Il carcinoma mammario metastatico HER2 low: quali novità?

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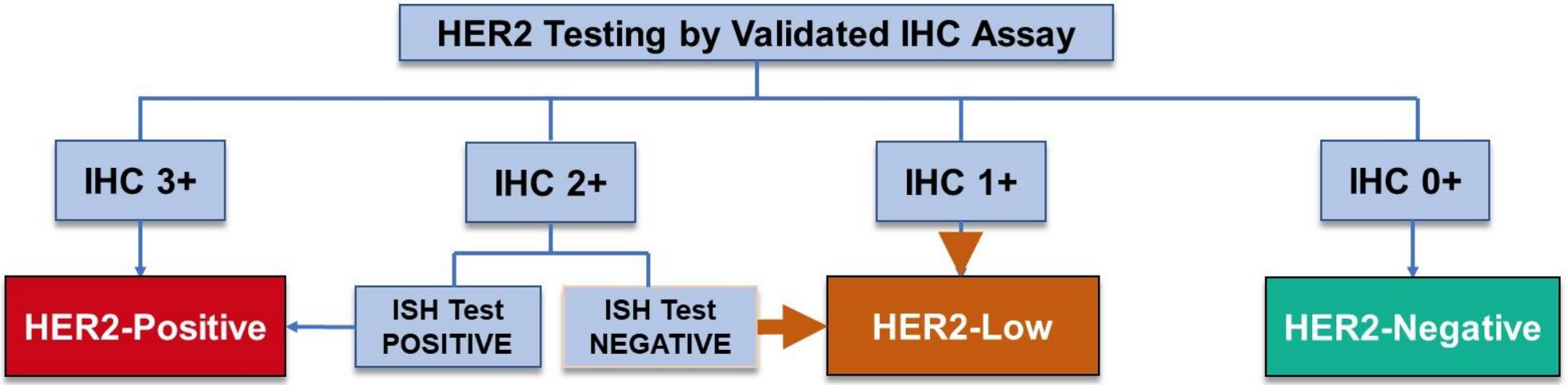
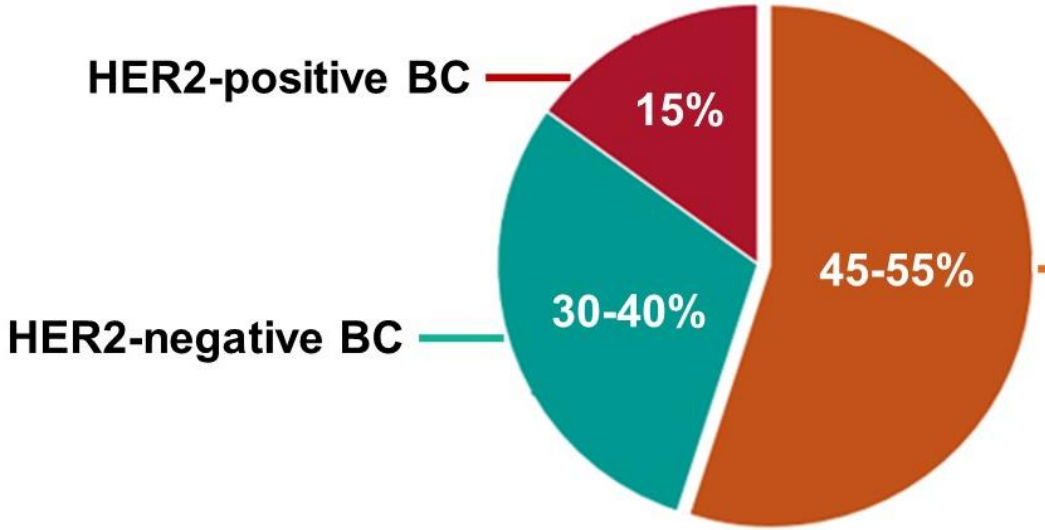
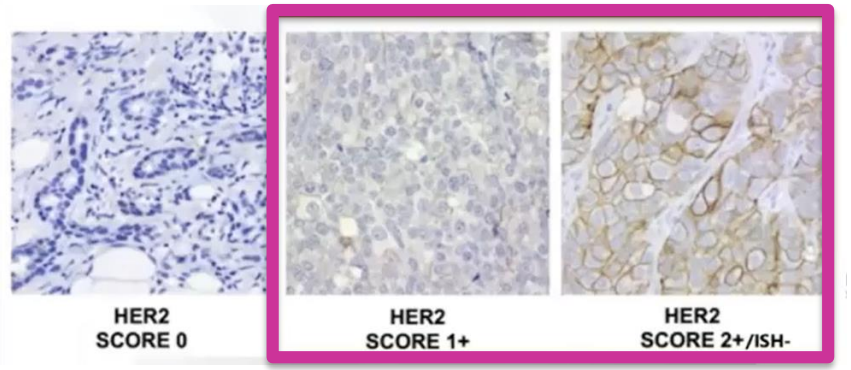
Topics

- **HER2-low BC Definition and Features**
- **Anti-HER2 Agents in HER2-low BC**
  - **Monoclonal Antibodies & *'Old'* Antibody Drug Conjugates (ADCs)**
  - **'New' ADCs: Trastuzumab-Deruxtecan (T-Dxd)**
- **Conclusions & Future Perspectives**

HER2-low BC Definition







- Most HER2-low BC expressed hormone receptors:
  - **~65%-85% HR+ HER2-low**
  - **~35%-15% HR- HER2-low**

