21st Annual Miami Cancer Meeting

MCM

Tampa Bay Edition

Fostering Multidisciplinary Care in the Era of Complex Cancer Treatments

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

Antibody Drug Conjugates for HER2-negative Breast Cancer

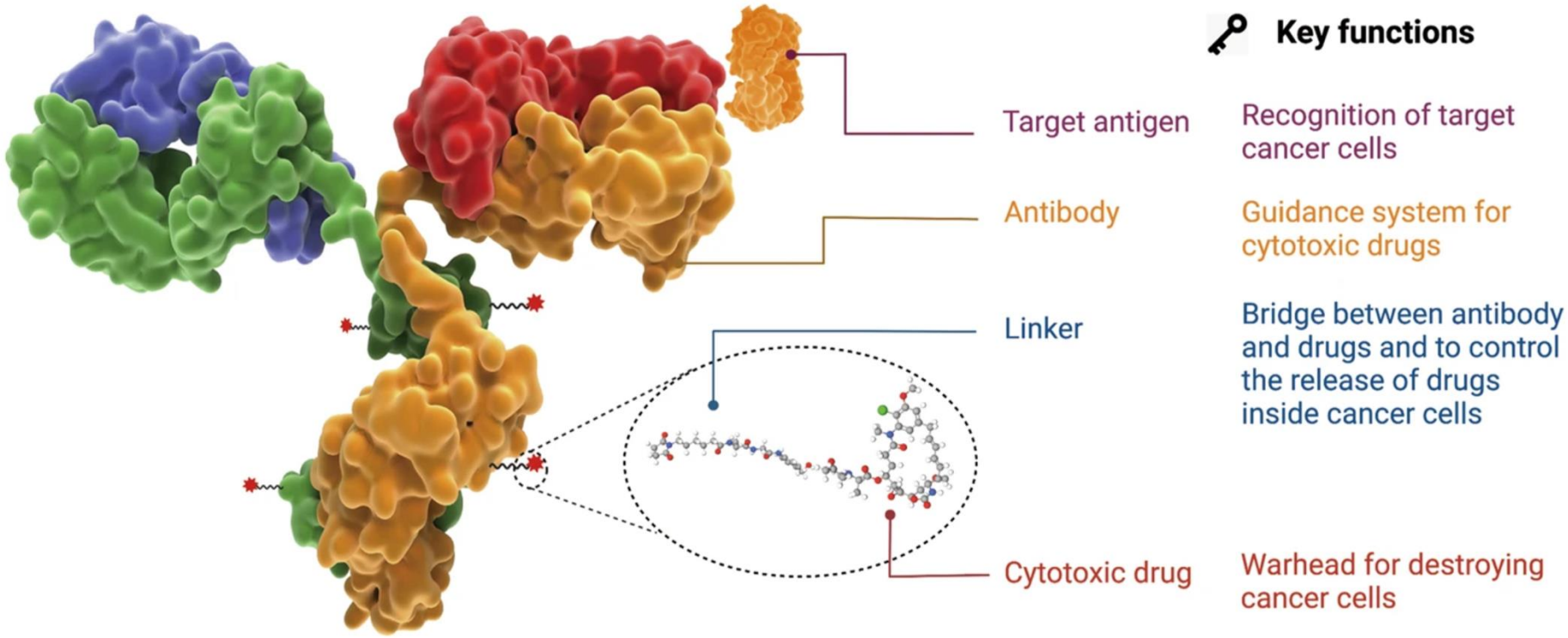
Mariana Chávez Mac Gregor MD, MSc, FASCO.

Professor

Health Services Research and Breast Medical Oncology Departments

The University of Texas, MD Anderson Cancer Center

ADCs have reshaped the treatment of patients with MBC



Chau el at. Lancet 2019; 394(10200)
Fu et al. Signal Transduction and Targeted Therapy 2022; 7(93)

Today's use of ADCs in ABC: All BC subtypes

HER2-positive

HER2-negative

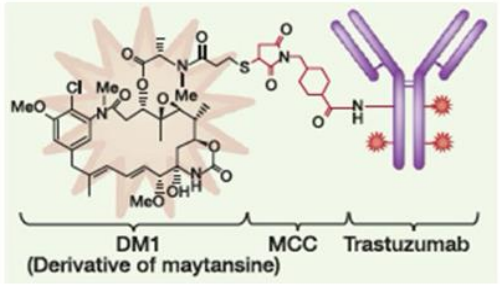
HER2-low (1+, 2+), ultralow

HR-positive

HR-negative

Trastuzumab emtansine (T-DM1)

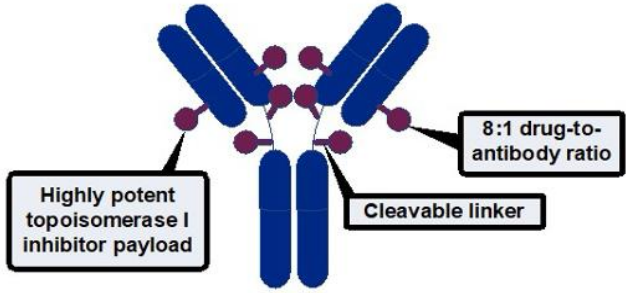
HER2-directed ADC



Previously treated metastatic **HER2+** breast cancer

Trastuzumab deruxtecan (T-DXd)

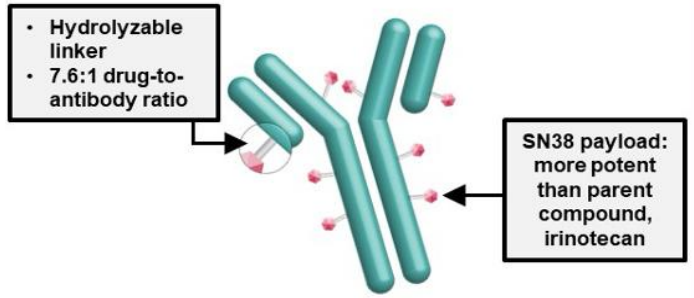
HER2-directed ADC



Previously treated unresectable or metastatic **HER2+** or **HER2-low** breast cancer

Sacituzumab govitecan (SG)

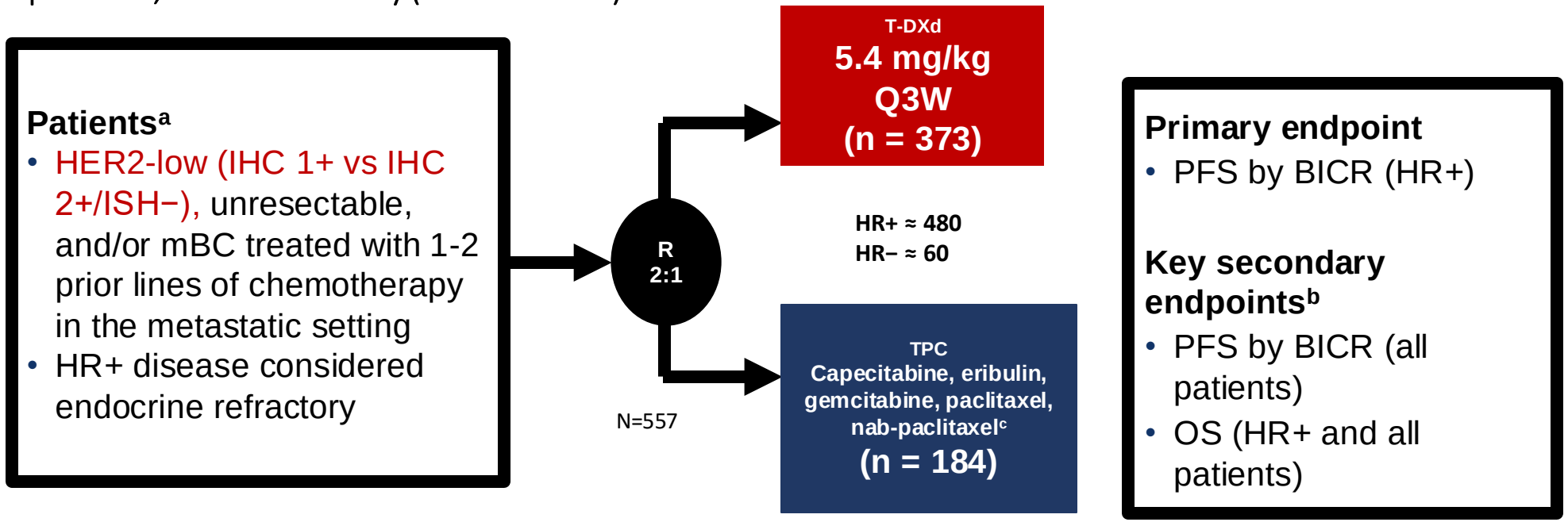
TROP2-directed ADC



Previously treated unresectable or metastatic **TNBC** or **HR+/HER2-** breast cancer

DESTINY-B04: Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

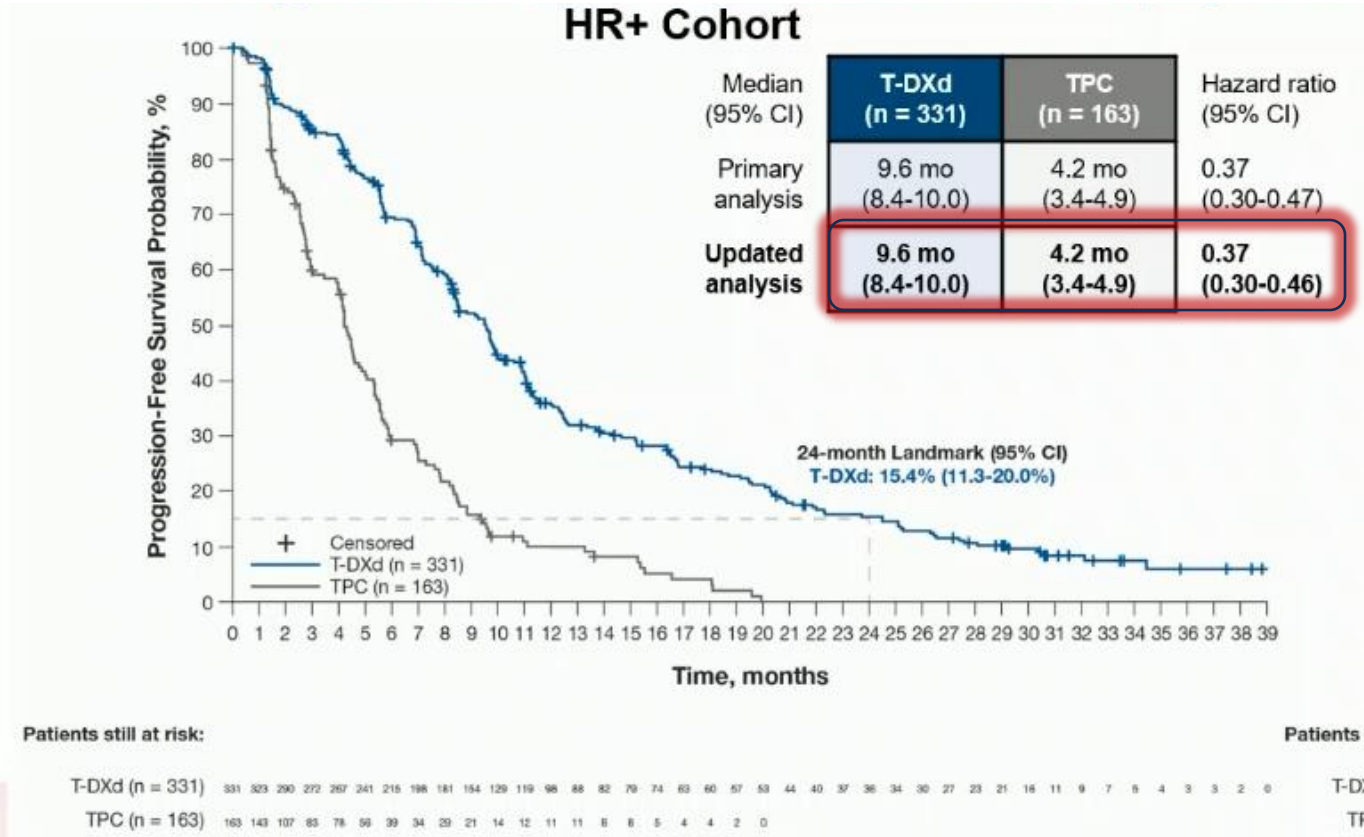
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

