 189/371 patients (50.9%) in the T-DXd arm and 64/172 patients (37.2%) in the TPC arm received antiemetic prophylaxis[a]
- Prophylaxis was not mandatory per study protocol, but was recommended

	Nausea		Vomiting	
n (%)	T-DXd n = 371	TPC n = 172	T-DXd n = 371	TPC n = 172
Dose reduction associated with N/V	17 (4.6)	4 (2.3)	3 (0.8)	1 (0.6)
Drug interruption associated with N/V	5 (1.3)	4 (2.3)	0	0
Drug discontinuation associated with N/V	1 (0.3)	0	1 (0.3)	0

Three Classes of Anti-Emetic Premedication is Recommended

This can be individualized to patient symptoms



N/V, nausea or vomiting; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice. [a]Prophylaxis included antiemetics and antinauseants, corticosteroids for systemic use, drugs for functional gastrointestinal disorders, or other.

Rugo et al, ESMO Breast 2023; NCCN 2023

DESTINY- Breast 06: Adverse events of special interest

Adjudicated as drug-related interstitial lung disease / pneumonitis*

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

Left ventricular dysfunction†

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
T-DXd (n=434)	1 (0.2)	31 (7.1)	3 (0.7)	0	0	35 (8.1)
TPC (n=417)	0	11 (2.6)	1 (0.2)	0	0	12 (2.9)
Cardiac failure						
T-DXd (n=434)	0	0	0	0	0	0
TPC (n=417)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.7)

*Grouped term. Median time to first onset of interstitial lung disease / pneumonitis for patients with T-DXd was 141 days (range 37–835). No pending cases of drug-related interstitial lung disease / pneumonitis to be adjudicated. One interstitial lung disease–related death per investigator assessment was upheld by the adjudication committee. An additional two deaths were adjudicated as interstitial lung disease–related by the adjudication committee; †data for the most common preferred terms are shown on the slide; additionally, one patient in each treatment group had the preferred term left ventricular dysfunction (Grade 3 with T-DXd, Grade 2 with TPC)
T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano G et al. ASCO 2024; Bardia et al NEJM 2024

Management of ILD: the 5 S rules

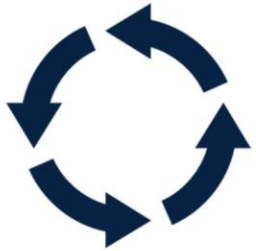
1 Screen

- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on the baseline risk
- Screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD

2 Scan

- The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest
- A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks

3 Synergy



- Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected

4 Suspend Treatment

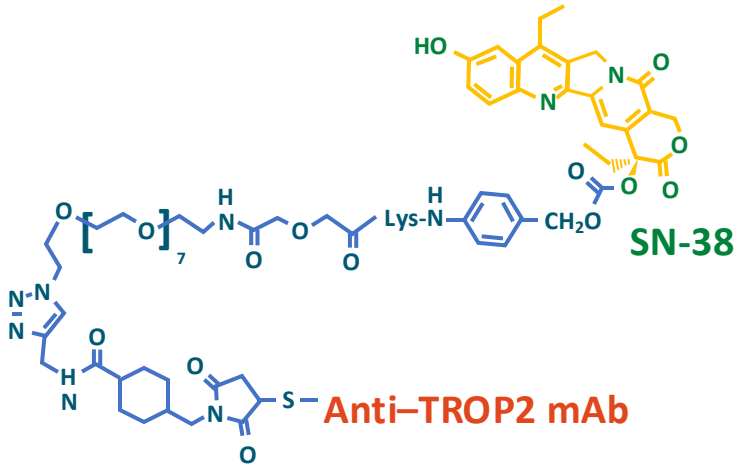
- T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves

5 Steroids

- The mainstay for treating T-DXd–induced ILD remains corticosteroids, with the dose to be adapted to the toxicity grade

Tarantino P. et al. JCO Onc Prac 2023

Sacituzumab Govitecan

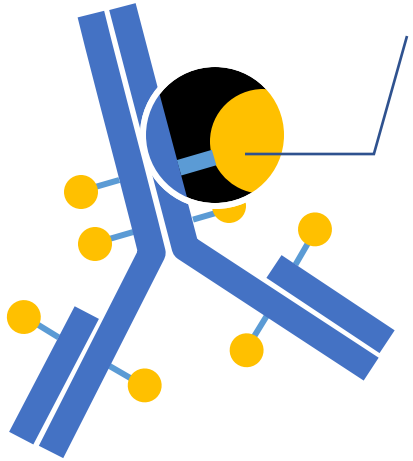


Humanized Anti-TROP2 Antibody

- Targets TROP2, an antigen expressed in many epithelial cancers
- Antibody type: hRS7 IgG1κ

SN-38 Payload Payload (Topoisomerase I Inhibitor)

- Delivers up to 136-fold more SN-38 to tumors than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor



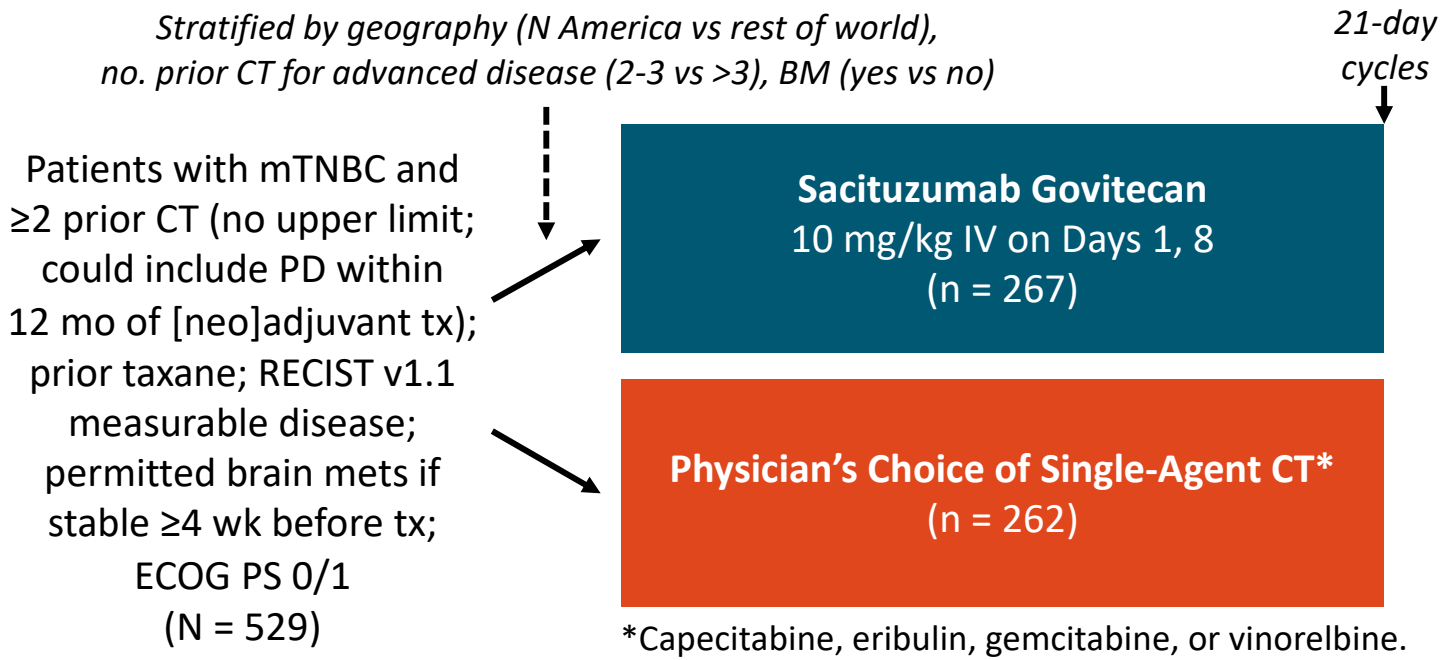
Linker for SN-38

- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

Bystander effect: In acidic tumor microenvironment, SN-38 is released from anti-TROP2 antibody, diffuses into neighboring cells

Goldenberg. Oncotarget. 2015;6:22496. Khoury. ASCO 2019. Abstr e14651; Ambrogi. PLoS One. 2014;9:e96993. Vidula. ASCO 2017. Abstr 1075; Sacituzumab govitecan PI. Tagawa. ASCO 2019. Abstr TPS3153; Bardia. JCO. 2017;35:2141; Goldenberg. MAbs. 2019;11:987; Sharkey. Clin Cancer Res. 2015;21:5131.