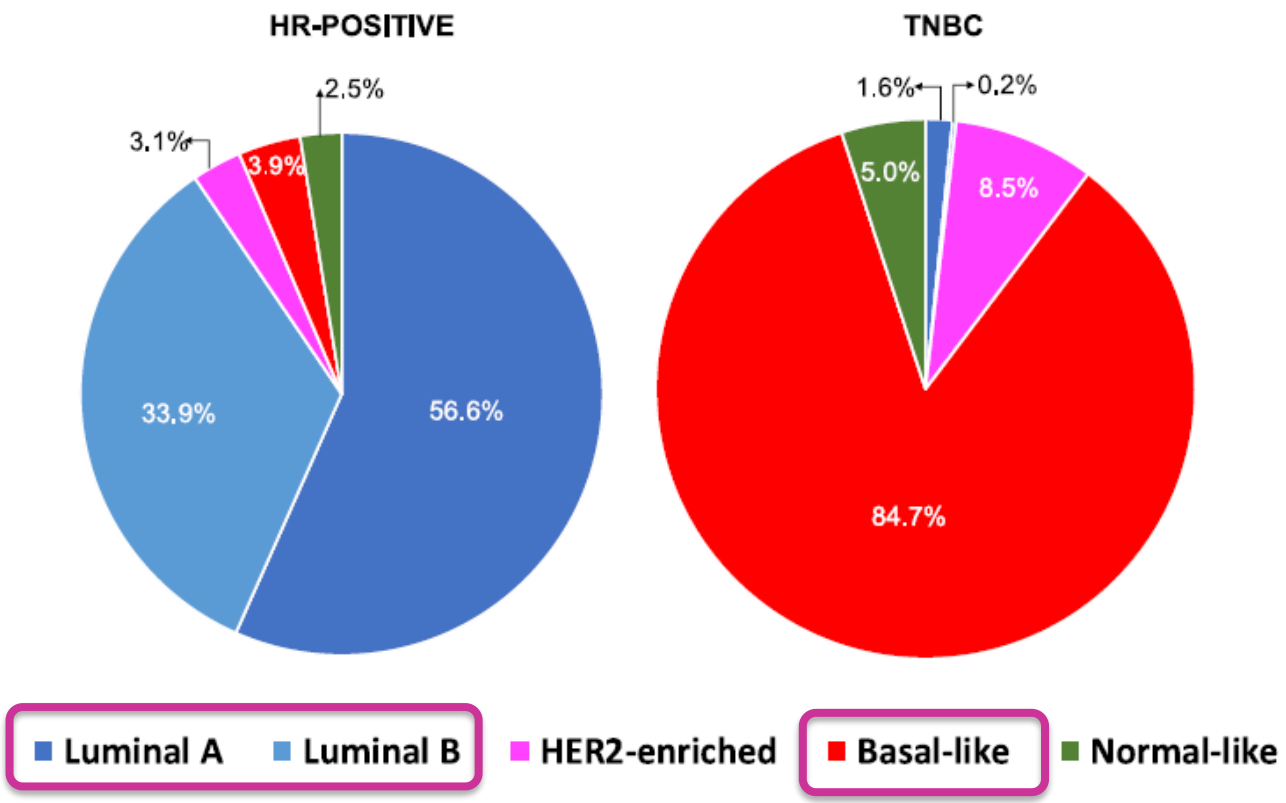
Modified from Tarantino P et al., J Clin Oncol 2020

HER2-low BC Features

- Retrospective clinicopathological and PAM50 analysis from 3,689 patients with HER2-negative disease.
- The proportion of HER2-low was higher in HR-positive disease (65.4%) than TNBC (36.6%).
- Within HR-positive disease, ERBB2 and luminal-related genes (90%) were more expressed in HER2-low than HER2 0.
- TNBC HER2-low are mostly (85%) basal-like. No gene was found differentially expressed in TNBC according to HER2 expression.

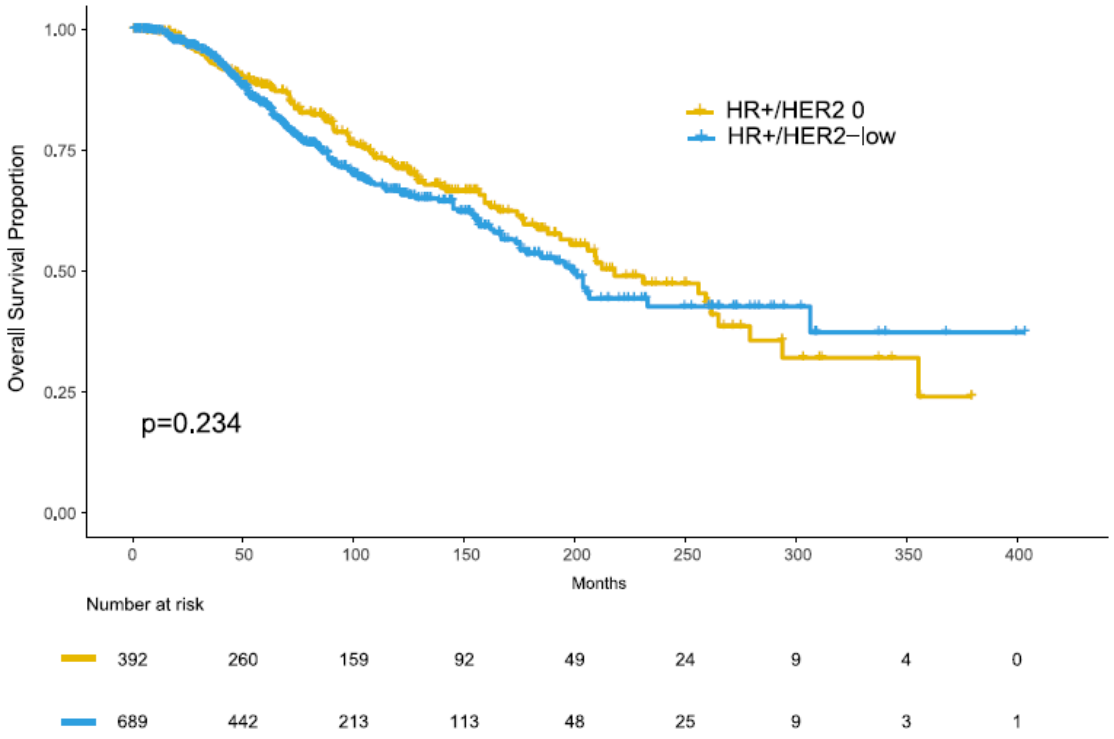
Similar biology between HER2 low and HER2 0

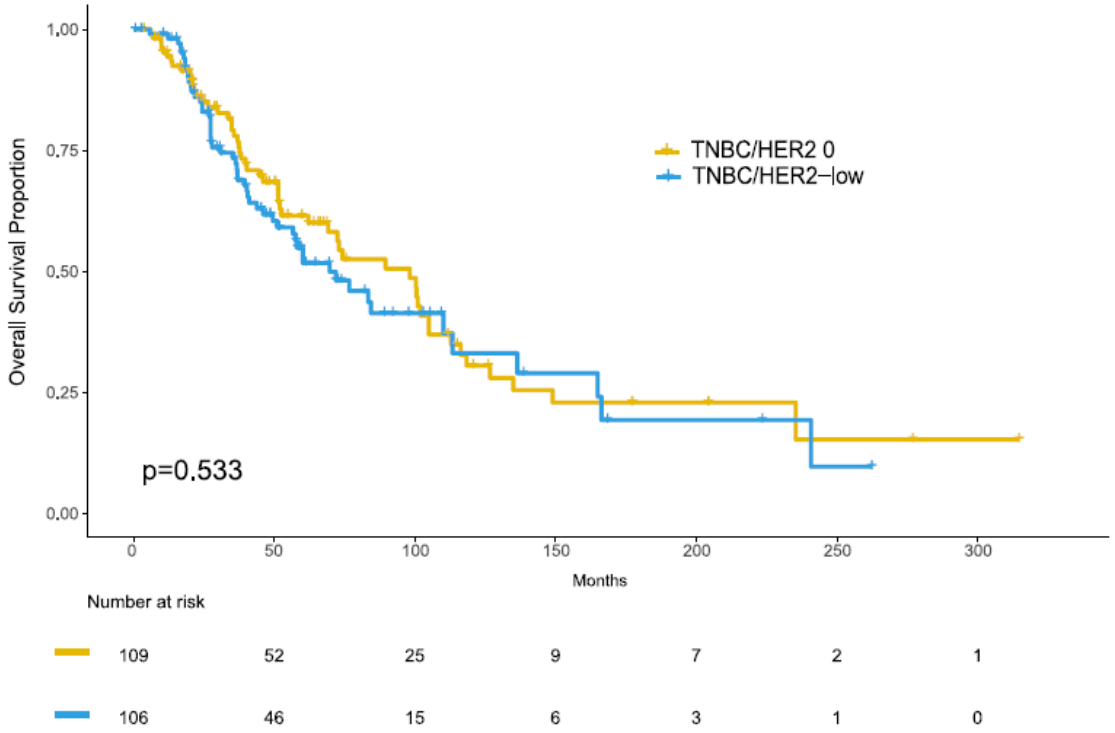
Intrinsic subtype distribution in HER2 low