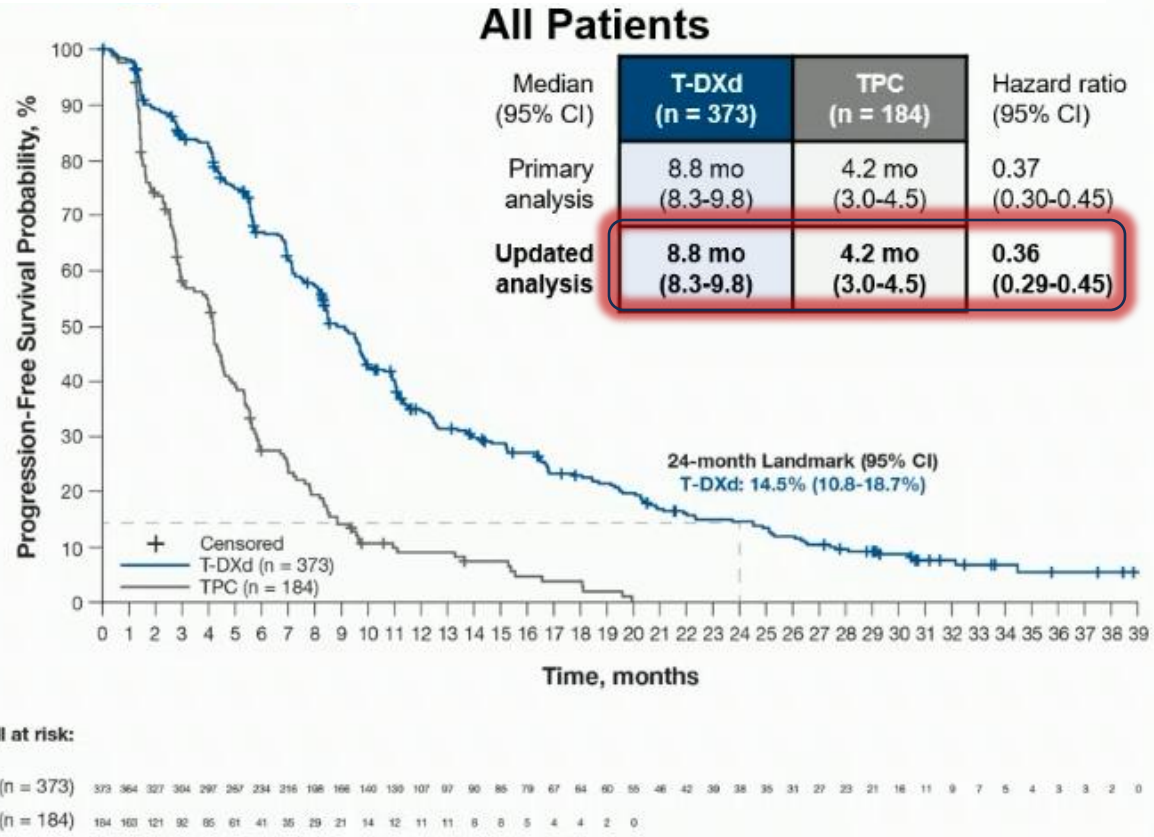
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; 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.

Modi S, el at. NEJM 2022

Updated PFS (median 32 months) by investigator





- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

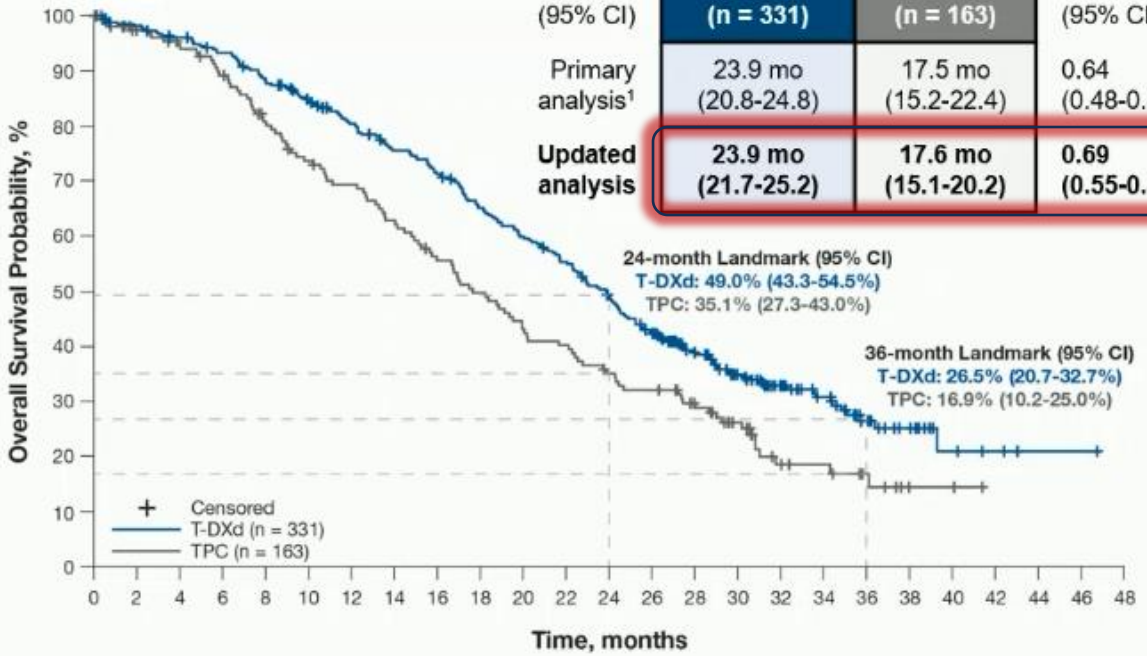
BICR, blinded independent central review; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.
1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

Modi S, el at. ESMO 2023

Updated OS (median 32 months) by investigator

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)**



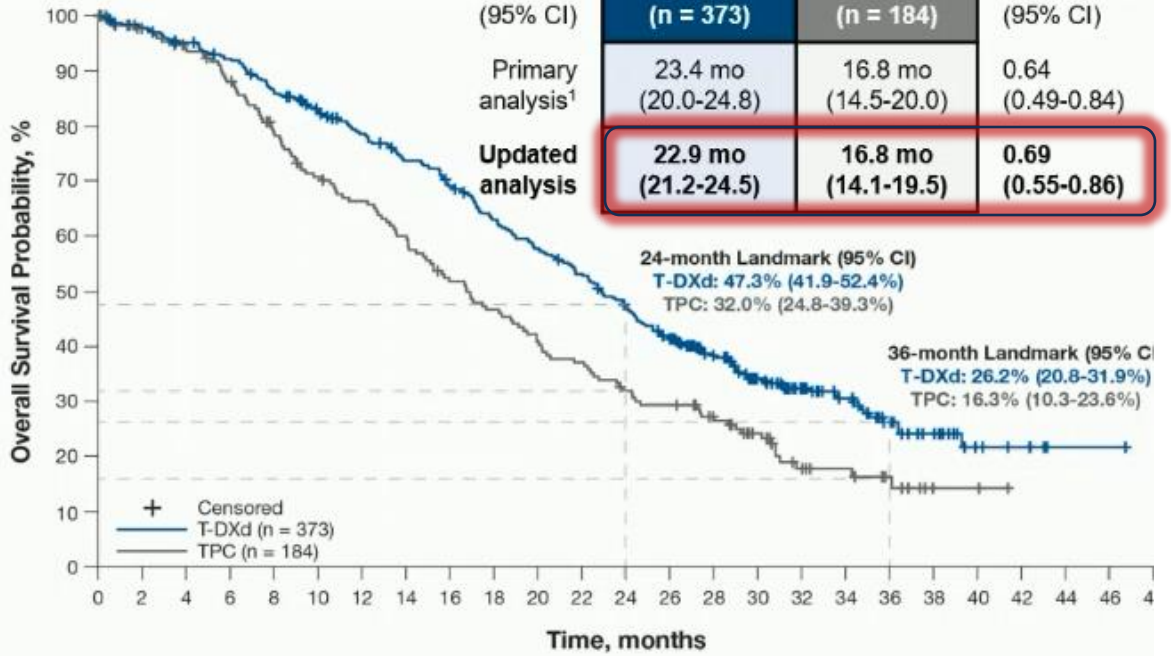
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 156 147 136 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 66 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 206 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 16 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

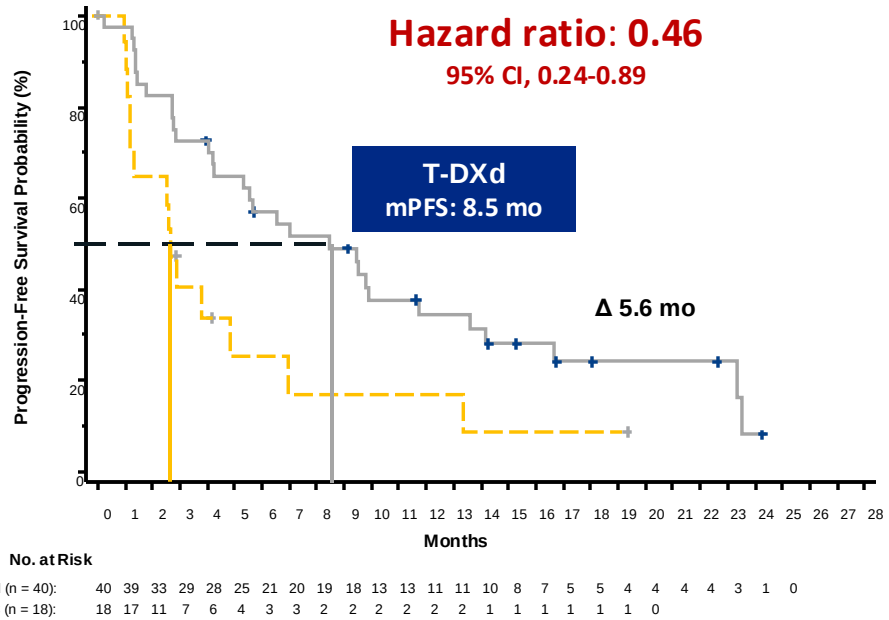
HR, hormone receptor; mo, month; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

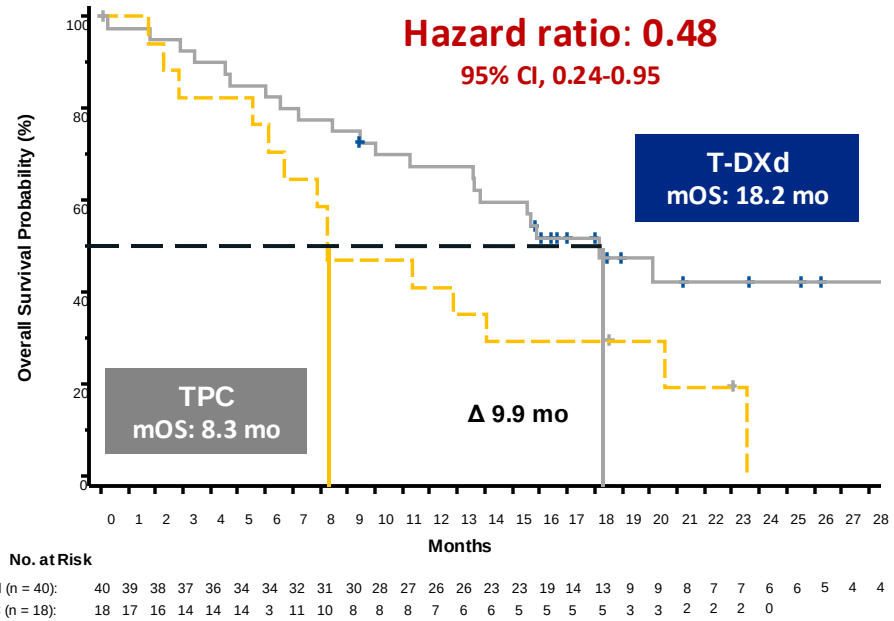
Modi S, el at. ESMO 2023

DESTINY-B04: PFS and OS in HR− (Exploratory Endpoints)

PFS



OS



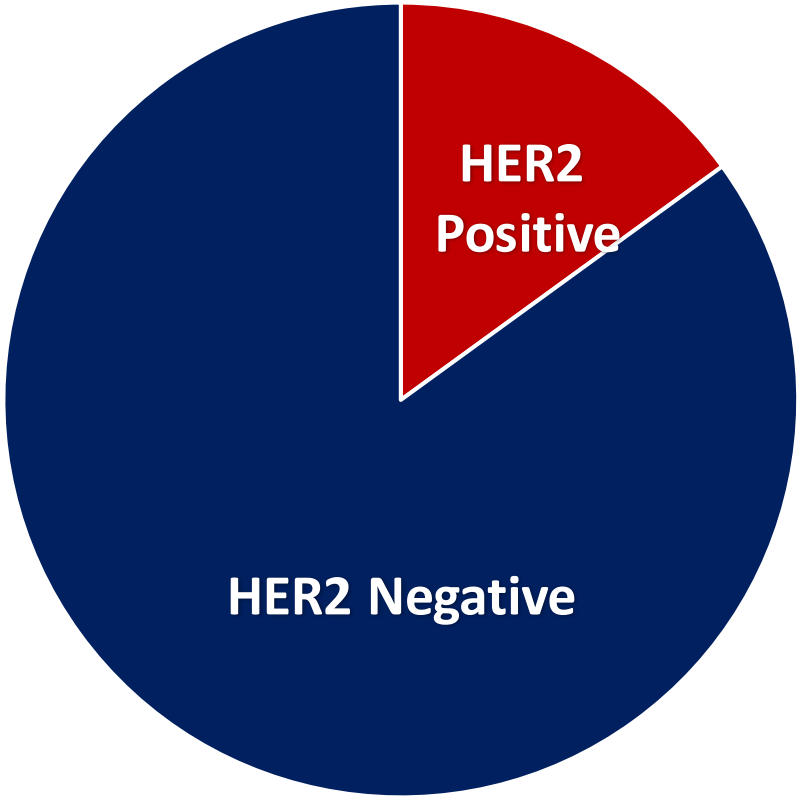
HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based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