Phase III ASCENT: Sacituzumab Govitecan vs CT in Relapsed/Refractory Metastatic TNBC



- **Primary endpoint:** PFS by BICR in patients without brain mets
- **Secondary endpoints:** investigator-assessed PFS in ITT, OS, ORR, DoR, TTR, safety, QoL

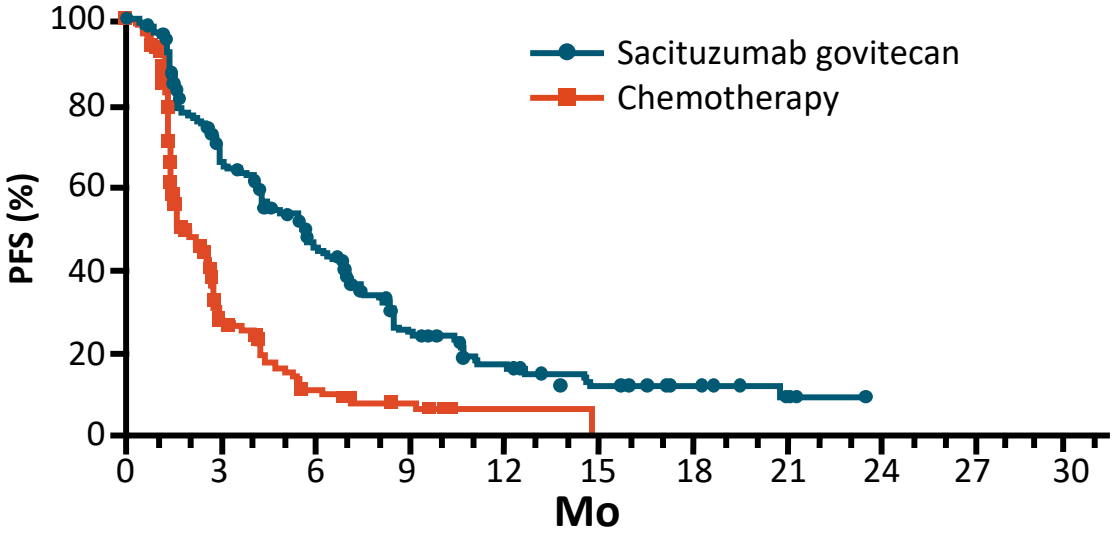
- **Trial halted early based on efficacy** per unanimous recommendation of DSMC

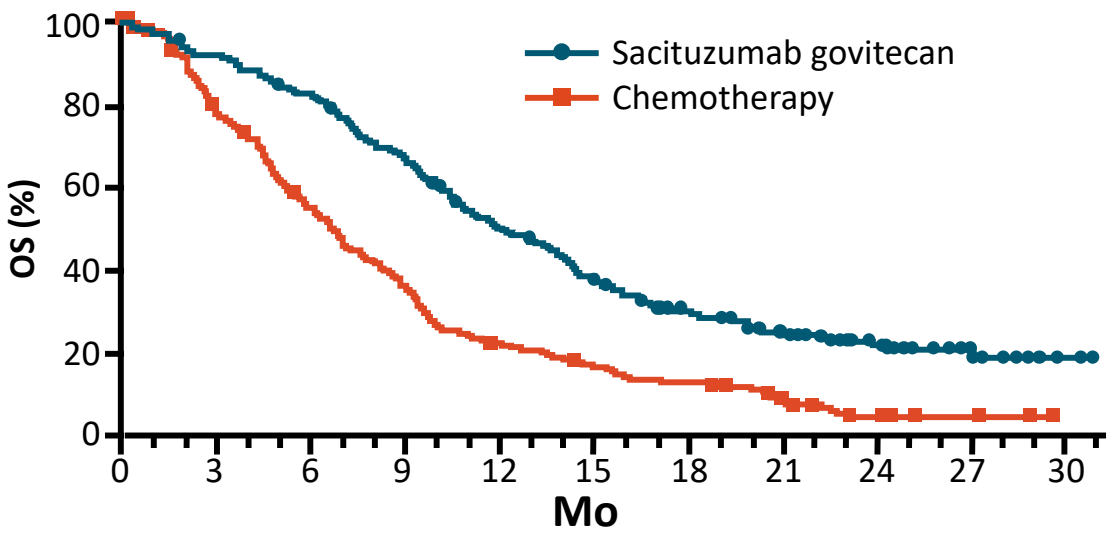
Bardia. NEJM. 2021;384:1529. Bardia. ASCO 2022. Abstr 1071. Sacituzumab govitecan PI.

ASCENT: PFS and OS Among Patients Without Brain Metastases (Final Analysis)

PFS Analysis	SG (n = 235)	CT (n = 233)
Events	167	150
Median PFS, mo	**5.6**	**1.7**
HR	**0.39 (95% CI: 0.31-0.49; *P* <.0001)**	

OS Analysis	SG (n = 235)	CT (n = 233)
Events	173	199
Median OS, mo	**12.1**	**6.7**
HR	**0.48 (95% CI: 0.39-0.59; *P* <.0001)**	

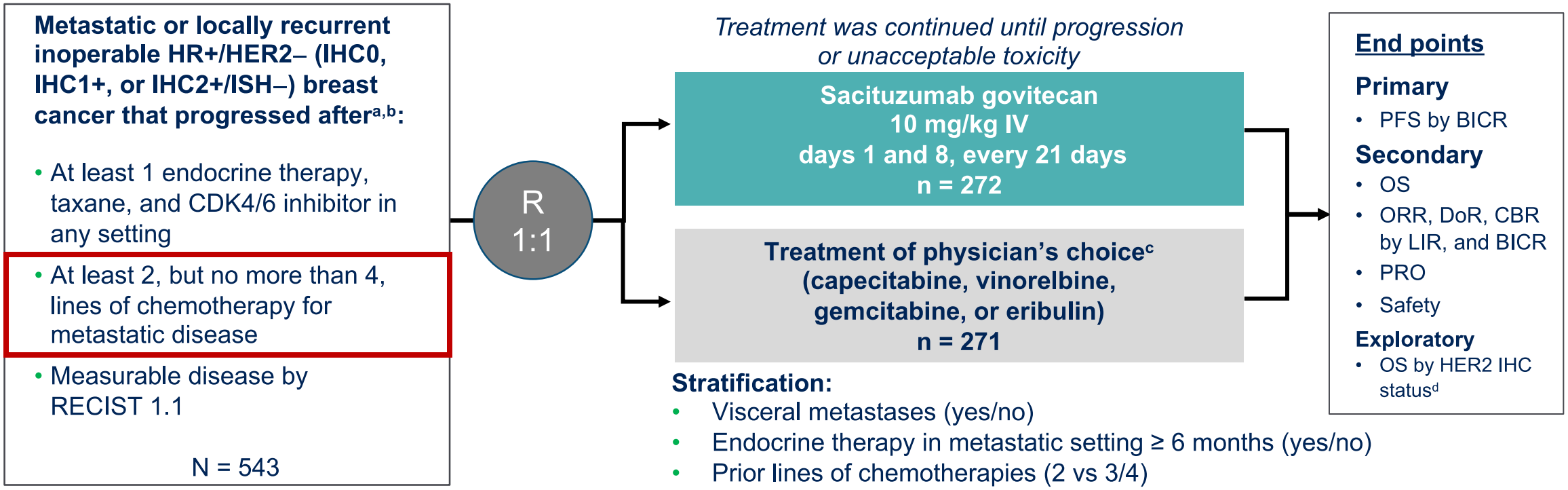




§ Based on confirmatory ASCENT trial, **FDA granted regular approval to SG for treatment of unresectable locally advanced/metastatic TNBC with ≥2 prior systemic therapies (≥1 for metastatic disease)**

Bardia. NEJM. 2021;384:1529. Bardia. ASCO 2022. Abstr 1071. Sacituzumab govitecan PI.

TROPiCS-02 phase 3 trial: Expanding the benefit of Sacituzumab Govitecan to the HR+ disease



ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

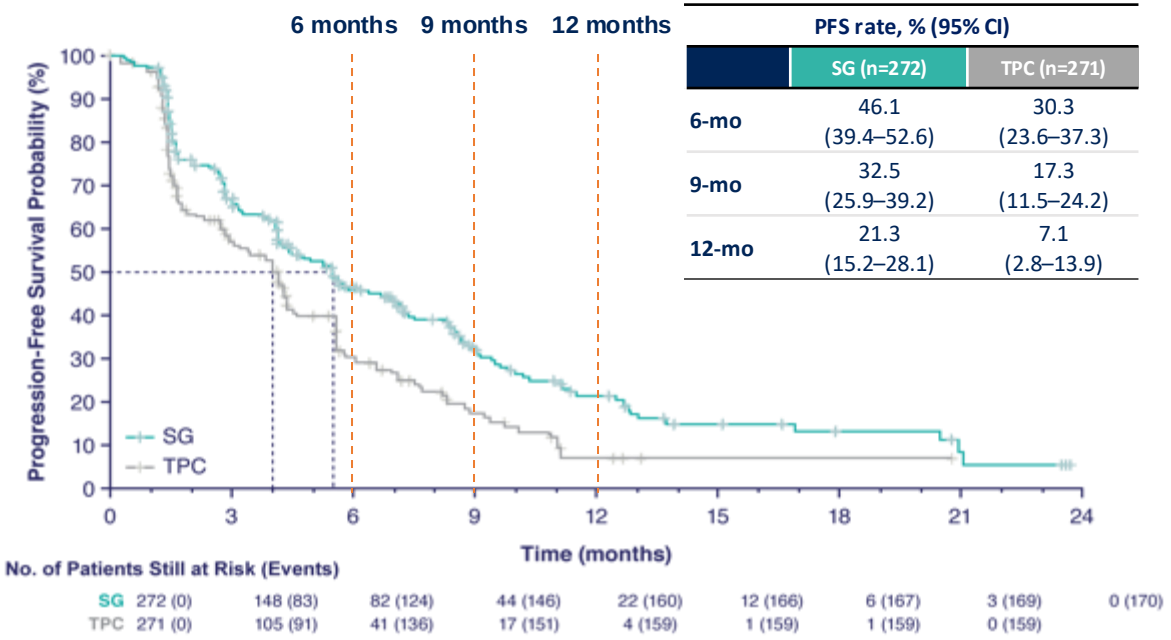
[a]ClinicalTrials.gov. NCT03901339. [b]Disease histology based on the ASCO/CAP criteria. [c]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. [d]HER2-low was defined as IHC score of 1+, or score of 2+ with negative ISH result; HER2 IHC0 was defined as IHC score of 0.