Schettini F et al., NPJ Breast Cancer 2021

HER2-low BC Prognosis





Similar prognosis between HER2 low and HER2 0

No prognostic role for HER2 low expression

Schettini F et al., NPJ Breast Cancer 2021

Topics

- HER2-low BC Definition and Features

- **Anti-HER2 Agents in HER2-low BC**
  - **Monoclonal Antibodies & *'Old'* Antibody Drug Conjugates (ADCs)**
  - **'New' ADCs: Trastuzumab-Deruxtecan (T-Dxd)**

- **Conclusions & Future Perspectives**

Negative Results of Monoclonal Abs & *'Old'* ADC in HER2-low BC

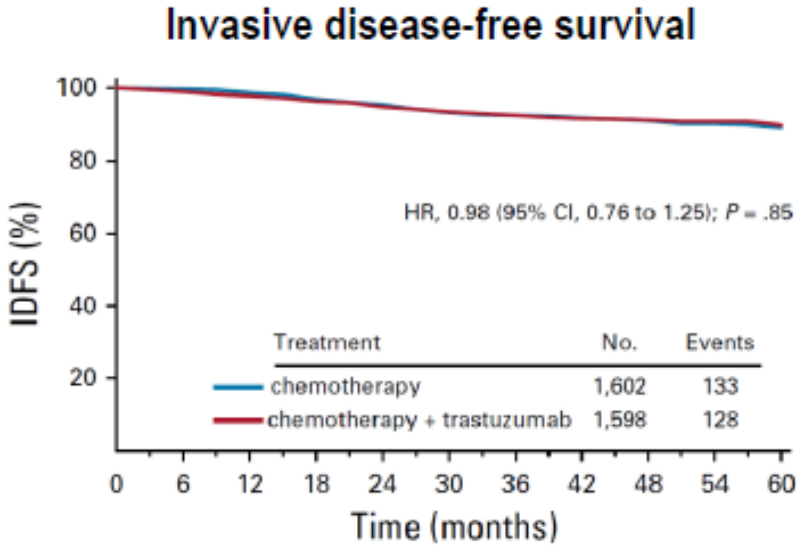
NSABP B-47 Trial: Adjuvant Trastuzumab in HER2 low BC

STRATIFICATION
- HER2 IHC Score (1+, 2+)
- Number of positive nodes (0–3, 4–9, 10+)
- Oestrogen receptor/progesterone receptor status
- Intended chemotherapy regimen (AC → WP, TC)

RANDOMISATION

GROUP 1
Chemotherapy*

GROUP 2
Chemotherapy* + Traztuzumab x 1 year



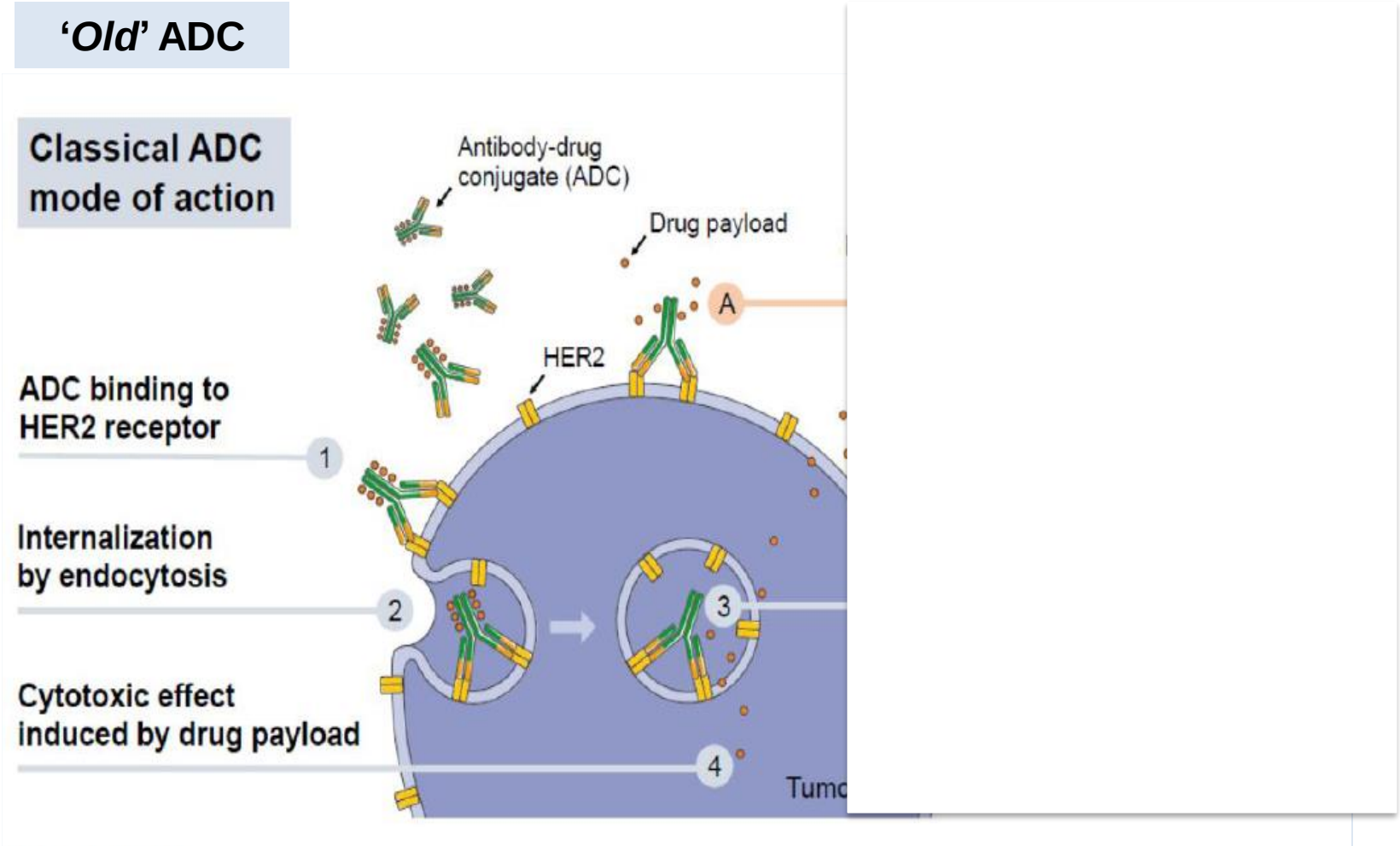
- In 2008, the centralized re-analysis of the NSABP B-31 trial identified 10% of HER2 non-amplified samples. These patients seemed to benefit from adjuvant trastuzumab.
- However, the NSABP B-47 showed absence of efficacy of adjuvant Trastuzumab in HER2 low BC.
- Similar negative results with Pertuzumab and T-DM1 in the advanced setting.