Modi S, el at. NEJM 2022

2022 FDA Approved T-DXd as the new SOC For HER2 Low MBC

~~Traditional View of HER2-Positive Breast Cancer~~

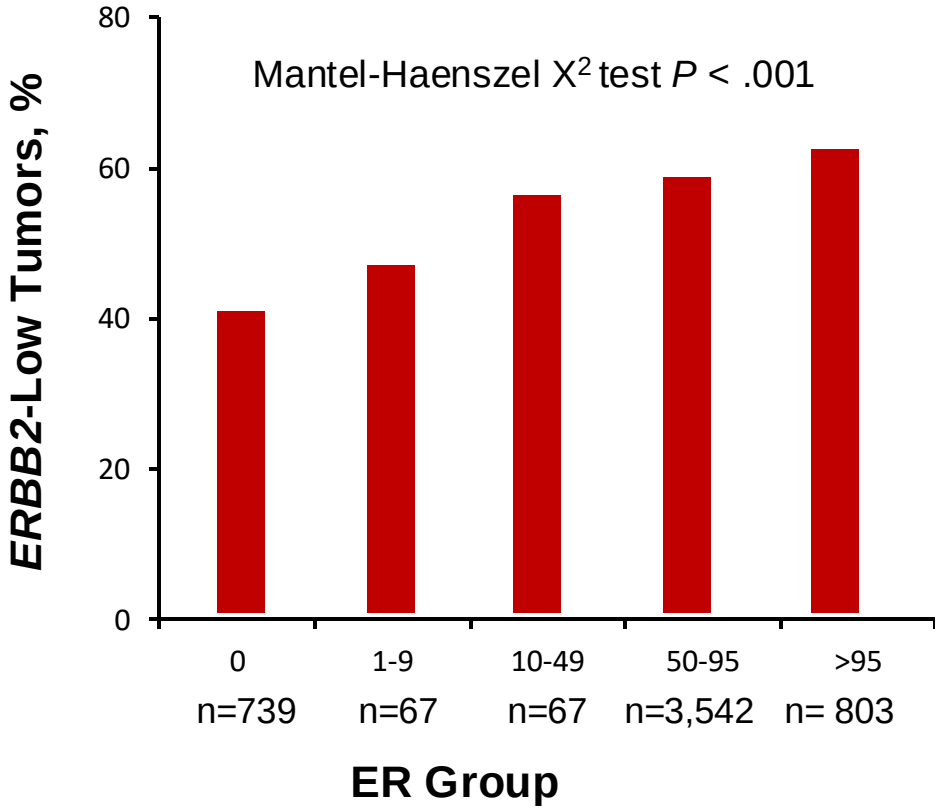
- Tumors lacking *ERBB2* overexpression or amplification are collectively defined as HER2 negative



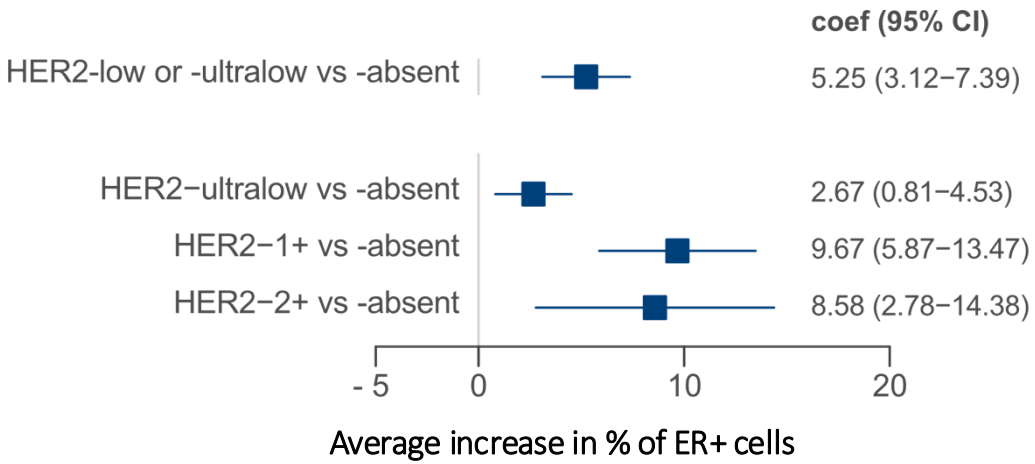
Wolff A et al. J Clin Oncol. 2018;36:2105-2122.

HER2-low disease increases as ER increases

Dana-Farber Cancer Institute Series



University Hospitals Leuven

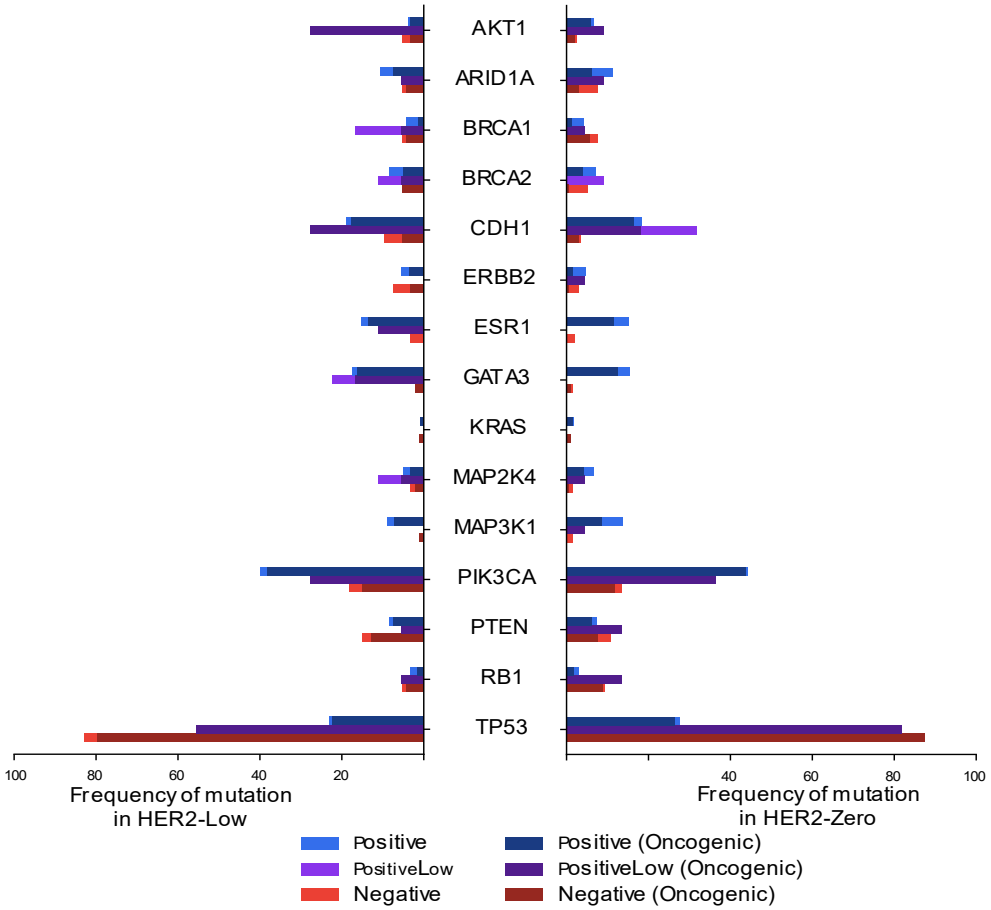


Modified from Sara Tolaney, MD.

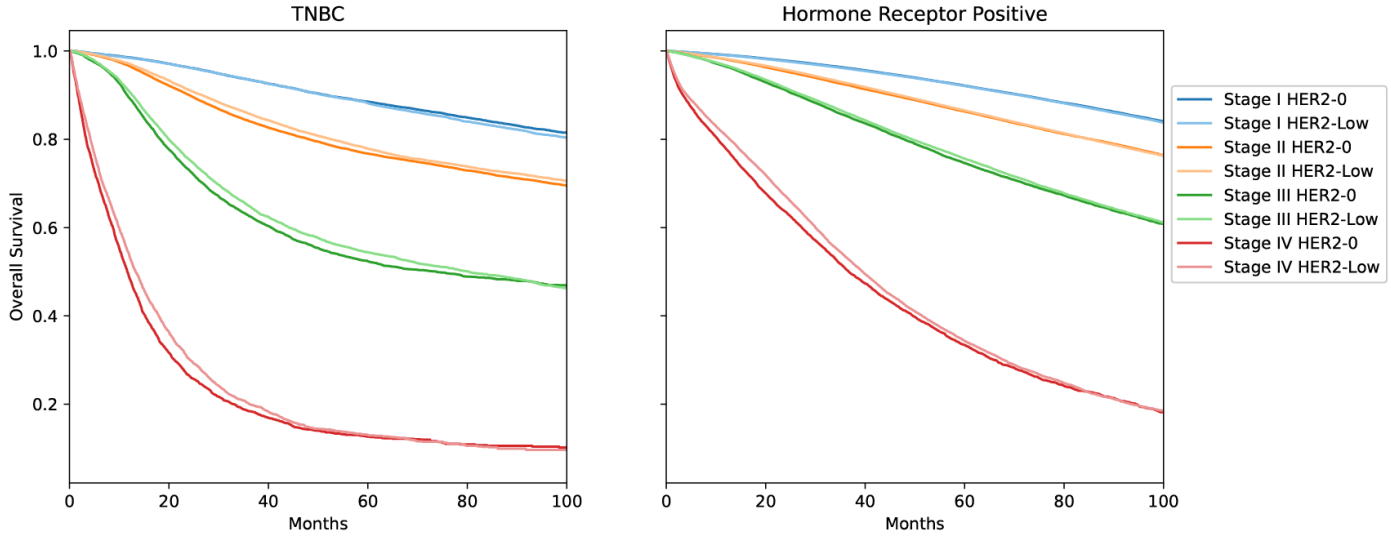
Geukens T et al, SABCS 2022.

Tarantino P et al. JAMA Oncol. 2022;8:1177-1183.

Similar genomic characterization and similar otcomes



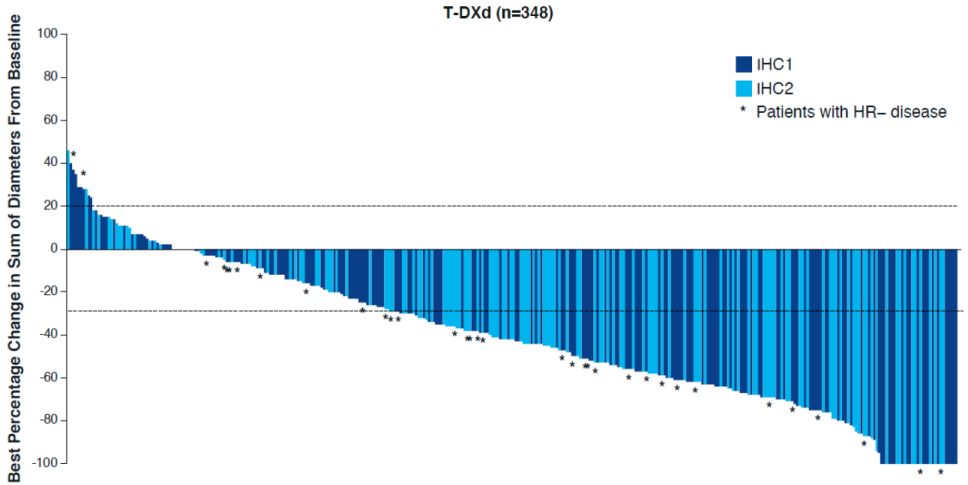
Retrospective Cohort Study: National Cancer Data Base (2010-2019)
N=1,136,016



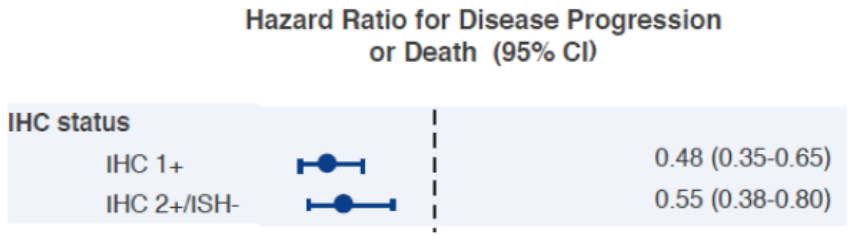
No significant differences in the incidence of oncogenic mutations (after correcting for ER) N=1039