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

TROPICS 02 for HR+/HER2- Disease: PFS & OS in the ITT Population

PFS[1]

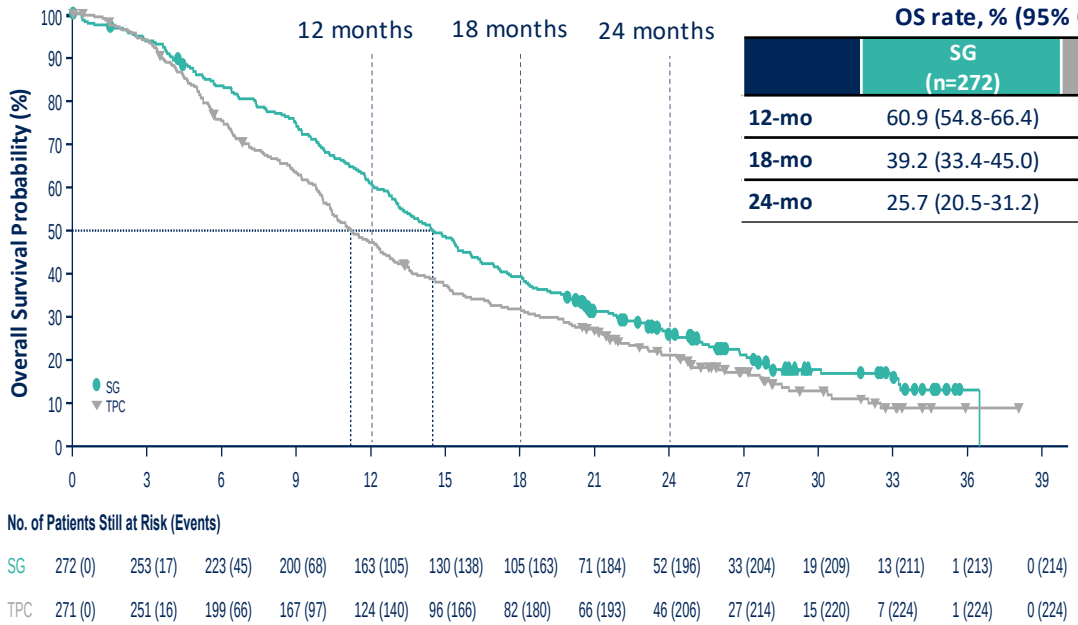
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

OS[2,3]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.5 (13.0–16.0)	11.2 (10.2–12.6)
Stratified HR (95% CI)	**0.79** (0.65–0.95)	
Nominal *P* value	*P*=0.0133	



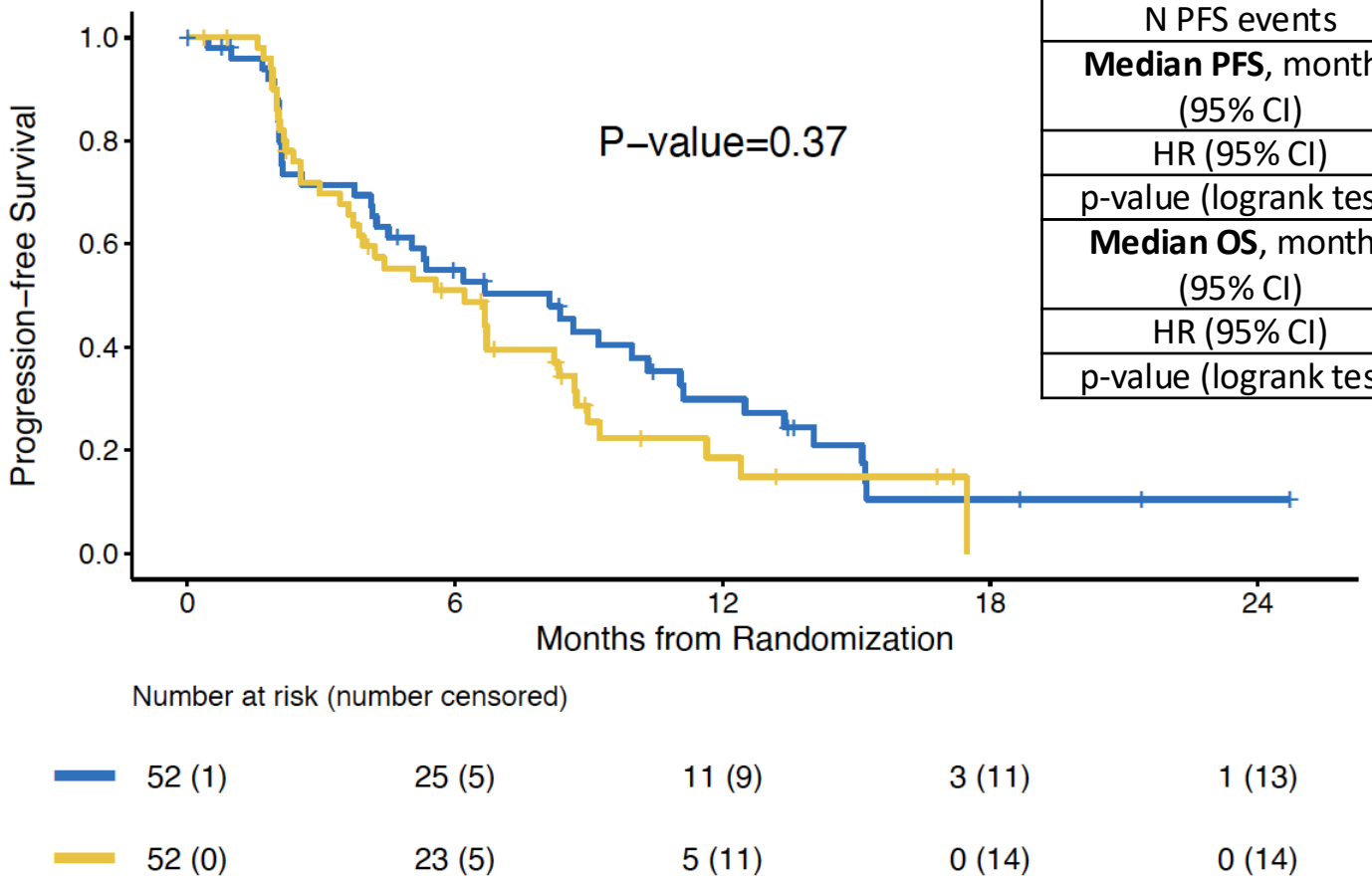
OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo	25.7 (20.5-31.2)	21.1 (16.3-26.3)

SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

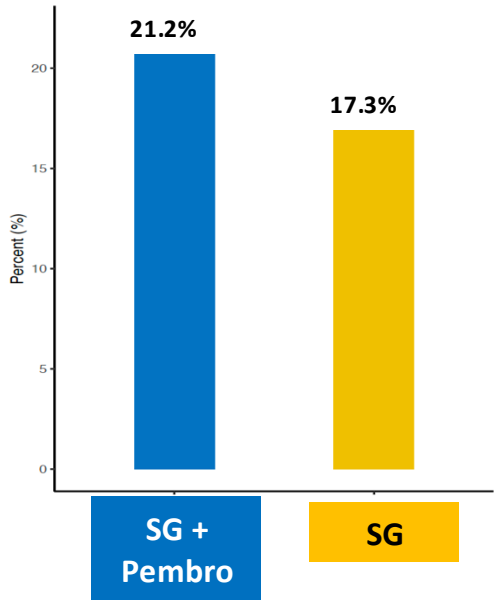
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. *J Clin Oncol. 2022*. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76. 3. Tolaney et al, ASCO Abstract 1003; Rugo et al, Lancet 2023

SACI-IO HR+: Progression-Free Survival



Treatment Arm	SG + Pembrolizumab (N=52)	SG (N=52)
N PFS events	38	38
Median PFS, months (95% CI)	**8.12** (4.51-11.12)	**6.22** (3.85-8.68)
HR (95% CI)	**0.81** (0.51-1.28)	
p-value (logrank test)	0.37	
Median OS, months (95% CI)	**18.52** (16.55-NA)	**17.96** (12.50-NA)
HR (95% CI)	**0.65** (0.33-1.28)	
p-value (logrank test)	0.213	