Paik S et al., NEJM 2008; Fehrenbacher L et al., JCO 2020; Gianni L et al., JCO 2010; Burris H etal., JCO 2011

The '*New*' ADCs

Antibody-Drug Conjugates (ADCs): Mechanism of Action

'*Old*' ADC

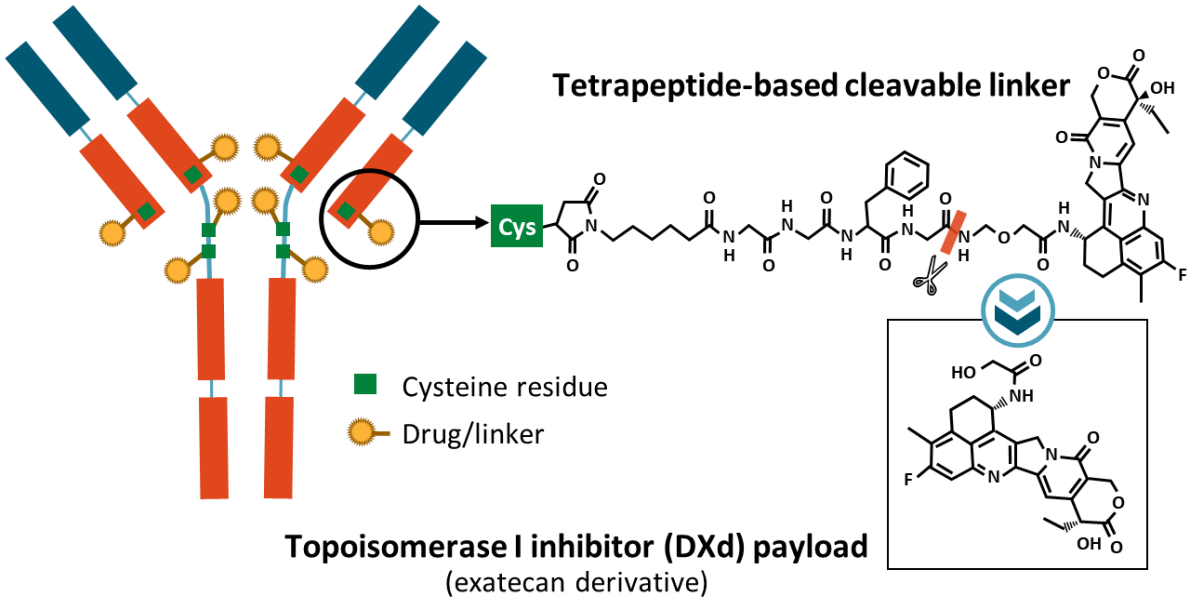


Rinnertalet G et al, Int J Mol Sci 2019

'*New*' ADCs in HER2-low BC

Trastuzumab Deruxtecan (T-Dxd)

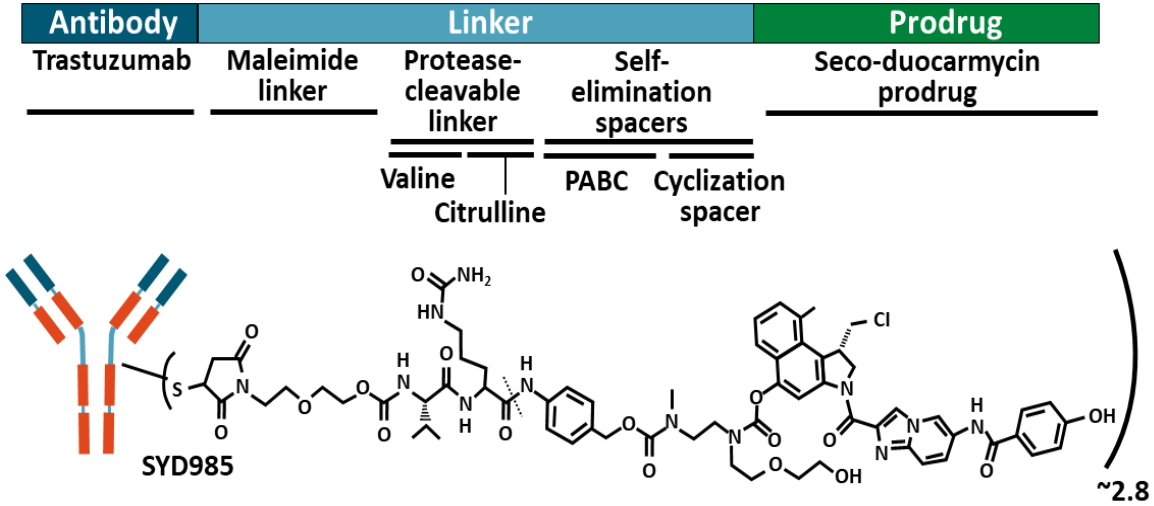
Humanized anti-HER2 IgG1 mAb with same AA sequence as trastuzumab



Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

Trastuzumab Duocarmazine (SYD985)

Trastuzumab-vc-seco-duocarmycin-hydroxybenzamide-azaindole



Dokter. Mol Cancer Ther. 2014;13:2618. Elgersma. Mol Pharm. 2015;12:1813.

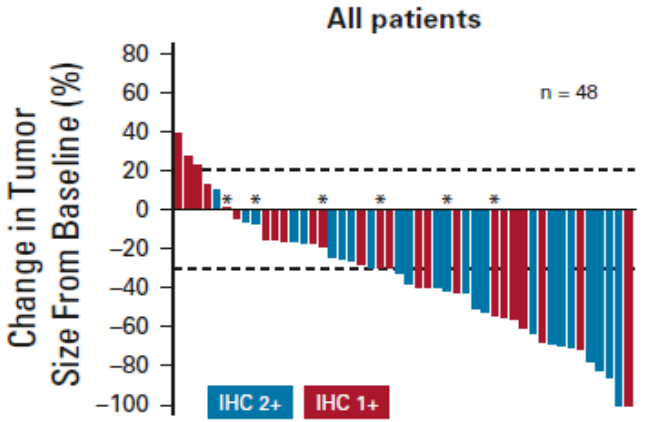
- Higher Drug-to-Antibody ratio (DAR).
- Cleavable linker.