Peiffer D et al, SABCS 2022
Tarantino P et al, SABCS 2022

Activity of T-DXd according to HER2 IHC levels from HER2-low DESTINY-04



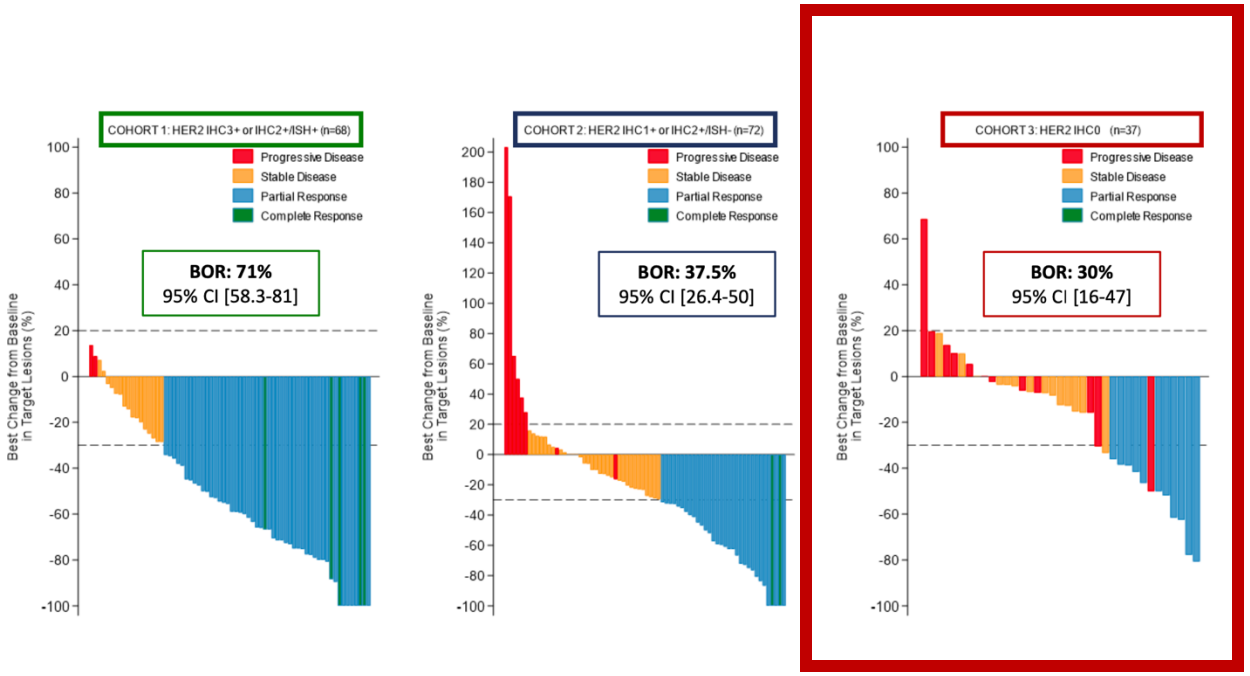
No differences in terms of ORR



No differences in terms of PFS

Modi et al. NEJM 2022

Phase 2 DAISY Trial of T-DXD: Activity seen in HER2 IHC 0 Cohort



IHC 0 Cohort med DoR: 6.8mo
med PFS: 4.2mo (CI: 2.0; 5.7)

Dieras, V et a; SABC 2021

DESTINY Breast06
Study design

PATIENT POPULATION

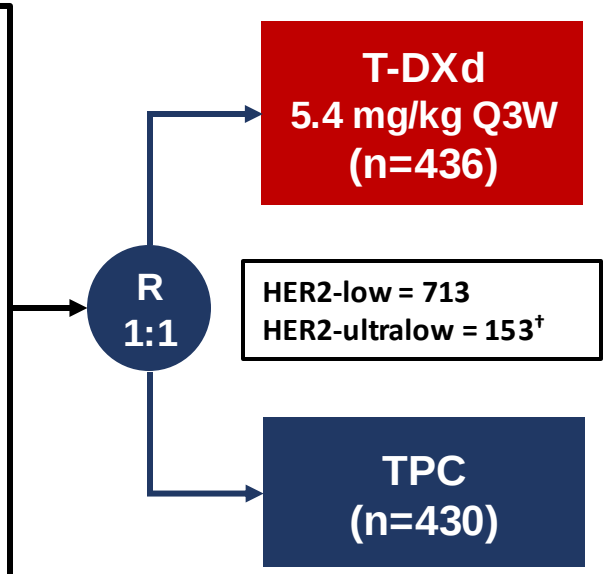
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

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

Stratification factors

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



ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

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

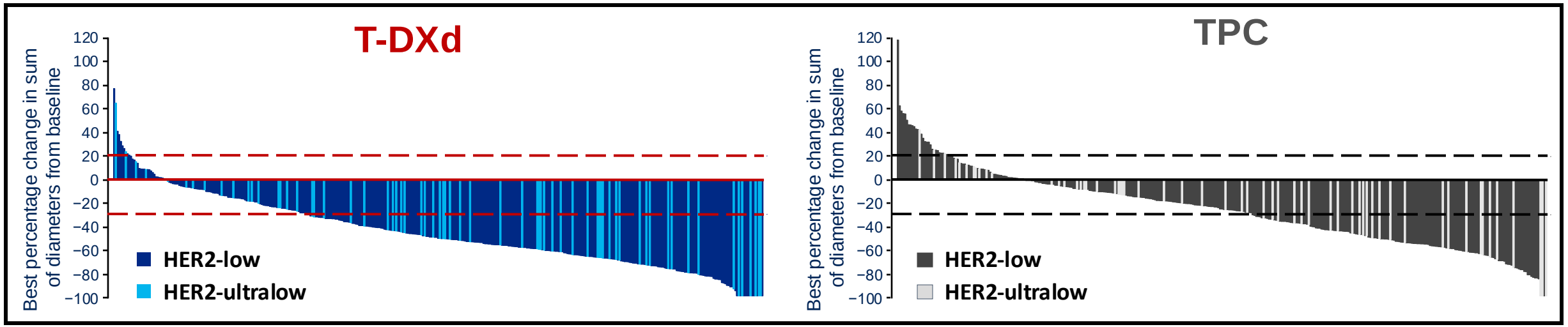
Other secondary

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

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

Curigliano et al, ASCO 2024

Antitumor activity

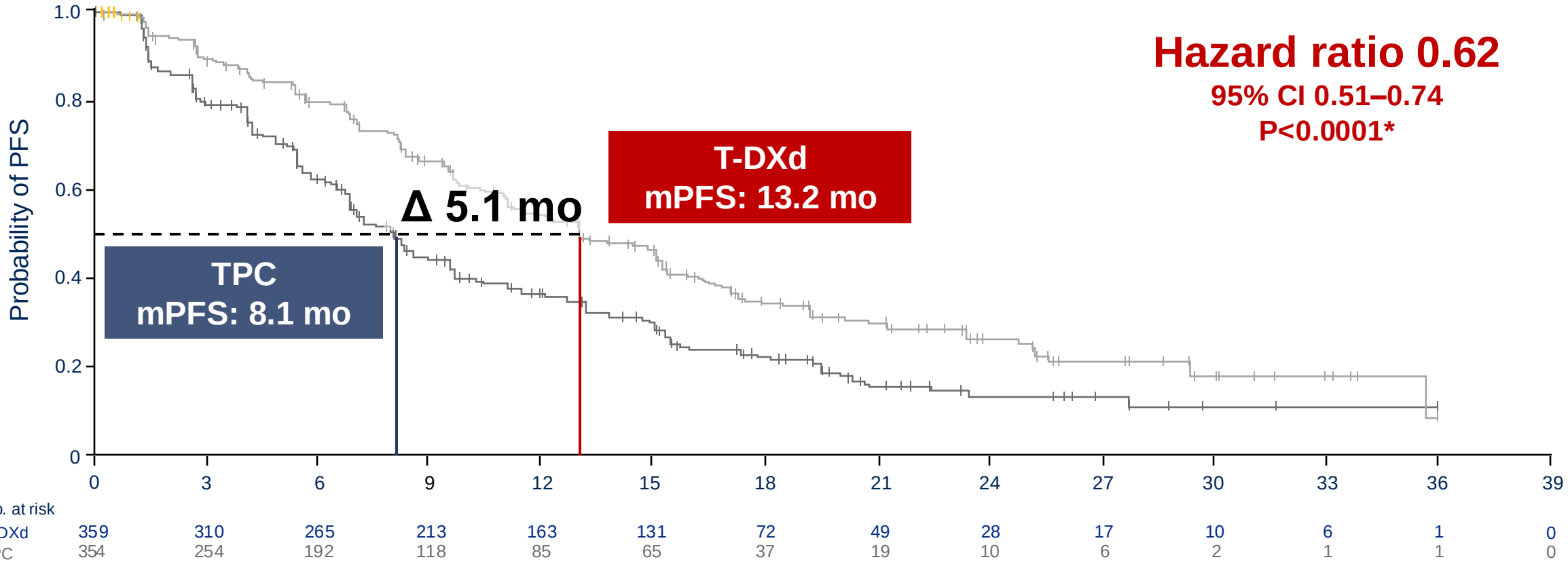


	HER2-low*		ITT		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Confirmed ORR, n (%)	**203 (56.5)**	**114 (32.2)**	**250 (57.3)**	**134 (31.2)**	**47 (61.8)**	**20 (26.3)**
Best overall response, n (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Duration of response, median, mo	14.1	8.6	14.3	8.6	14.3	14.1

- ORR based on RECIST v1.1; response required confirmation after 4 weeks
- *HER2-low status determined per IRT data, and HER2-ultralow status determined per central laboratory data; †defined as complete response + partial response + stable disease at Week 24, by blinded independent central review
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ITT, intent-to-treat; mo, months; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano et al, ASCO 2024

PFS (BICR) in HER2-low: primary endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

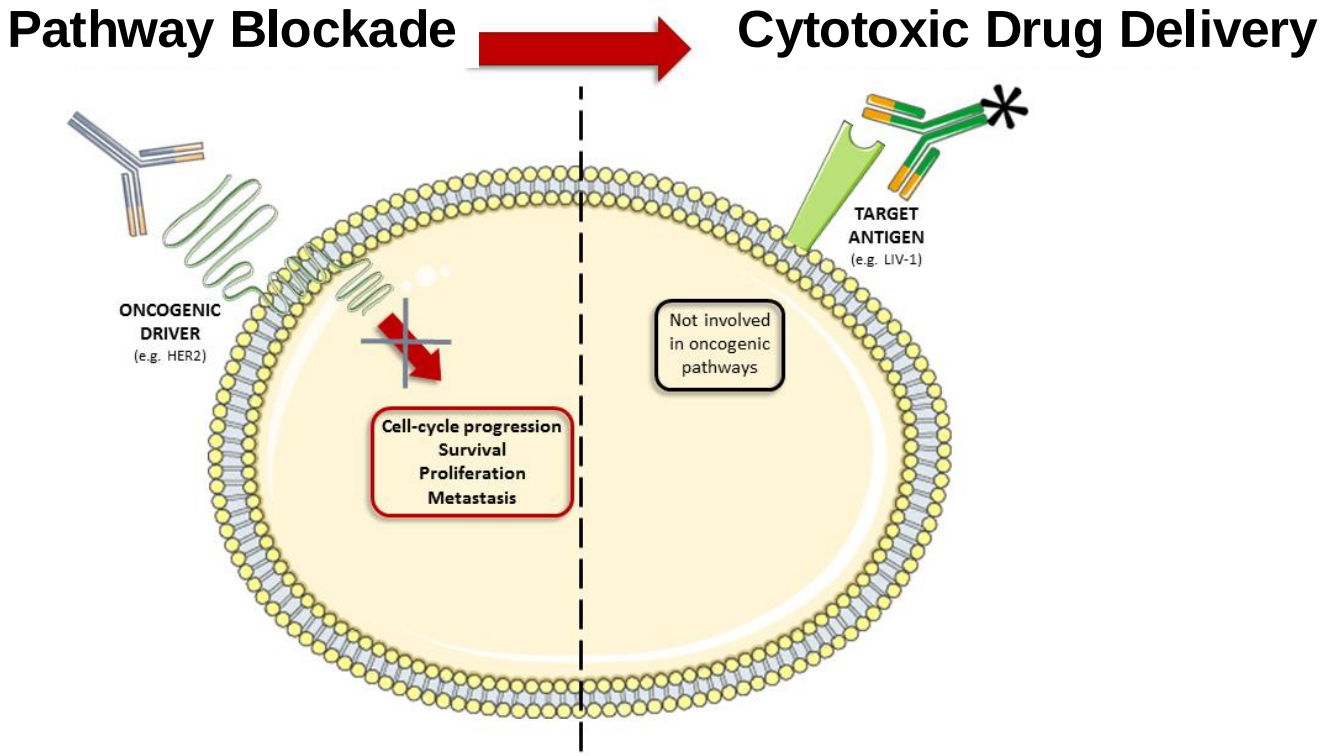
*P-value of <0.05 required for statistical significance

BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano et al, ASCO 2024

HER2 Low: Activity of HER-directed ADCs not likely related to blockade of an oncogenic driver

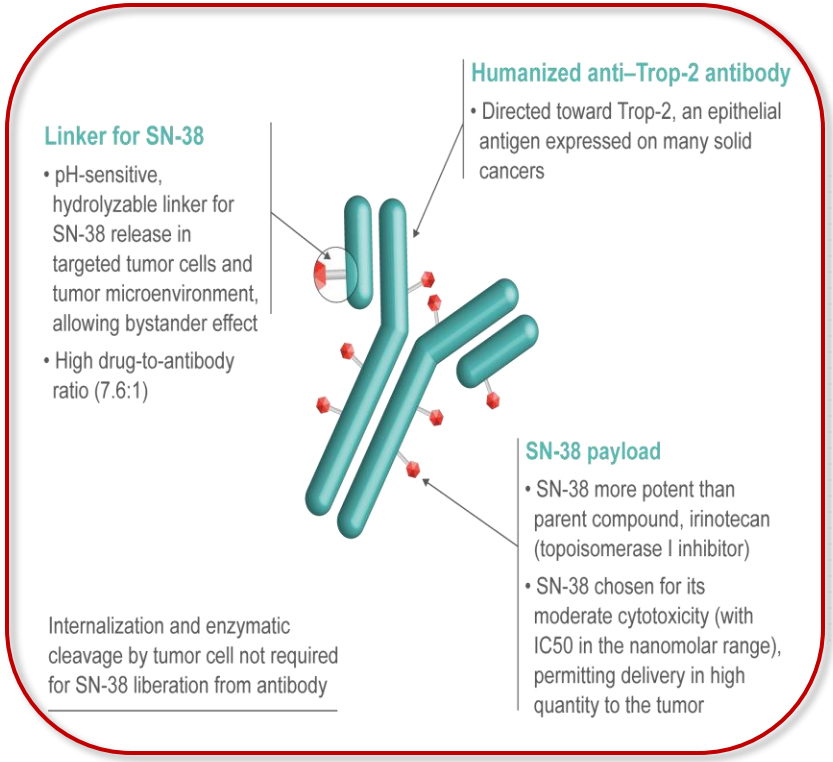
- No benefit with HER2-blockade
- But encouraging activity with the delivery of cytotoxic payloads through ADCs
- Such activity is not likely related to the blockade of an oncogenic pathway, but rather to the **targeted delivery of a highly potent payload**



Modified from Sara Tolaney, MD.

Tarantino P et al. Expert Opin Biol Ther. 2020;20:1009-1024.

ASCENT: A Phase 3 Study of Sacituzumab Govitecan in mTNBC



NCT02574455

Metastatic TNBC

(per ASCO/CAP)

≥2 chemotherapies for advanced disease

[no upper limit; 1 of the required prior regimens could be from progression that occurred within a 12-month period after completion of (neo)adjuvant therapy)]

N=529

R 1:1

Sacituzumab Govitecan (SG)
10 mg/kg IV
days 1 & 8, every 21-day cycle
(n=267)

Treatment of Physician's Choice (TPC)*
(n=262)

Continue treatment until progression or unacceptable toxicity

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Endpoints

Primary
- PFS†

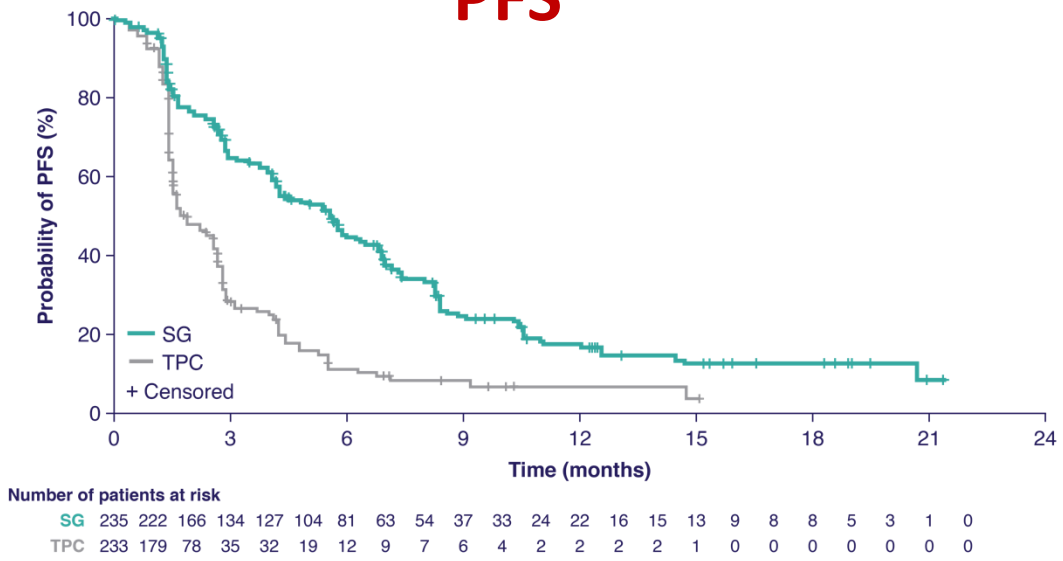
Secondary
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

A. Bardia, NEJM 2021

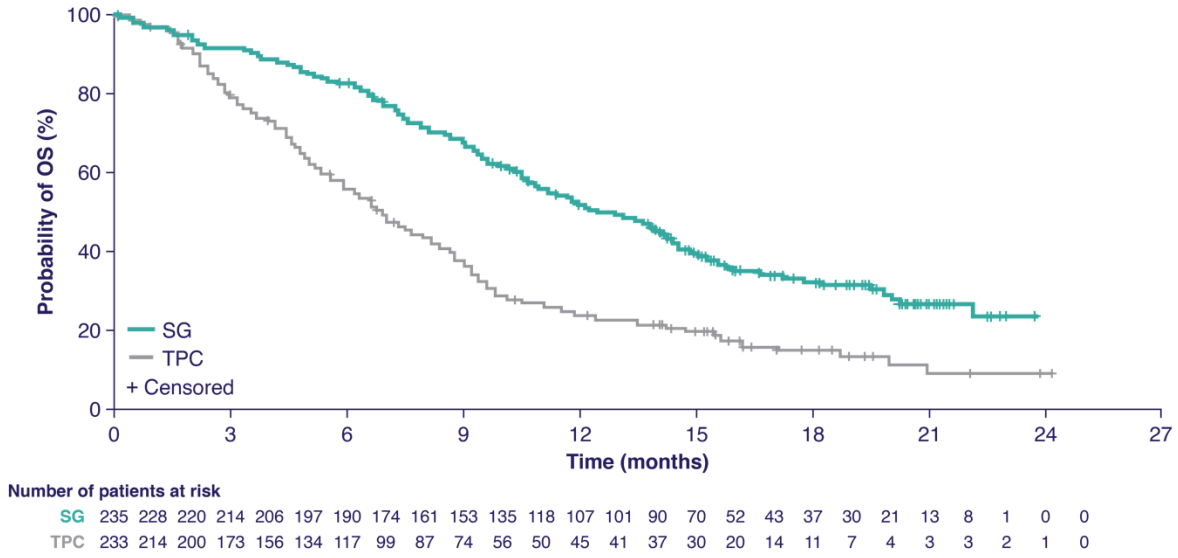
ASCENT: PFS by BICR and OS

PFS



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

OS



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

A. Bardia, NEJM 2021

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer

NCT03901339

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice[b]
(capecitabine, vinorelbine, gemcitabine or eribulin)
n=271

Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

Endpoints

Primary
- PFS by BICR

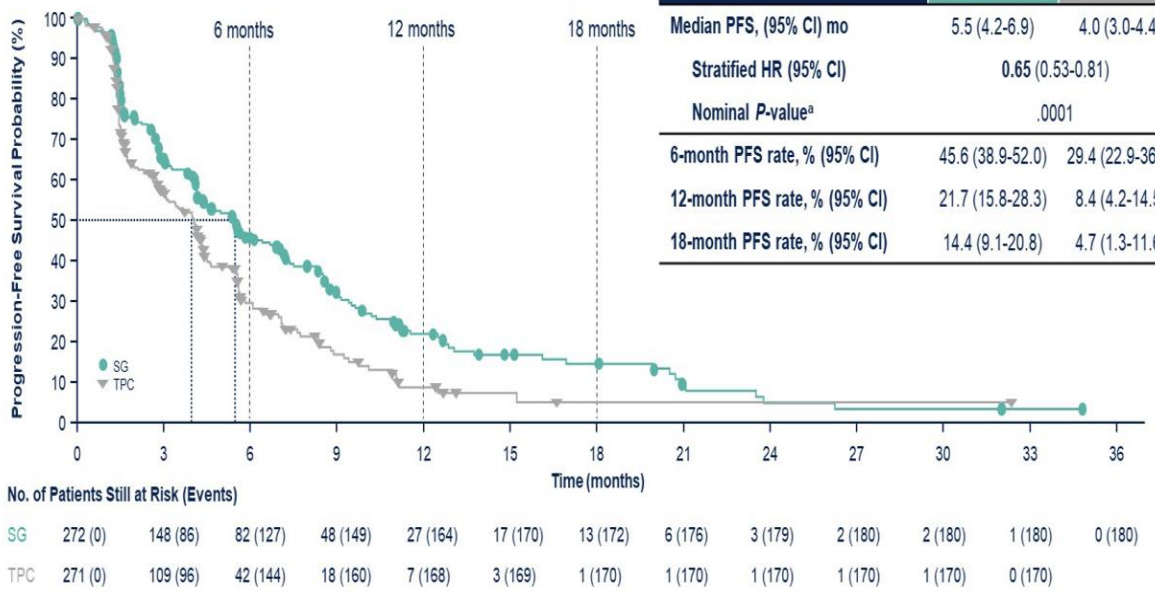
Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

[a]Disease histology based on the ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; (Neo)adjuvant, neoadjuvant or adjuvant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

TROPiCS-02: PFS & OS in the ITT Population

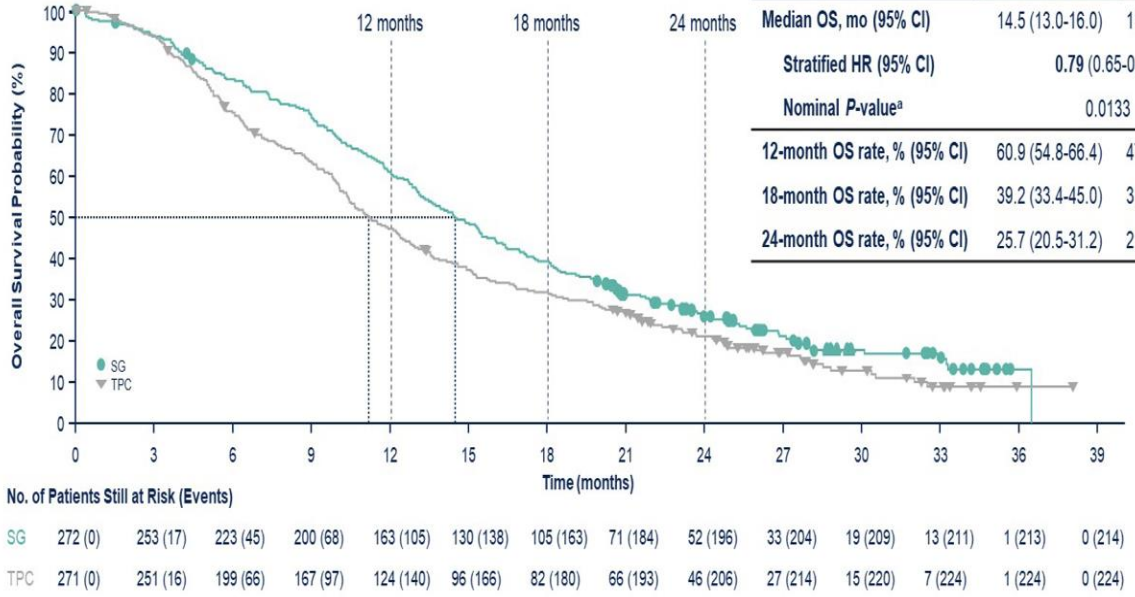
Extended follow-up

Progression-Free Survival



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	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)

Overall Survival



	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[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

Tolaney S, el at. ASCO 2023

New ADC’s, new combinations, earlier settings…

TROPION-Breast01 Study Design

Randomized, phase 3, open-label, global study (NCT05104866)

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

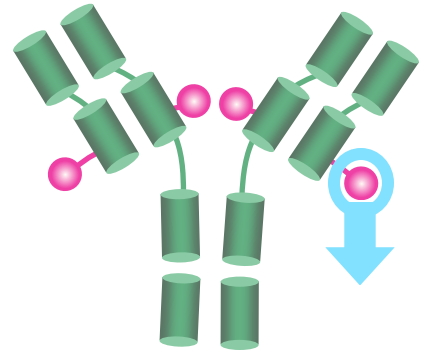
Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