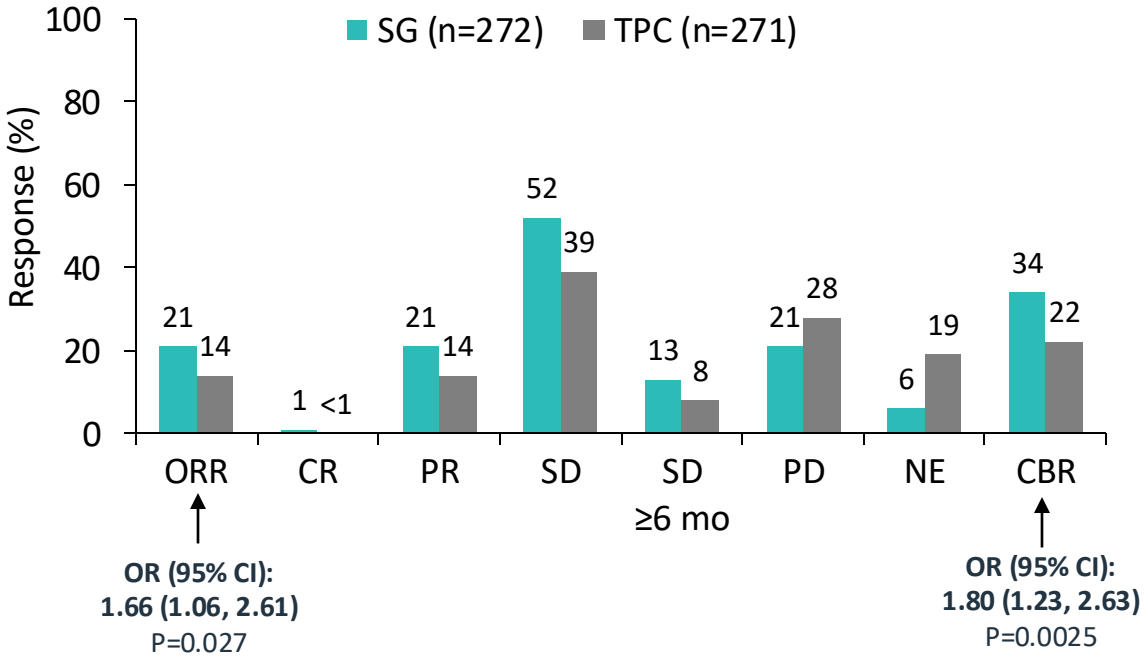
Objective response rate



- **No significant contribution with addition of CPI**
- **Similar findings with CPI + conventional chemotherapy in HR+ MBC**

TROPiCS-02: Responses and Safety Summary

Tumor response



Median DoR, months (95% CI): 8.1 (6.7, 8.9) vs **5.6** (3.8, 7.9)

Safety summary

n (%)		SG (n=268)		TPC (n=249)	
AE Grade ≥3		199 (74)		149 (60)	
AEs → discontinuation		17 (6)		11 (4)	
AEs → dose delay		178 (66)		109 (44)	
AEs → dose reductions		91 (34)		82 (33)	
SAEs		74 (28)		48 (19)	
AEs → death[a]		6 (2)		0	
		Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic	Neutropenia	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia	17 (6)	1 (<1)	41 (16)	9 (4)
GI	Diarrhea	166 (62)	27 (10)	57 (23)	3 (1)
	Nausea	157 (59)	3 (1)	87 (35)	7 (3)
	Constipation	93 (35)	1 (<1)	61 (24)	0
	Vomiting	64 (24)	3 (1)	39 (16)	4 (2)
	Abdominal pain	53 (20)	10 (4)	34 (14)	2 (1)
Other	Alopecia	128 (48)	0	46 (18)	0
	Fatigue	105 (39)	16 (6)	82 (33)	9 (4)
	Asthenia	62 (23)	6 (2)	50 (20)	5 (2)
	Decreased appetite	57 (21)	4 (1)	52 (21)	2 (1)
	Dyspnea	49 (18)	5 (2)	39 (16)	11 (4)
	Headache	44 (16)	1 (<1)	36 (14)	2 (1)
	Pyrexia	39 (15)	2 (1)	45 (18)	0
	AST increased	33 (12)	4 (1)	44 (18)	8 (3)

[a]Of 6 AEs leading to death, 1 (septic shock due to neutropenic colitis) was considered treatment related by investigator

Rugo et al, JCO 2022; Rugo et al, ESMO 2022; Rugo et al, SABCS 2022; Tolaney et al. ASCO 2023. Abstract 1003; Rugo et al, Lancet 2023

Sacituzumab: Ongoing Trials for Late Stage

ASCENT-03 (NCT05382299): PD-L1 negative
N=540

First-line therapy
- PD-L1 neg TNBC
- TNBC Rxd with IO in early stage

→ Sacituzumab govitecan

→ TPC: paclitaxel, nab-paclitaxel, gem/carbo

ASCENT-04 (NCT05382286): PD-L1 positive
N=570

1L mTNBC PD-L1+
- Previously untreated, inoperable, locally advanced, OR metastatic TNBC
- PD-L1+ (CPS ≥10, IHC 22C3 assay)
- PD-L1 and TNBC status centrally confirmed
- Prior anti-PD-(L)1 allowed in the curative setting
- ≥6 months since treatment in curative setting

1:1

N=570
(≤25% *de novo*)

→ SG + pembrolizumab
(SG: 10 mg/kg IV on days 1 and 8 of 21-day cycles; Pembro: 200 mg IV on day 1 of 21-day cycles)

→ TPC chemotherapy + pembrolizumab
(Pembro dosed as above. TPC: gem 1000 mg/m² with carbo AUC 2 IV on days 1 and 8 of 21-day cycles OR paclitaxel 90 mg/m² IV on days 1, 8, and 15 of 28-day cycles OR nab-paclitaxel: 100 mg/m² IV on days 1, 8, and 15 of 28-day cycles)

Ascent-07: (NCT05840211)
First-line Chemotherapy in HR+

Key eligibility criteria:
- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)

N = 654
2:1 randomization

→ Sacituzumab govitecan
10 mg/kg IV
Days 1 and 8, every 21 days

→ Treatment of physician's choice (capecitabine, paclitaxel, nab-paclitaxel)

Stratification:
- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint
- PFS by BICR

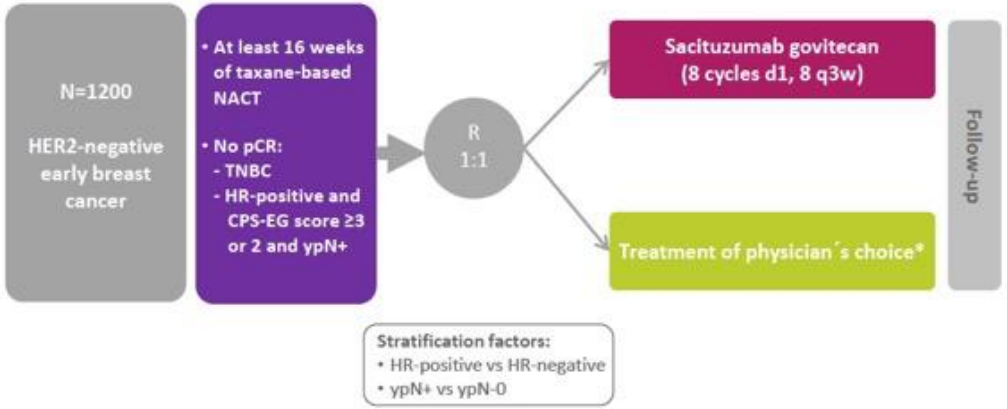
Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints
- PFS by investigator
- ORR by investigator
- DOR
- Safety

Sacituzumab: Ongoing Trials for Early Stage

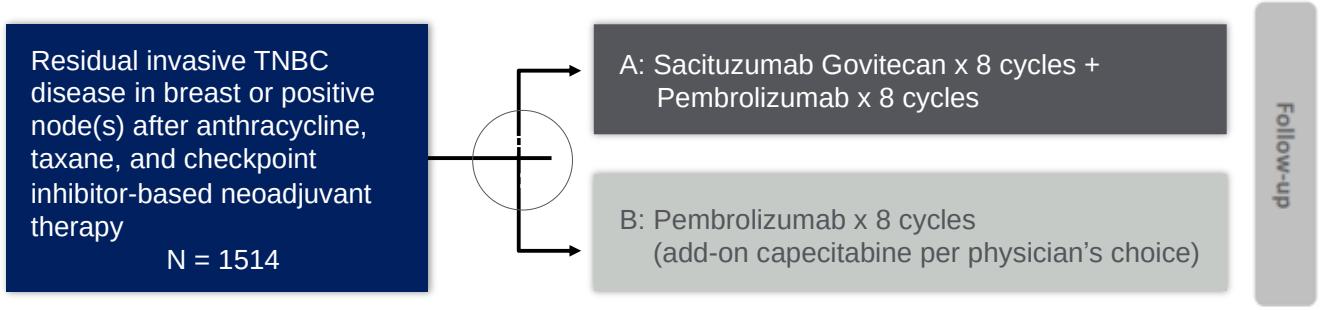
GBG: SASCIA Post-Neoadjuvant Trial

NCT04595565



Phase III Trial: Optimice-RD/ASCENT-05

Residual disease in TNBC



PI: Sara Tolaney; Alliance Foundation Trial

TROPION-Breast01 phase 3 trial

Positive results from TB01 may lead to the approval of a third Topo1 ADC (Dato-DXd) for patients with HR+/HER2- MBC