Modified from clinicaloptions.com

T-DXd in Heavily Pretreated HER2-low MBC

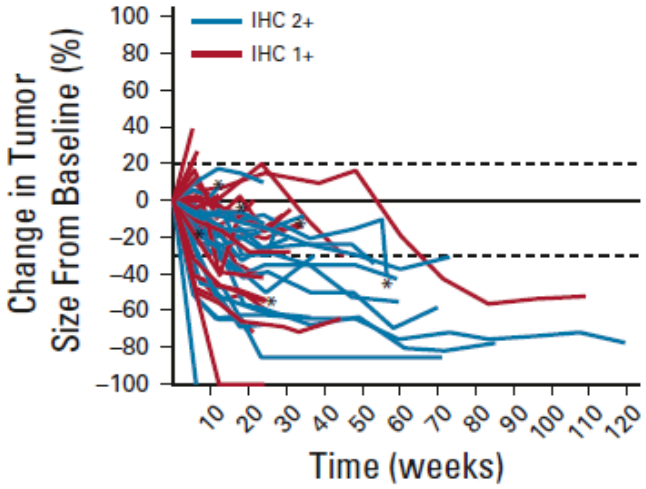
- Dose escalation and expansion phase I study.
- Population: advanced HER2 expressing/mutated solid tumors.
- HER2-low BC in cohorts 2c and 2e and treated with ≥ 1 dose of T-DXd at 5.4 (n = 21) or 6.4 mg/kg (n = 33).
- Median PFS: 11.1 mo [95% CI, 7.6-NE]
- Median DOR, 10.4 mo [95% CI, 8.8-NE]

Characteristic	HER2-Low Breast Cancer N = 54
Median age (range), years	56.6 (33-75)
Country	
Japan	27 (50.0)
United States	27 (50.0)
ECOG performance status	
0	36 (66.7)
1	18 (33.3)
Median time from initial diagnosis (range), months[a]	105.0 (13.0-290.3)
Median No. of prior cancer regimens (range)	7.5 (2-16)
≥ 5 prior cancer regimens	45 (83.3)
CDK4/6 inhibitor	16 (29.6)
HER2-targeted therapy	10 (18.5)
Trastuzumab	10 (18.5)
Pertuzumab	7 (13.0)
T-DM1	5 (9.3)
Other	1 (1.9)
Previous cancer surgery	48 (88.9)



ORR (N = 54): 37%
[95% CI, 24.3%-51.3%]

D



Modi S et al., J Clin Oncol 2020

DESTINY-Breast04: Phase III Study of T-Dxd in HER2-low MDC

An open-label, multicenter study (NCT03734029)

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

R 2:1

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

HR+ ≈ 480
HR− ≈ 60

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

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−

Key Eligibility Criteria
- HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable and/or MBC
- ≥1 prior line(s) of chemo in the metastatic setting or disease recurrence ≤6 months after adjuvant therapy
- ≥1 line(s) of endocrine therapy if HR+ MBC

Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

Primary endpoint
- PFS by BICR (HR+)

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

Hierarchical testing

PFS in HR+
↓
PFS in all patients
↓
OS in HR+
↓
OS in all patients

Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04: Baseline Characteristics

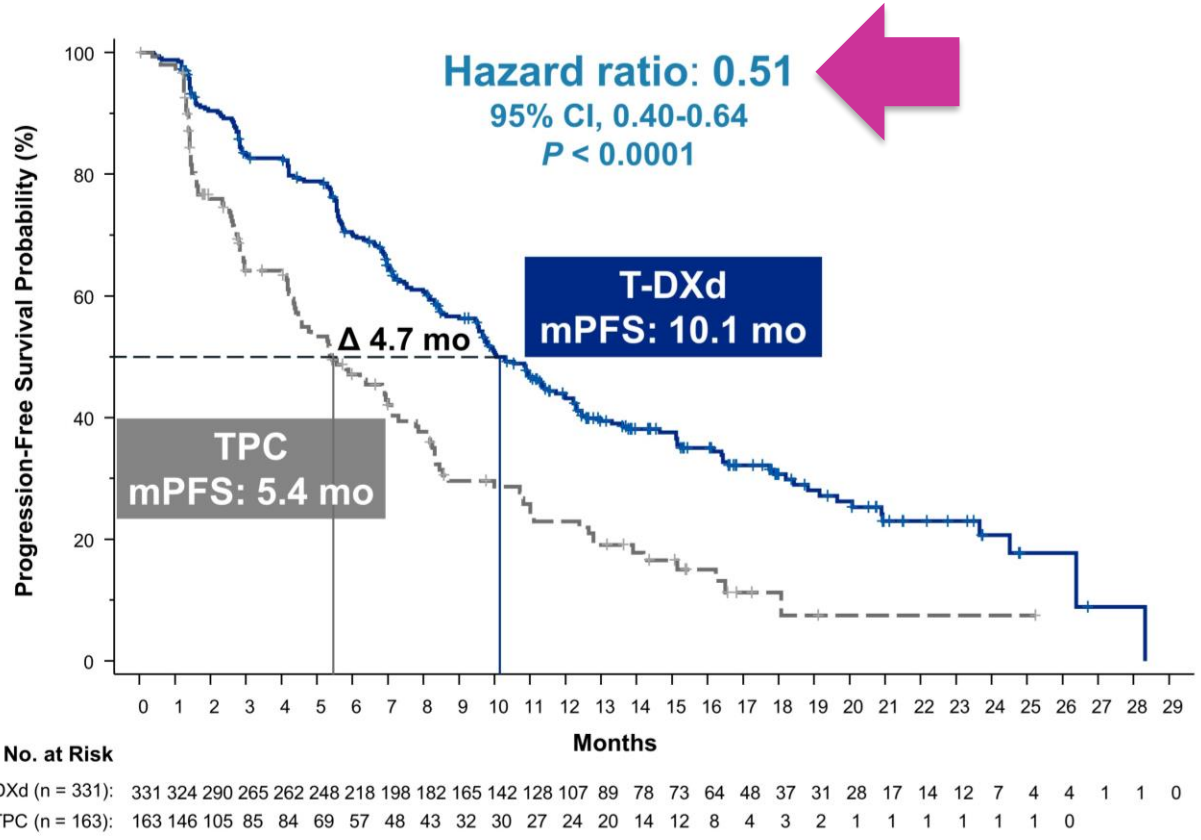
	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)