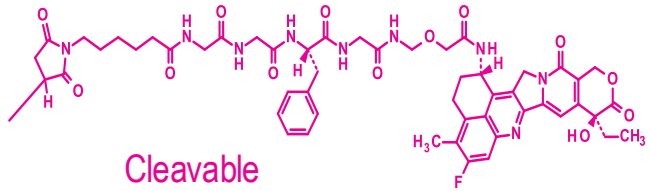
Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

Dato-DXd: Humanized anti-TROP2 IgG1 monoclonal antibody





Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

Randomization 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)

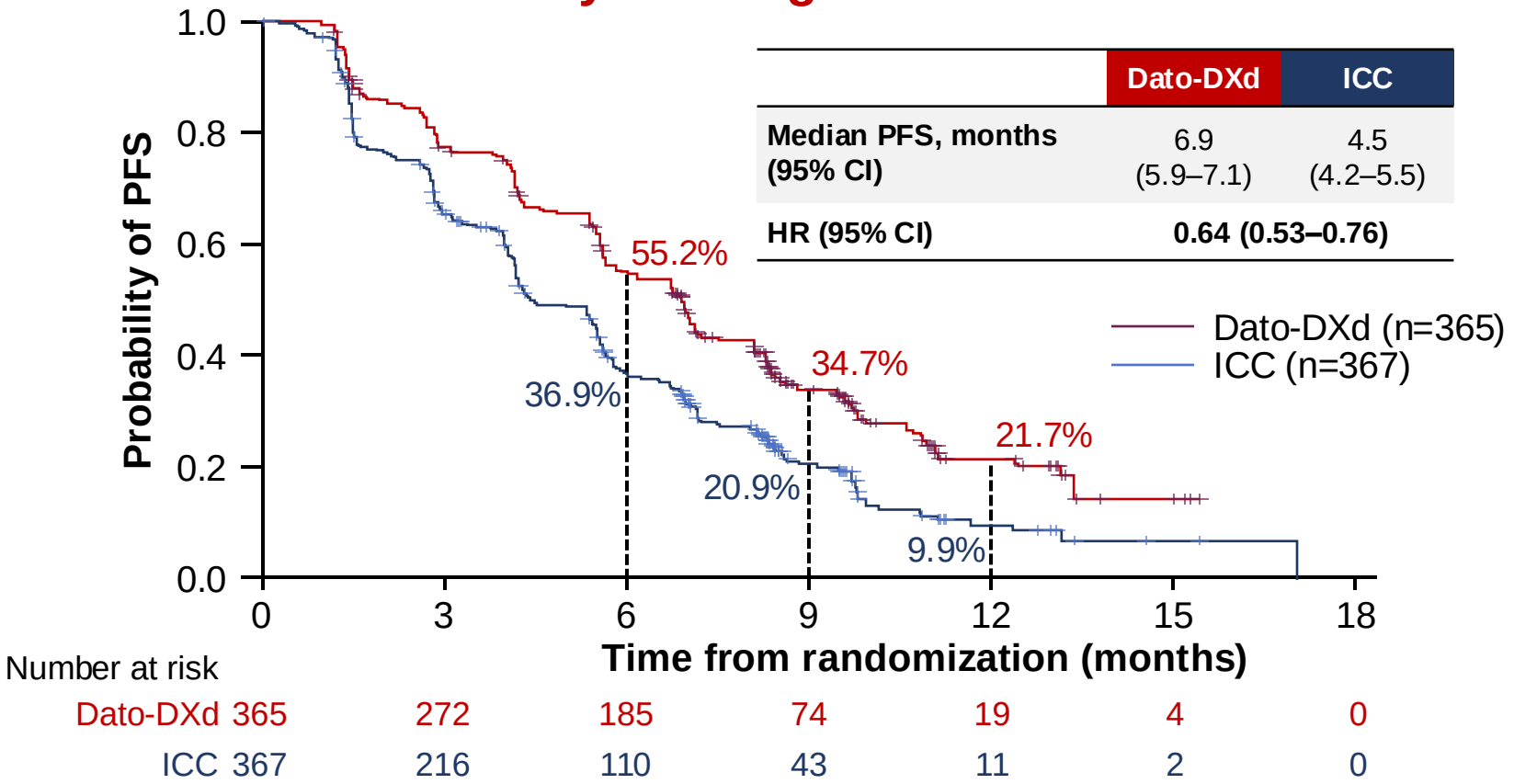
- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

*Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice). CDK4/6, cyclin-dependent kinase 4/6; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in-situ hybridization; IV, intravenous; PD, progressive disease; PROs, patient-reported outcomes; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; TFST, time to first subsequent therapy.

Bardia, et al. ESMO 2023

Progression-Free Survival

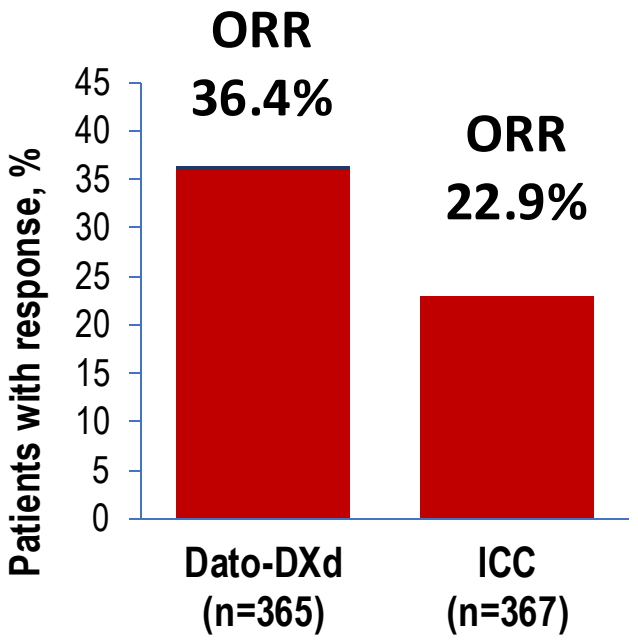
PFS by investigator assessment



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	0.64 (0.53–0.76)	

Number at risk

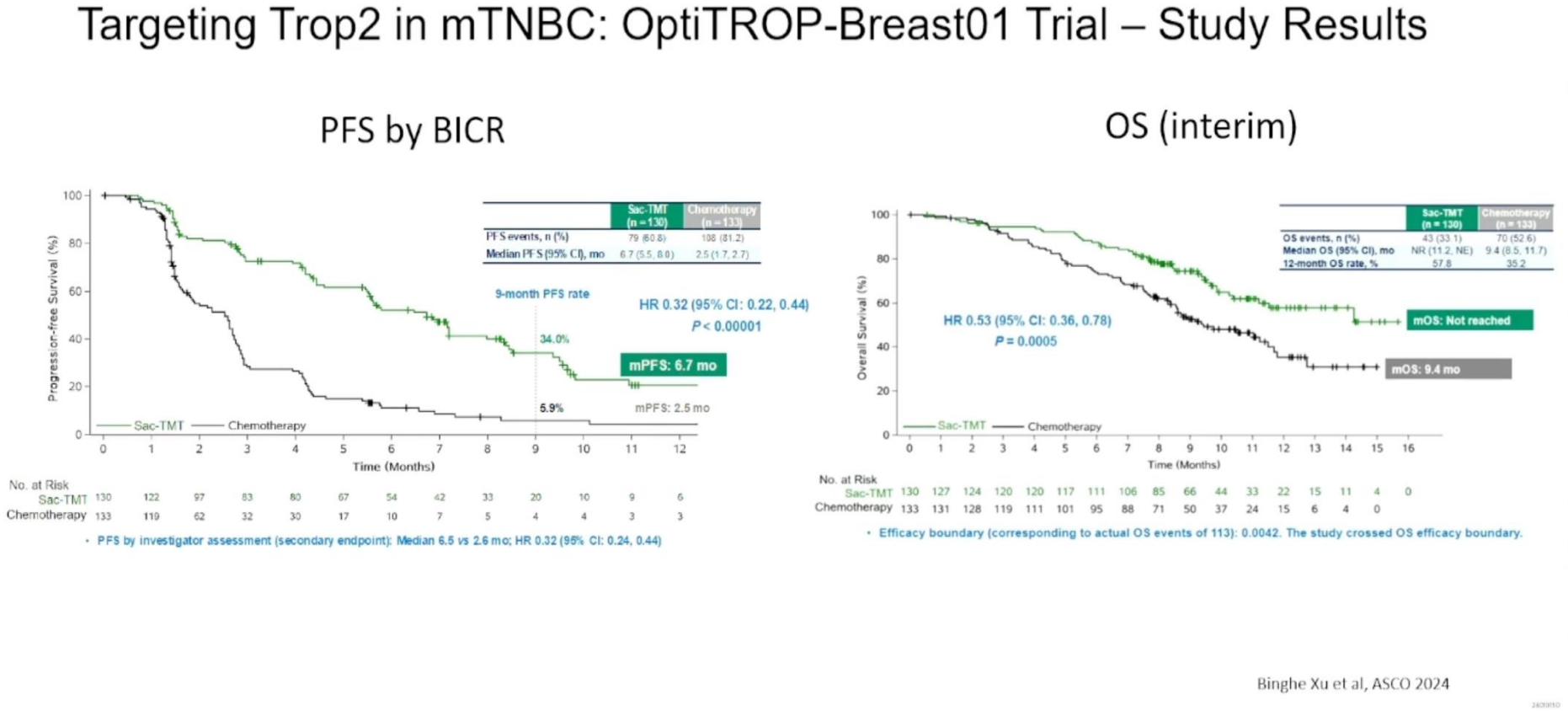
Dato-DXd	365	272	185	74	19	4	0
ICC	367	216	110	43	11	2	0

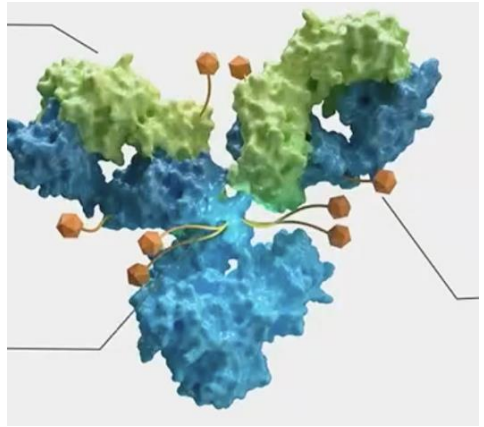


PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Bardia, et al ESMO 2023

Sacituzumab Timurotecan (sac-TMT) OptiTROP-Breast01





- Humanized anti-TROP2
- Novel Topo I inhibitor paylod (belotecan derivative)

Targeting HER3- ICARUS Breast 01
Patritumab Deruxtecan

ICARUS BREAST01: Study Design

Multi-center, single-arm, phase 2 study (NCT04965766)

KEY ELIGIBILITY CRITERIA*:
-unresectable locally advanced/metastatic BC
-HR+/HER2-neg[a]
-progression on CDK4/6inh + ET
-progression on 1 prior chemotherapy for ABC
-prior PI3K/AKT/mTORinh allowed
-no prior T-DXd

HER3-DXd 5.6 mg/kg every 3 weeks until PD or unacceptable toxicity

Primary Endpoint:
- Investigator-assessed confirmed ORR

Secondary Endpoints:
- DOR, PFS, CBR, OS
- Safety and tolerability

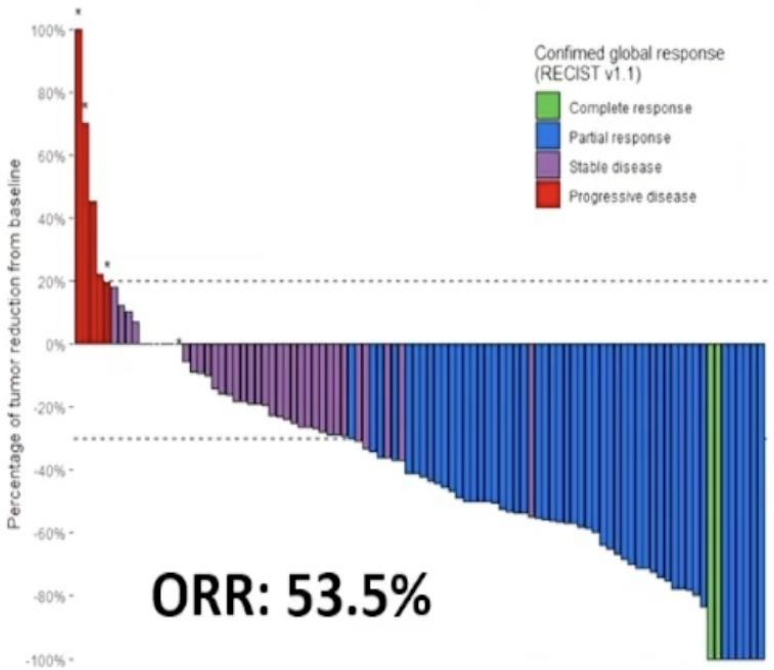
Mandatory:
-tumor biopsy (1 frozen + 3 FFPE)
-blood (whole blood + serum)