Key inclusion criteria:

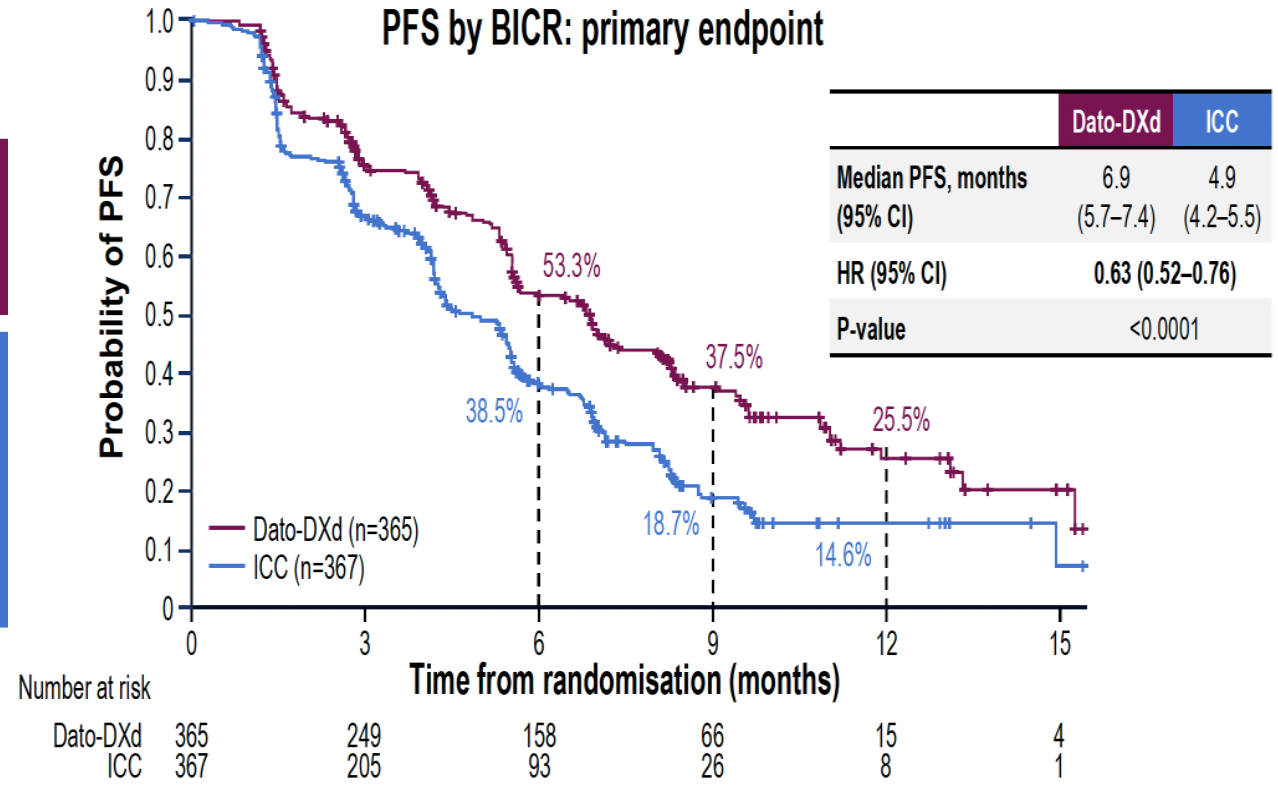
- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Randomisation stratified by:
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)



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

Bardia A. et al. ESMO Congress 2023; Bardia, Jhaveri et al..JCO 2024

ESMO Breast 2024: TROPION BREAST01: Updated Safety Data

TRAEs Occurring in ≥15% of Patients

System Organ Class Preferred term, 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

Overall Safety Summary

TRAEs, n (%)	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (93.6)	303 (86.3)
Grade ≥3	75 (20.8)	157 (44.7)
Associated with dose reduction	75 (20.8)	106 (30.2)
Associated with dose interruption	43 (11.9)	86 (24.5)
Associated with discontinuation	9 (2.5)	9 (2.6)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (5.8)	32 (9.1)
Grade ≥3	17 (4.7)	31 (8.8)

- **Rate of grade ≥3 TRAEs with Dato-DXd was less than half that with ICC**
- Fewer TRAEs leading to dose reductions or interruptions with Dato-DXd compared with ICC
- **AESIs with Dato-DXd* included:**
  - Oral mucositis / stomatitis
  - Ocular surface events
  - Adjudicated drug-related ILD

Jhaveri, K. ESMO Breast 2024, Bardia, Jhaveri et al JCO 2024

Datopotamab: Ongoing Trials for Late Stage

TROPION-Breast02 (n=625)

NCT05374512

Key eligibility criteria:

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1 / PD-L1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

- Geographic location
- DFI (*de novo* vs DFI >12 months)

Dual primary endpoint:
PFS (BICR) and OS

Secondary endpoints:
PFS (inv), ORR, DoR, safety

1:1

- **Dato-DXd**
- **Investigator's choice of chemotherapy**

- 1st line therapy for TNBC
- PD-L1 negative

TROPION Breast05 (n=625)

NCT06103864

Key Eligibility Criteria

- Previously untreated locally recurrent inoperable or metastatic TNBC
- ECOG PS 0 or 1
- Measurable disease as defined by RECIST 1.1
- Adequate haematologic and end-organ function
- PD-L1 centrally confirmed
- PD-L1 positive by 22C3 assay CPS ≥ 10 IHC
- No systemic steroids
- No active autoimmune diseases
- No active brain metastases
- DFI ≥ 6 months since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

Stratification Factors

- DFI history (de novo versus prior DFI 6 to 12 months[a] versus prior DFI > 12 months)
- Geographic location (US/Canada/Europe versus Dato-DXd Monotherapy Enrolling Countries versus Rest of World)
- Prior PD-1/PD-L1 treatment for early stage TNBC (yes versus no)

N=625

1:1:1[c]

Arm 1
Dato-DXd
6.0 mg/kg IV Q3W
+
Durvalumab
1120 mg IV Q3W
(n=275)

Arm 2
Investigator's Choice Chemotherapy[b]
+
Pembrolizumab
200 mg IV Q3W
(n=275)

Arm 3
Dato-DXd
6.0 mg/kg IV Q3W
(n=75)[d]

Primary endpoint:
PFS (BICR)

Key secondary endpoint:
OS

Secondary endpoints including:
PFS (inv), ORR, DoR, CBR, TTD, PRO, Safety, Tolerability, PK, and Immunogenicity

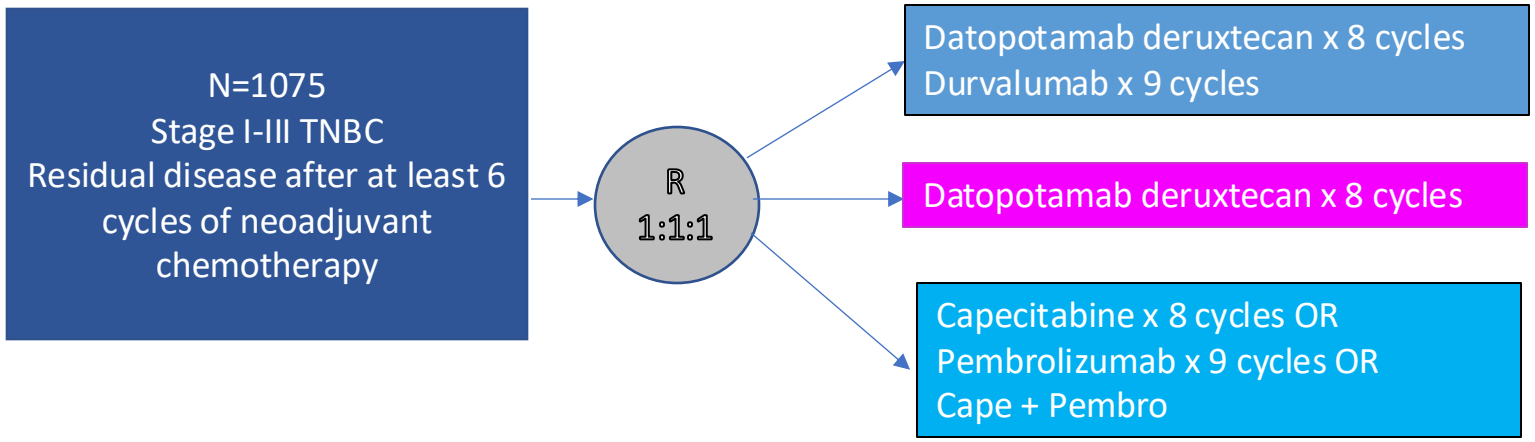
Exploratory endpoints including:
TROP2

[a] DFI 6 to 12 months capped at 20%.
[b] Chemotherapy options include paclitaxel (90 mg/m² IV on days 1, 8, and 15, Q4W), nab-paclitaxel (100 mg/m² IV days 1, 8, and 15, Q4W) or gemcitabine 1000 mg/m² IV + carboplatin AUC 2 IV days 1 and 8 Q3W.
[c] Once approximately 75 participants are randomised to Arm 3, this cohort will close, and all countries will continue with a 1:1 randomisation strategy for Arms 1 and 2.
[d] In selected countries only.