Modi S et al., ASCO 2022 & NEJM 2022

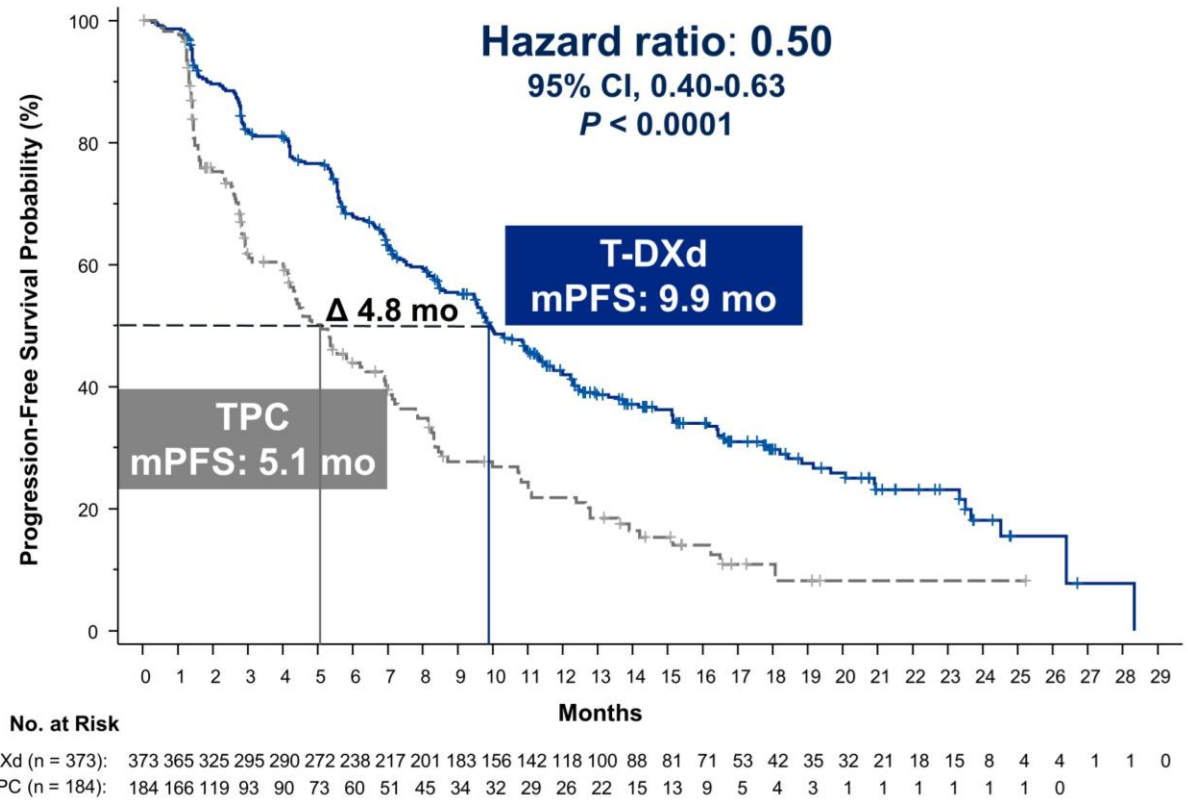
DESTINY-Breast04: PFS

median follow-up was 18.4 months

Hormone receptor–positive



All patients



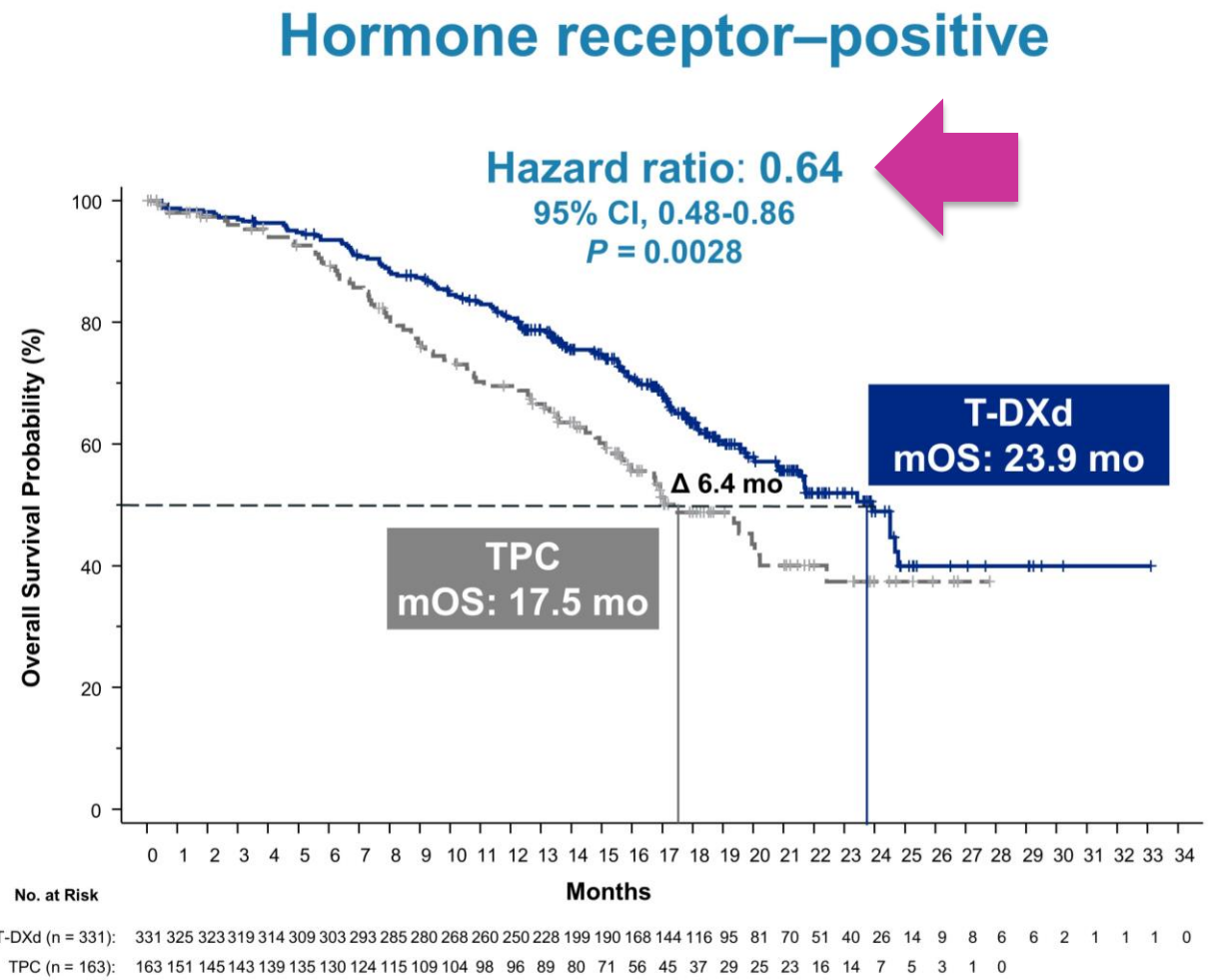
Benefit was observed across all stratification subgroups, including according to HER2-low (IHC 1+ or IHC 2+/ISH-) and prior CDK4/6i