Exploratory Endpoints:
- Predictors of response/resistance
- Dynamics of HER3 expression before and after treatment
- CTCs levels during treatment

*HER3-expression prescreening (75% of membrane positivity at 10x) was removed by amendment on April 21st 2022[b]

Pistilli, ESMO 2024

Patritumab deruxtecan

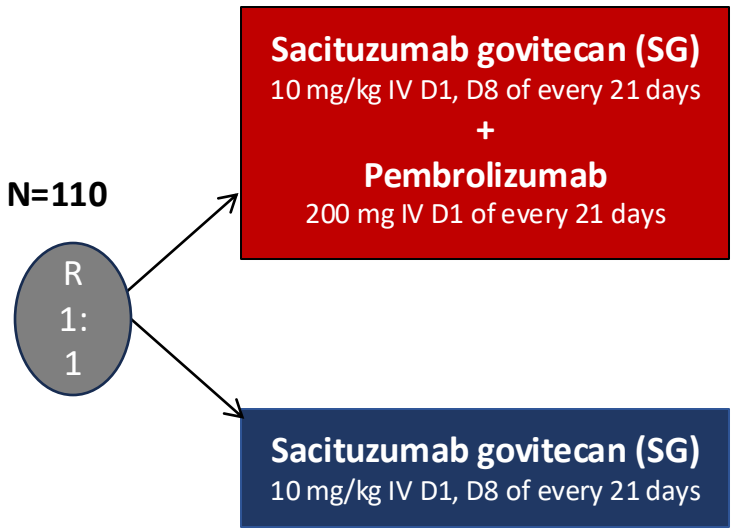


SACI-IO HR+: Study Schema

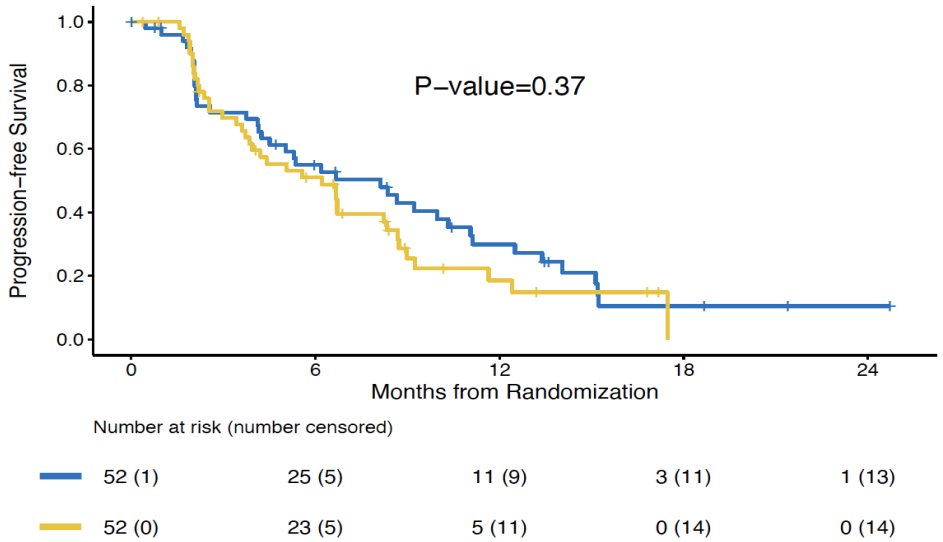
NCT04448886

Metastatic or locally advanced unresectable BC

- HR-positive (ER ≥ 1% or PR ≥ 1%), HER2-negative (IHC 0, 1+, or 2+/ ISH-)
- No restriction on PD-L1 status[a]
- ≥1 endocrine therapy for mBC or progression on or within 12 months of adjuvant endocrine therapy
- 0-1 prior chemotherapy for mBC
- No prior topoisomerase I-inhibitor ADC, irinotecan, or PD-1/-L1 inhibitor
- No known active brain metastases or leptomeningeal disease



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	0.37	



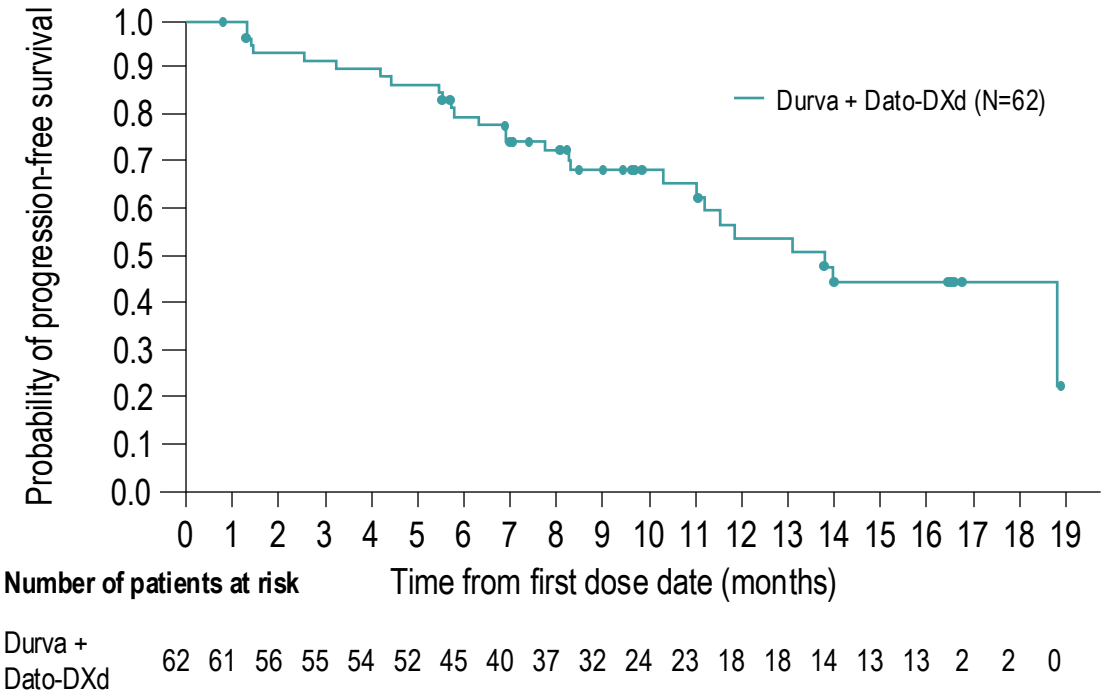
The addition of pembrolizumab to SG showed a numerical improvement in median PFS (Δ = 1.9 months) compared to SG alone that did not reach statistical significance

BEGONIA Arm 7: Dato-DXd + Durvalumab

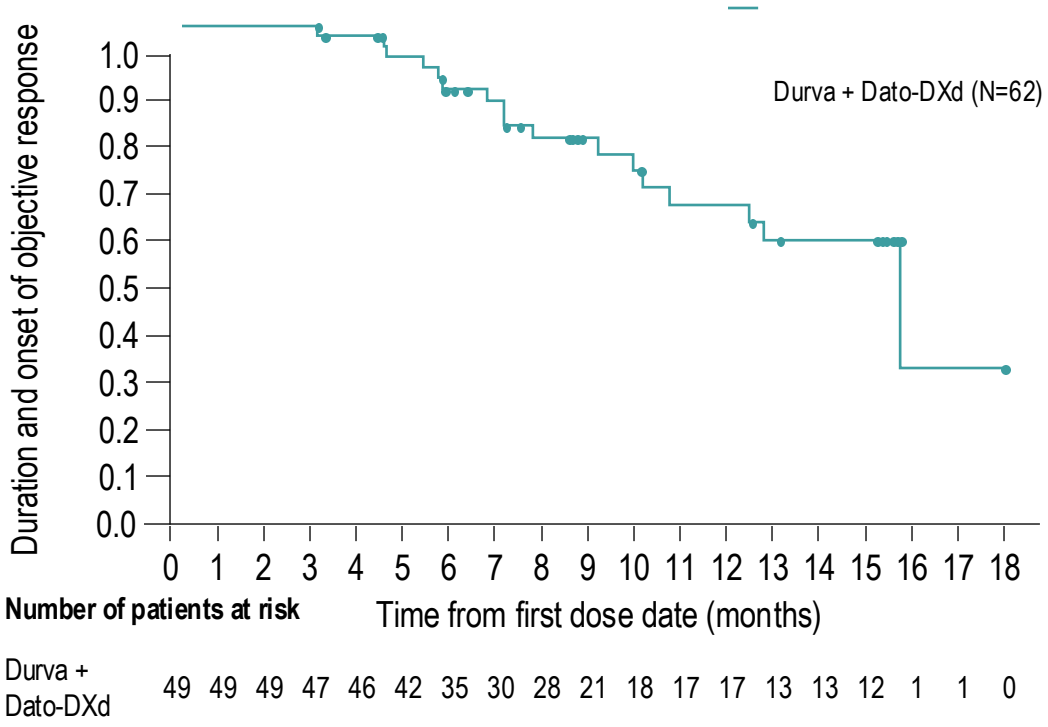
Antitumour Responses in 1L a/mTNBC (n=62)

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR Antitumor responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods

Median PFS was **13.8** months (95% CI, 11.0–NC)



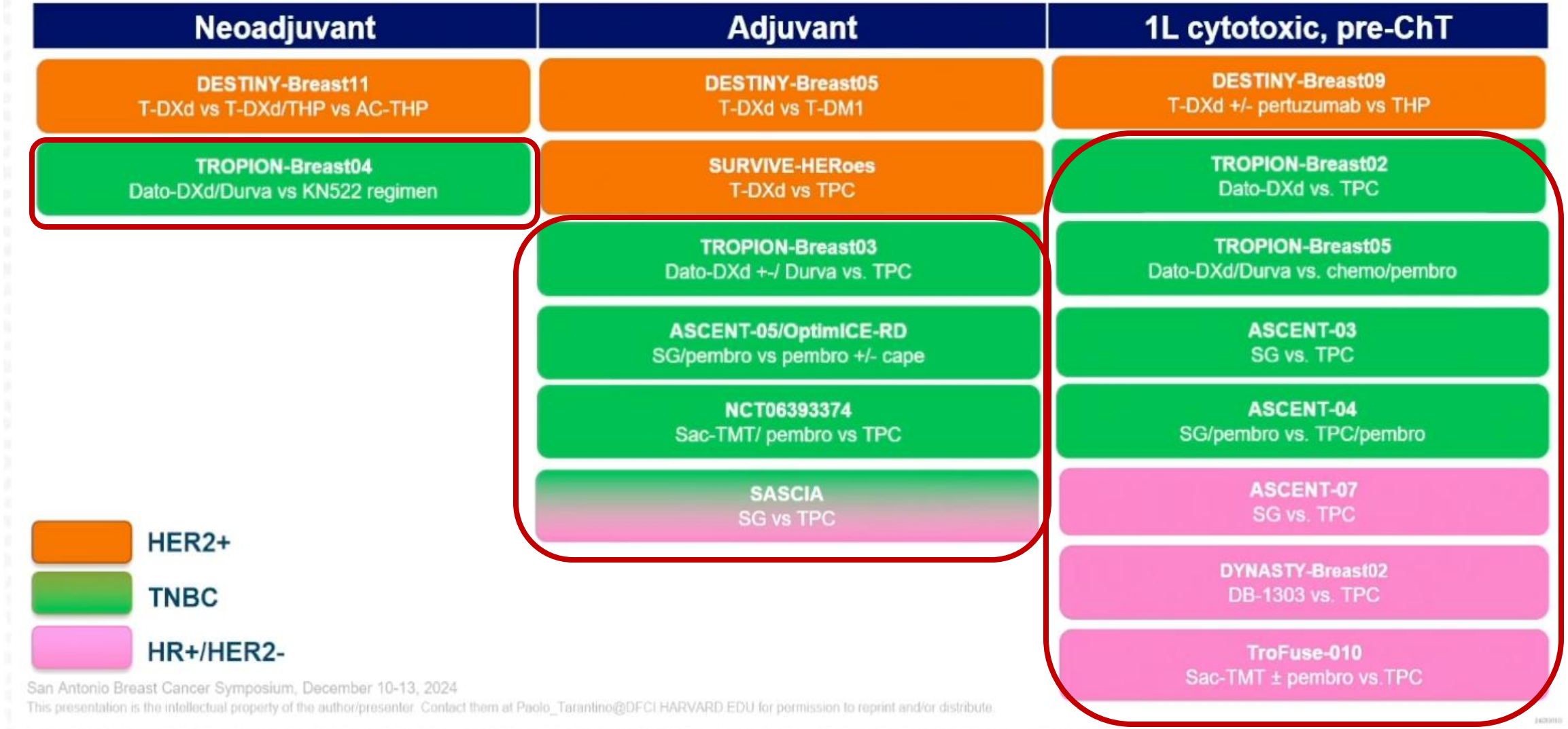
Median DoR was **15.5** months (95% CI, 9.92–NC)



Kaplan-Meier analysis was performed. Circles indicate censored observations.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; PFS, progression-free survival.