Datopotamab: Ongoing Trials for Early Stage

TROPION Breast03 (n=1075)

NCT05629585



TROPION Breast04 (n=1728)

NCT06112379

Neoadjuvant therapy for TNBC

Durvalumab + Dato-DXd x 8 cycles followed by surgery; durva x 9 cycles postop

vs

KN522

Single-arm basket trial (Phase 1/2) of SKB264 (MK-2870): 2L among HR+/HER2−MBC

- SKB264 (MK-2870) is a TROP2-directed ADC with sulfonyl pyrimidine-CL2A-carbonate cleavable linker to belotecan-derivative topoisomerase I inhibitor; DAR of 7.4
- As of April 2023 41 HR+/HER2- mBC patients enrolled
- Median follow up was 8.2 months

Key Eligibility Criteria

- Diagnosis of HR+/HER2- (including HER2-low and HER2-zero) mBC
- Progression on endocrine-based therapy and at least one prior chemotherapy for mBC

SKB264 (MK-2870) 5 mg/kg, Q2W

Until disease progression or unacceptable toxicity or patient requests to discontinue the treatment. (Tumor assessments were performed every 8 weeks)

Primary End Points

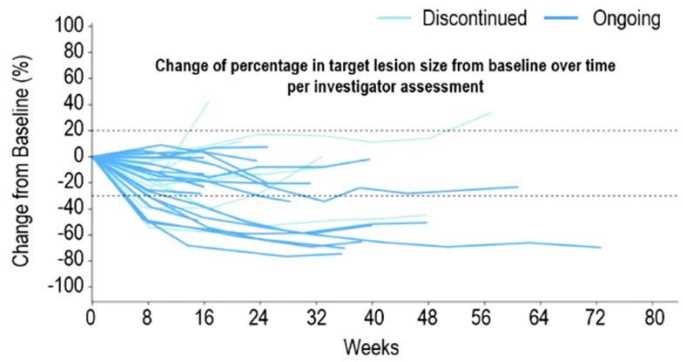
- ORR in HR+/HER2- mBC per RECIST v1.1 by investigator

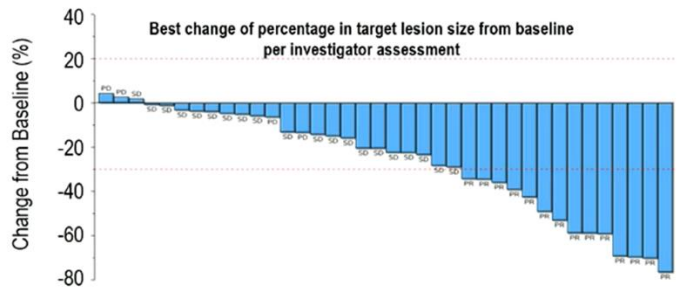
Secondary End Points

- DoR, PFS, OS
- Safety

	All patients (N=38)[a]
ORR, n (%)	**14 (36.8)**
Confirmed PR	12
DCR, n (%)	**34 (89.5)**
DoR	
Median (Range), mo	7.4 (4.2~14.9+)
6-mon DoR rate, % (95% CI)	80.0 (40.9, 94.6)
PFS	
Median (95% CI), mo	11.1 (5.4, 13.1)
6-mon PFS rate, % (95% CI)	61.2 (41.3, 76.1)
OS	
Median (95% CI), mo	NE (10.71, NE)
9-mon OS rate (95% CI), %	81.4 (57.1, 92.7)

a. of 41 patients were enrolled, 38 patients were evaluable for response assessment (defined as ≥1 on-study scan).





A Study of Sacituzumab Tirumotecan (MK-2870) as a Single Agent and in Combination With Pembrolizumab (MK-3475) Versus Treatment of Physician's Choice in Participants With HR+/HER2- Unresectable Locally Advanced or Metastatic Breast Cancer (MK-2870-010) NCT06312176

Radosa J, et al. ESMO 2023. Abstract 380MO

Impact of DB06 on treatment sequencing

≈90% of the patients

HR+ HER2-low
or HER2-ultralow
MBC

→ EXHAUST ENDOCRINE TREATMENT STRATEGIES

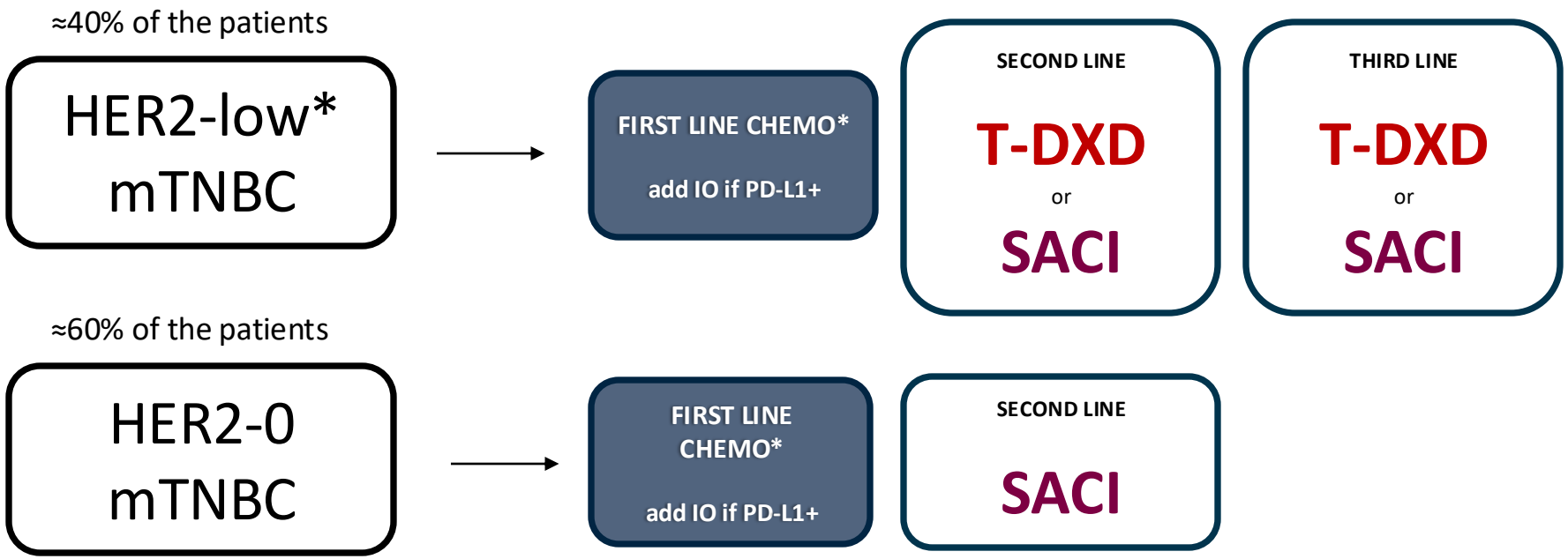
FIRST LINE
T-DXd or CHEMO

SECOND LINE
SACI or **CHEMO**

1L T-DXd preferred for patients with:

- **symptomatic disease**
- **extensive visceral disease burden**
- **Primary endocrine resistant disease**
- in all cases when there is the **suspicion that the patient may not receive T-DXd in later lines**