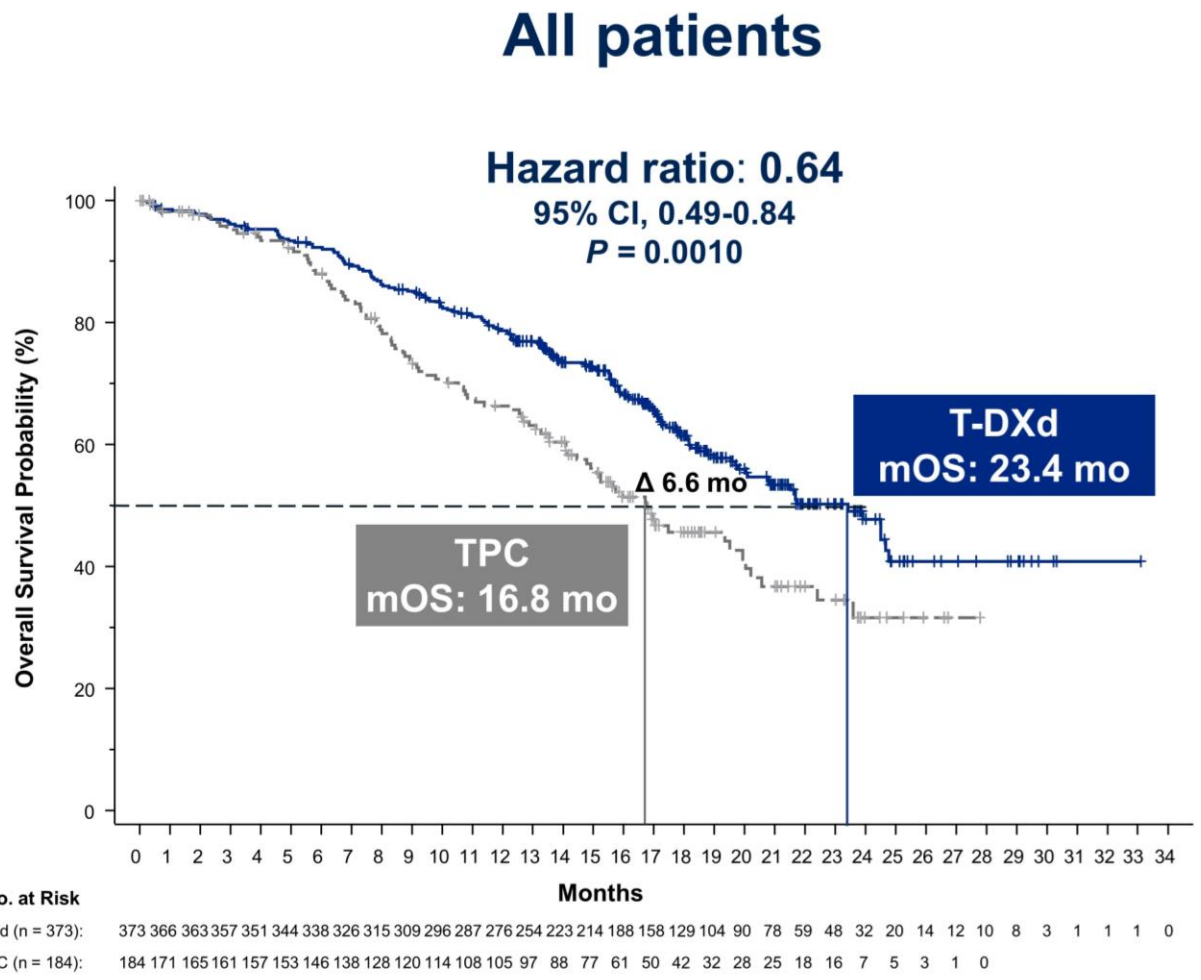
PFS by blinded independent central review.