Schmid, et al. ESMO 2023

ADC in early-stage BC and 1st line setting



Tarantino P, SABCS 2024

ADCs in Breast Cancer- Some questions

Sequencing

- What is the best sequence?
  - Among Her2-low patients, in what order should T-DXd and SG be used?
  - Similar sequence for patients with HR+ and HR- BC?
- Will ADCs move to 1st line? , How will thye affect the management in the metasttic setting?
- How will we incorporate new agents (Dato-DXd)?

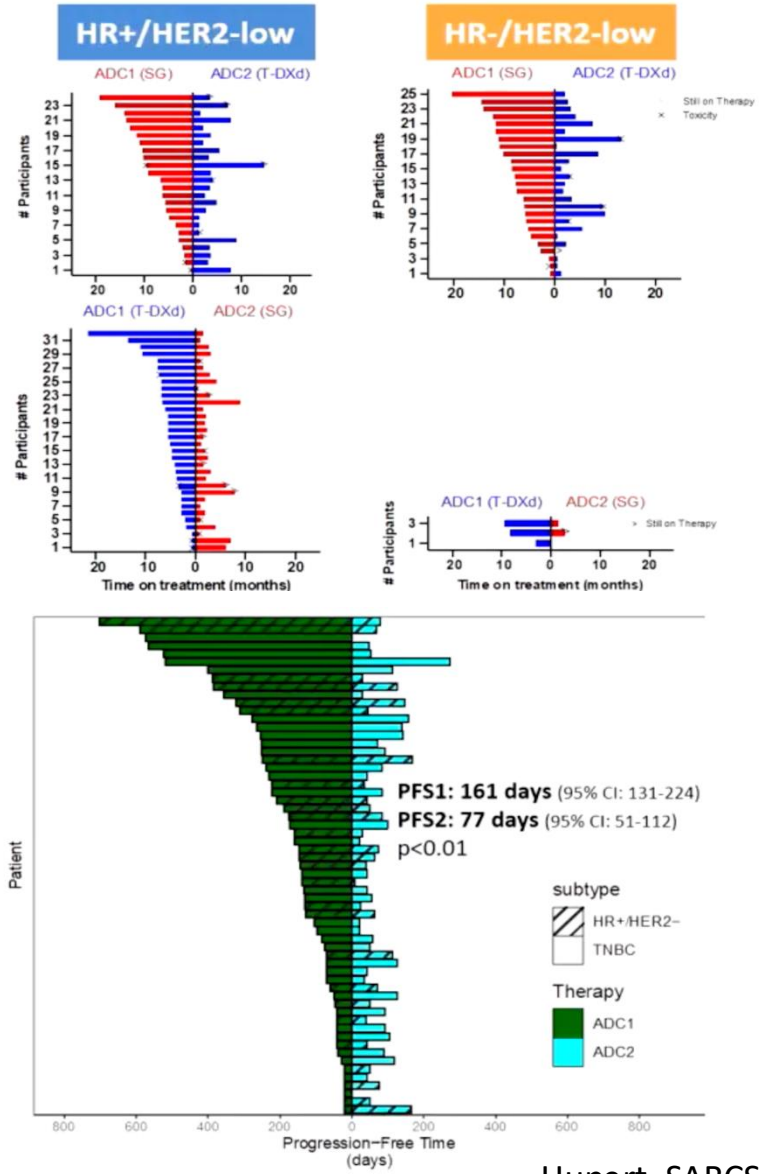
Resistance

- What are the main mechanisms of resistance?
  - Impacting payload
  - Impacting target
- Can we use sequential agents that have similar payloads?
- Will combinations be more effective?

How to optimize the use of ADCs for the benefit of our patients?

ADC after ADC?

- Current data limited by its retrospective nature
  - Patient heterogeneity, selection and indication bias, differences in # lines of treatment, not immediate sequencing, etc.
  - Clinical trials are needed
- Today the best sequence is unclear → individualize
- **Data suggest that after ADC1, ADC2 has shorter duration of response in most (but not all) patients**
  - <u>mPFS2 is shorter</u>, but how it compares to chemotherapy?
  - How to identify?
  - Topo 1 variant as possible mechanism of resistance?



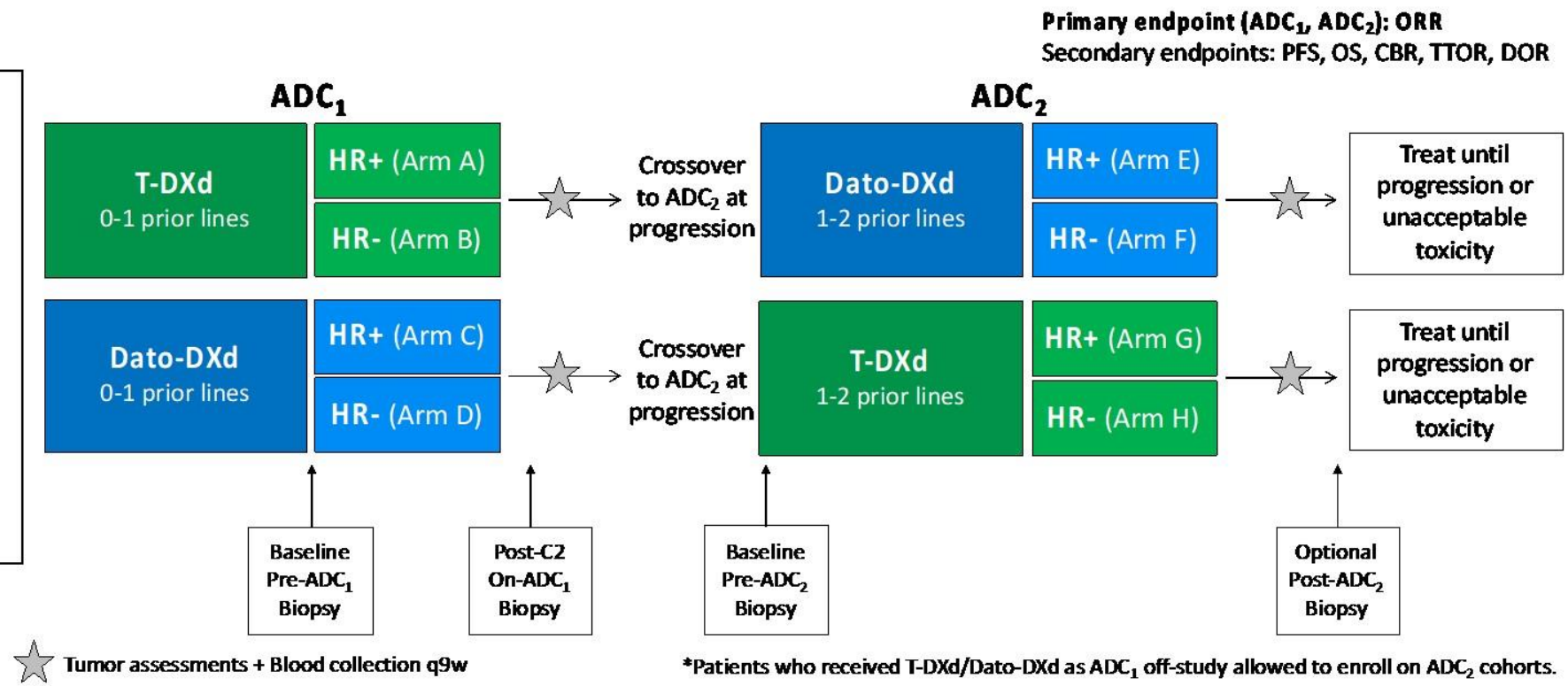
Hupert, SABCS 2023
Abelman, SABCS 2023

TBCRC 064: Treatment of ADC-Refractory BC with Dato-Dxd or T-Dxd (TRADE-DXD)

Eligibility:

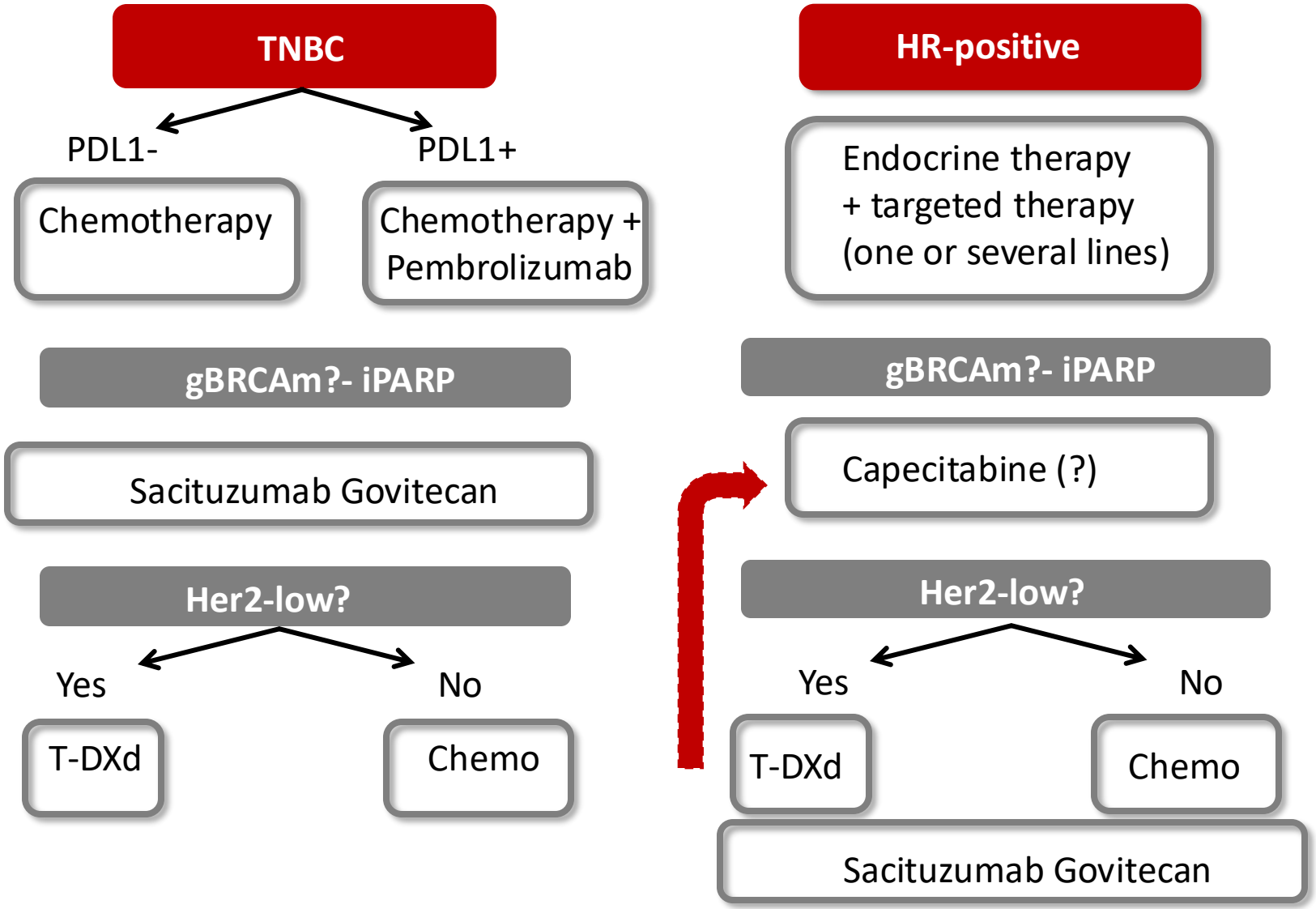
- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low breast cancer (any prior primary or metastatic tumor) defined as IHC 1+ or 2+/ISH non-amplified
- Most recent pathology: HER2 IHC 0 or HER2-low
- Measurable disease
- No prior topo-I inhibitor-based therapy

Allocation 1:1 to T-DXd or Dato-DXd as ADC_1



Study Chair/Overall PI: A. Garrido-Castro

My (very) rough attempt at an algorithm for discussion…



HER2-positive

- 1st: THP
- 2nd: T-DXd
- 3rd: T-DM1, Tucatinib+C+T

Take home points

- ADCs have revolutionized the care of patients with ABC
- More drugs available translating into more options for our patients
- Many questions regarding resistance and biomarkers remain unanswered
  - SEQUENCING-What is the optimal strategy?
  - New algorithms
    - Challenged by incorporation of new therapies in EBC
    - Different clinical and biologic profiles
    - Unique characteristics
  - Partnering with patients
    - Different patients
    - Shared-decision
      - Efficacy, side effects, cost, time, etc.

Thank you

BCRF BREAST CANCER RESEARCH FOUNDATION

SUSAN G. KOMEN FOR THE CURE