Treatment of mTNBC with ADCs

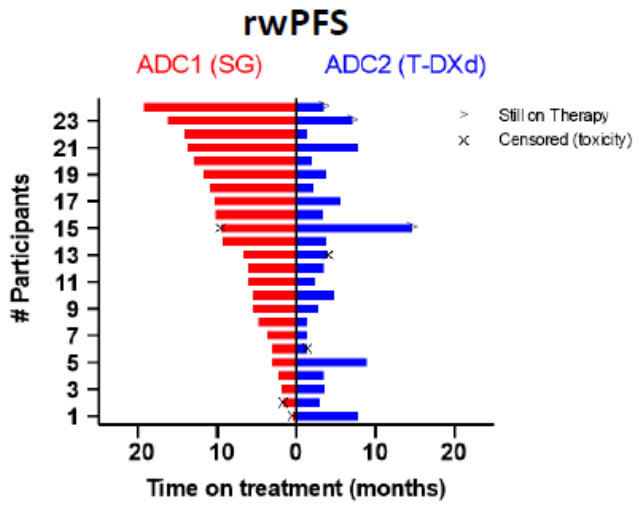


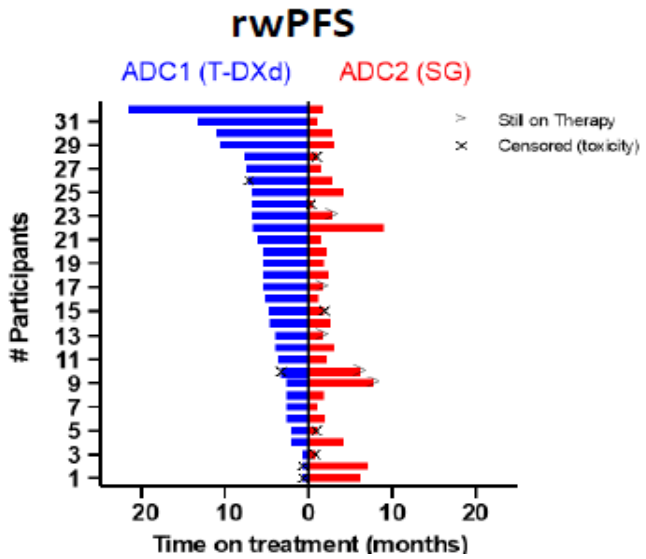
*PARP inhibitors can be considered in the first through third line setting for BRCAm patients

Sequencing of ADCs

Real world evidence study

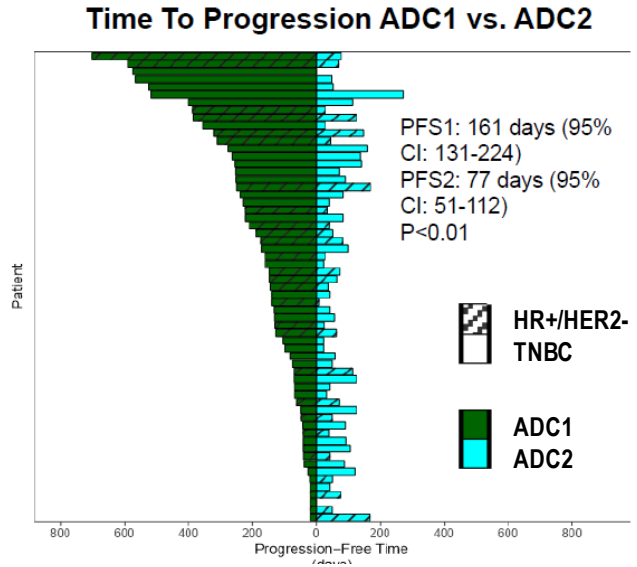
sequencing T-DXd and sacituzumab in patients with HER2-low MBC





A3 study

HR+/HER2- MBC and mTNBC with 2+ ADCs

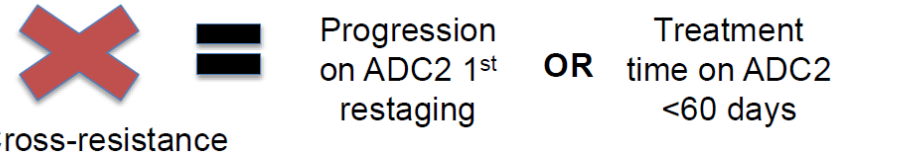


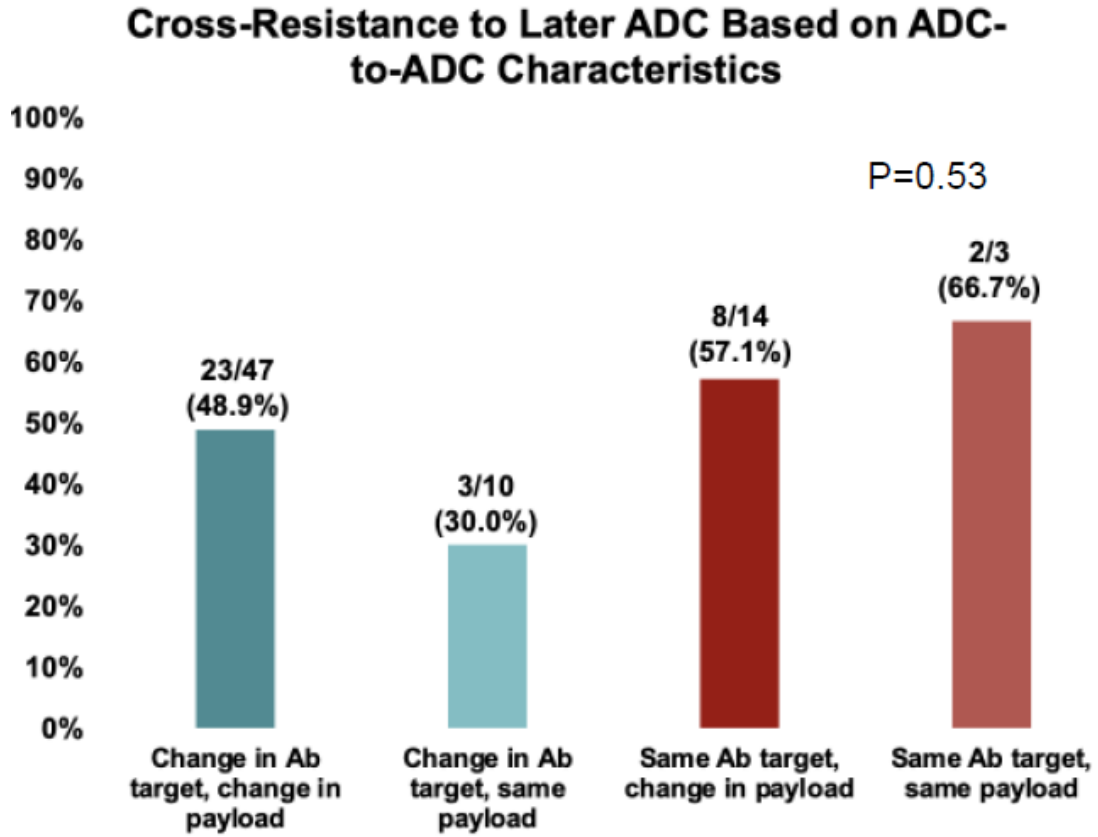
- Almost universally, greatest magnitude of benefit is derived from the 1st ADC used
- So, does it matter which ADC you choose first?

Huppert L et al. SABCS 2023; Abelman R et al. ASCO 2023

Sequencing of ADCs

A3 study





- Cross resistance lowest with different antibody target vs. payload
- Sequencing with ADCs against novel targets (for ex: HER3 or c-MET in breast and lung cancer) might mitigate cross resistance

Abelman R et al. ASCO 2023

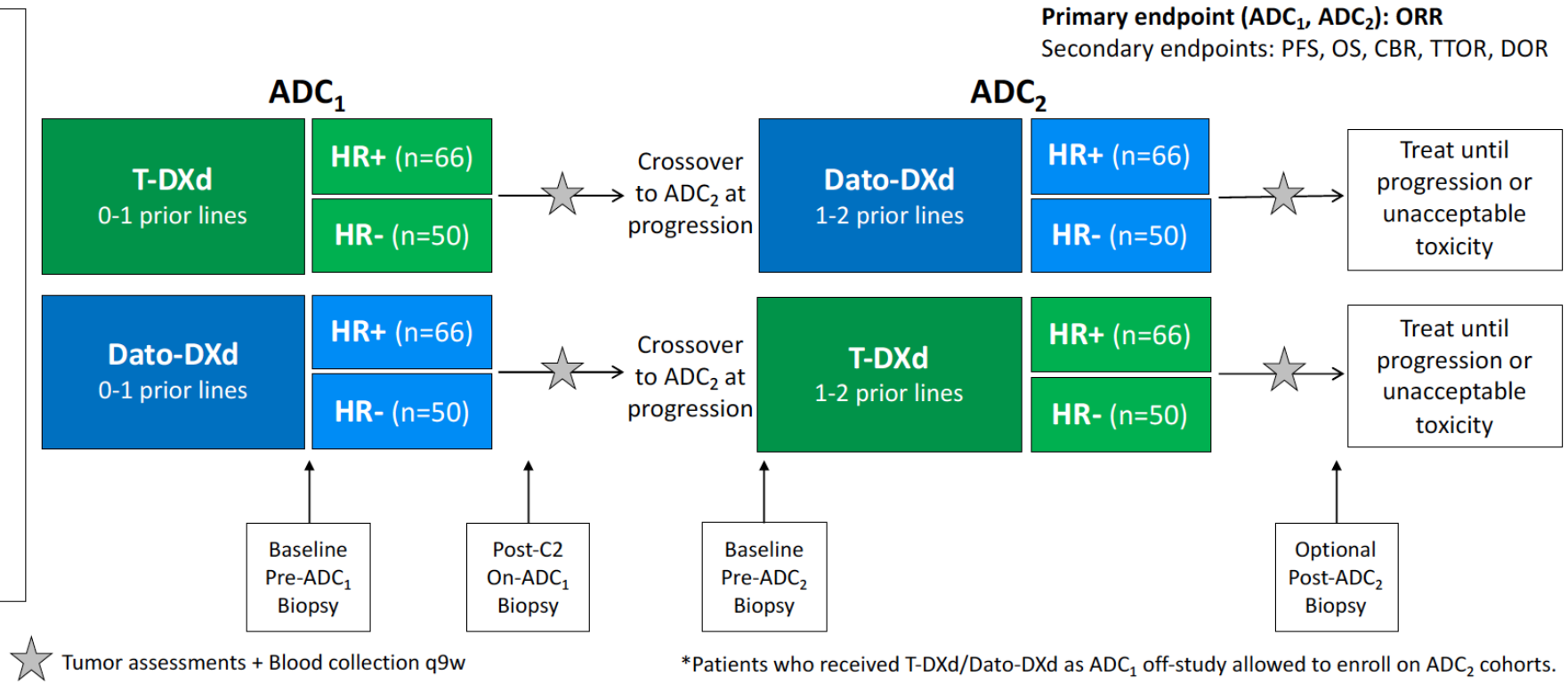
TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE DXd)

PI: Ana Garrido-Castro (DFCI)

Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low BC: IHC 1+ or 2+/ISH- (any sample: primary or met)
- Measurable disease
- Prior endocrine therapy and CDK4/6 inhibitor for HR+ MBC
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

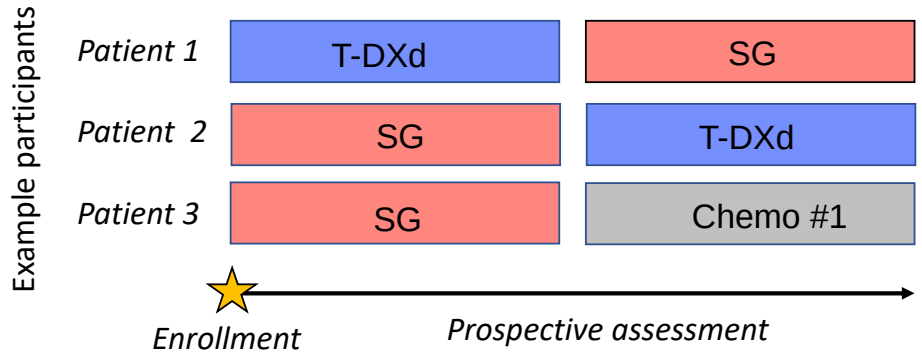
*Randomization 1:1 to T-DXd or Dato-DXd as ADC_1 for allocation purposes.



ENCORE Registry Sequencing Study: TDX-d and SG

PI: Laura Huppert (UCSF)

Cohorts 1 & 2: Enrollment Prior to ADC #1



Cohort 1: HR+/HER2- HER2 low
~35 patients

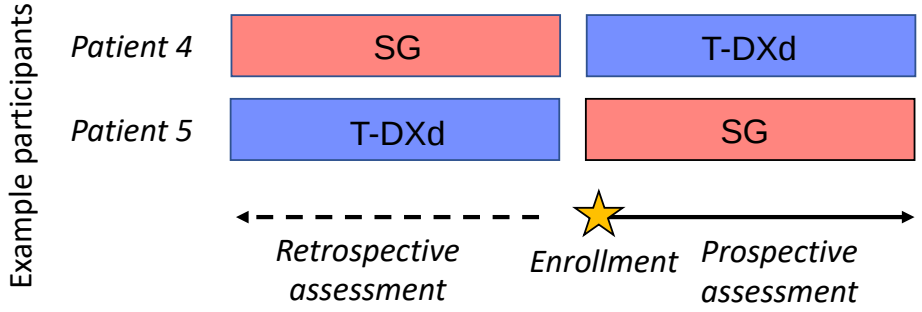
Cohort 2: TNBC, HER2 low
~25 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

Objectives/considerations:

- Allows for prospective assessment of ADC #1 and ADC #2 efficacy, including PRO data and collection of blood for translational endpoints
- Potential barrier: Patient not guaranteed to get ADC #2 (e.g., example patient #3 shown here)

Cohorts 3 & 4: Enrollment Prior to ADC #2



Cohort 3: HR+/HER2-
~25 patients

Cohort 4: TNBC
~15 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

Objectives/considerations:

- Allows for prospective assessment of ADC #2 safety and efficacy, including PRO data and translational endpoints
- Allows for retrospective safety and efficacy of ADC #1

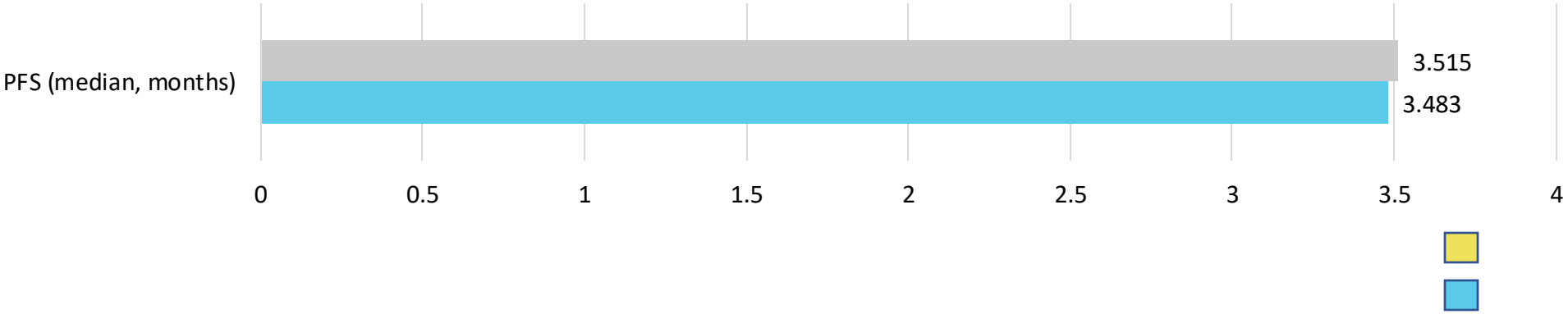
Sequencing: Enfortumab vedotin after Sacituzumab

Phase 2 trial of Enfortumab vedotin in metastatic HR+ and TNBC

-No difference in Nectin-4 expression between responders and non-responders

TNBC cohort subgroup analysis

PFS by prior SG treatment



Sequencing using an ADC with novel target (Nectin-4) and different payload (MMAE) led to similar PFS as in ADC-naïve pt population

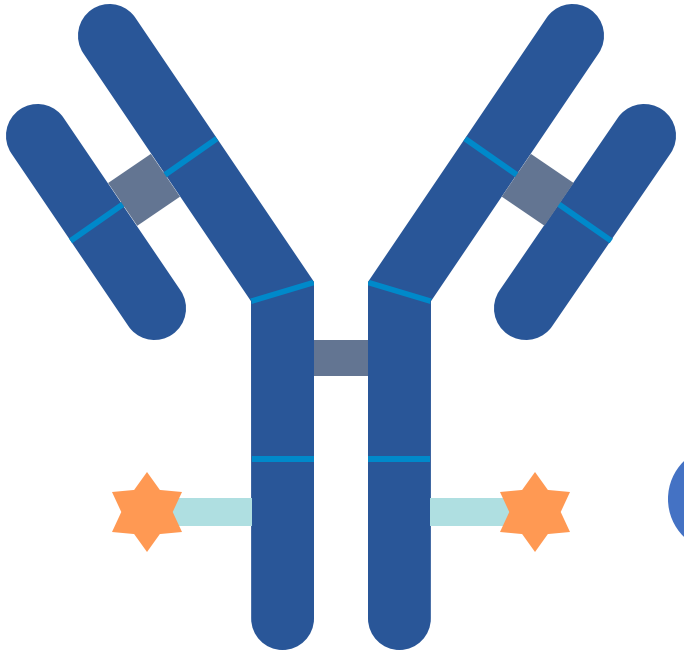
Giordano A et al. ASCO 2024

Mechanisms of Resistance to ADCs

1

Antigen binding

Downregulation of antigen expression
Alteration/masking of binding site
TROP2/TACTD2 mutations



2

Payload

Drug efflux transporters
Intrinsic resistance to cytotoxic payload
Mutations in TOP1 (gene encoding topoisomerase I)

3

Internalization/Trafficking

Altered intracellular trafficking
Altered Cell-surface recycling kinetics
Reduced lysosomal processing

Key Take Aways

ADCs are our present and here to stay

-Remarkable efficacy in HER2+ disease

-TDX-d and Sacituzumab govitecan approved in HER2 Low and TNBC as well

-TDX-d might be approved for HER2 Ultra-low

-Newer TROP2 and HER2 ADC might get approved in future

-Ongoing trials in earlier lines, early-stage disease, and new ADCs in development

-Mechanisms of resistance and optimal sequencing not well understood; prospective trials ongoing

-Optimizing toxicity management is critical

@jhaveri_komal

Acknowledgements

Patients and their families who inspire us everyday

Questions?

@jhaveri_komal