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

Modi S et al., ASCO 2002 & NEJM 2022

DESTINY-Breast04: OS

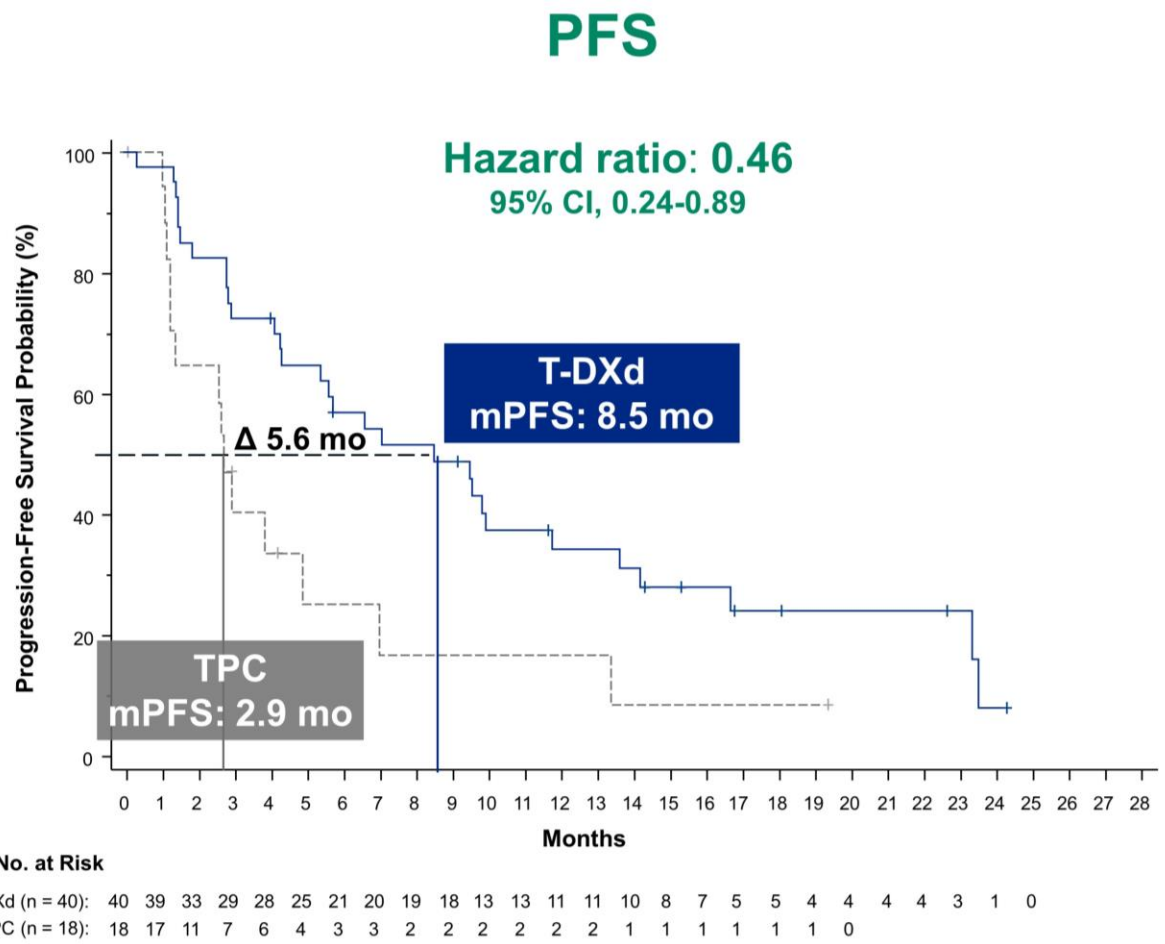


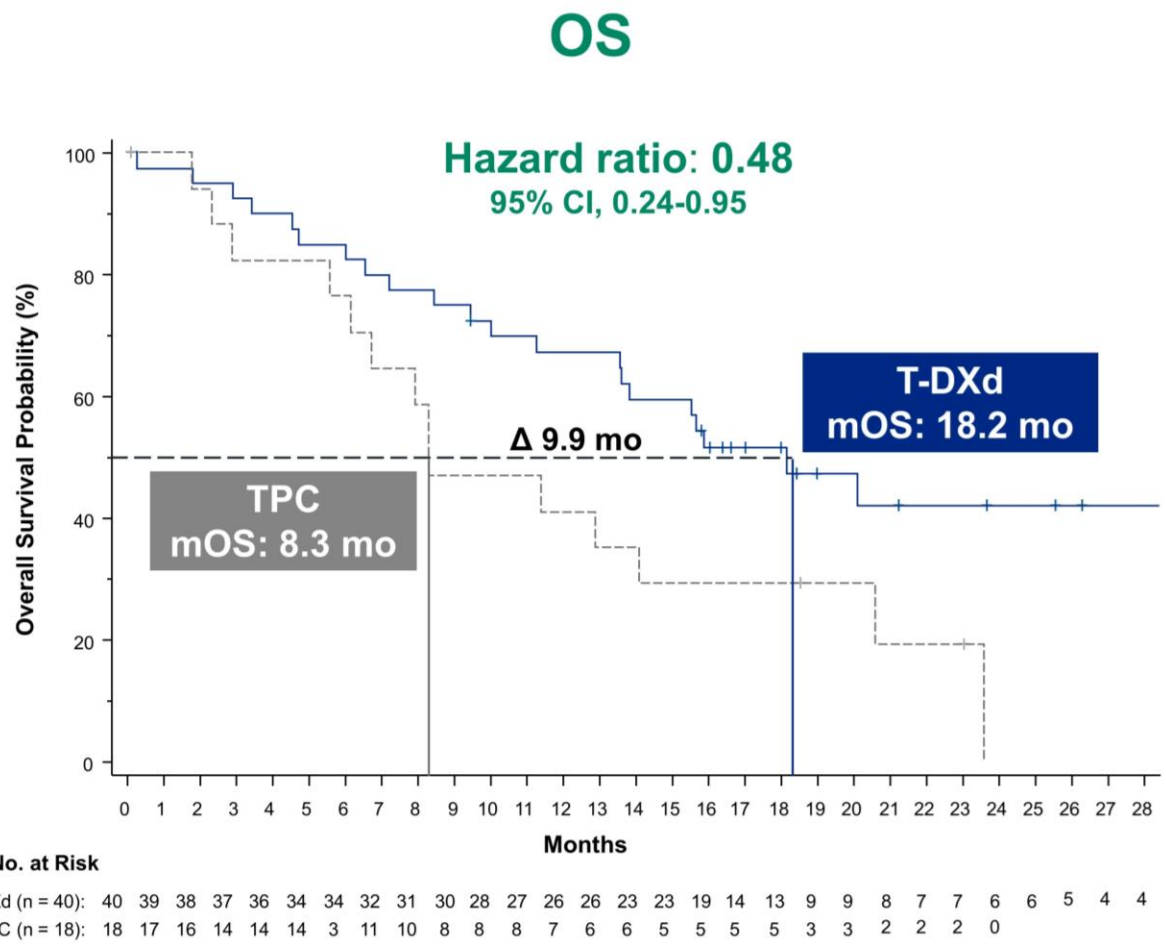


HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04: similar results in HR- (Exploratory analysis)

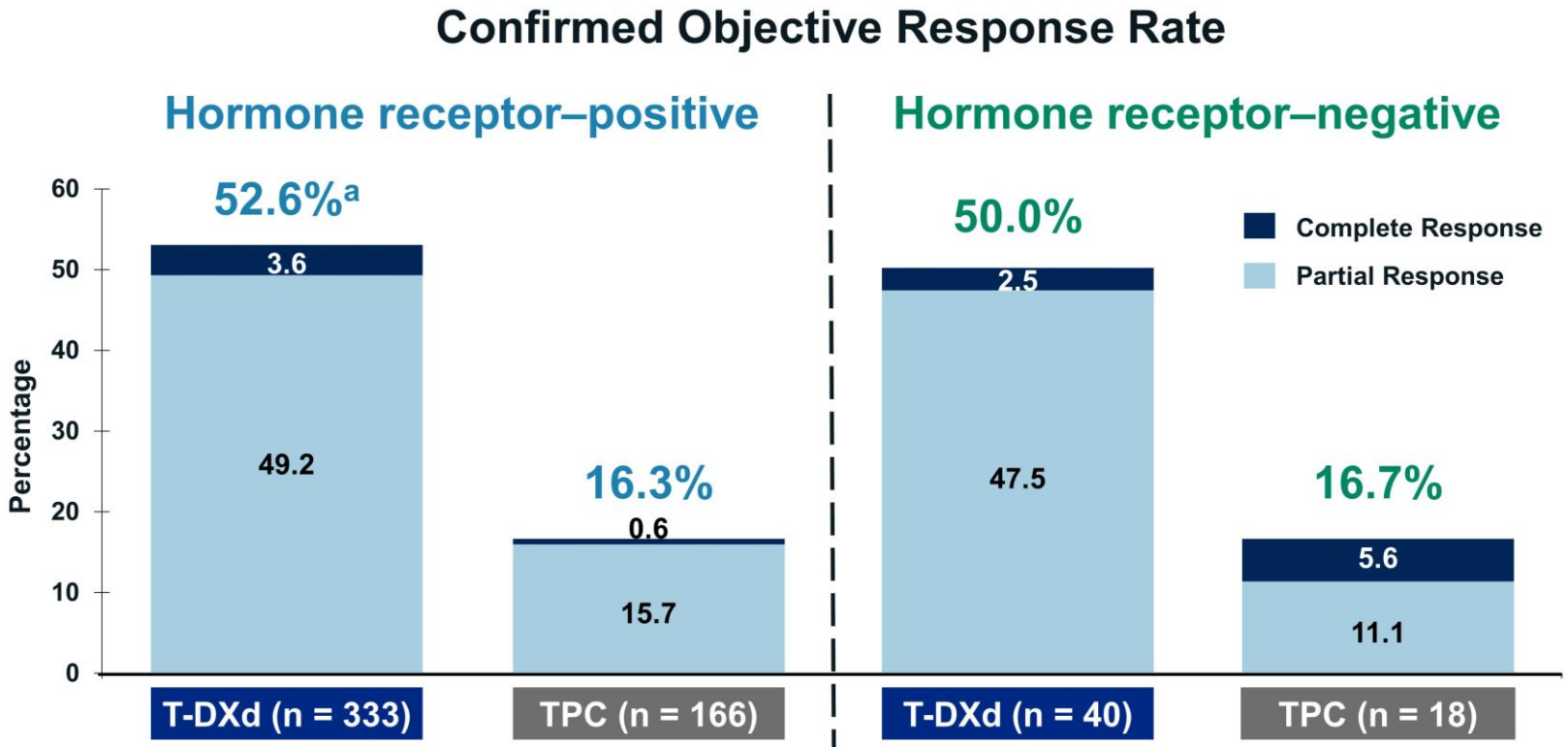




HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based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

Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04: ORR

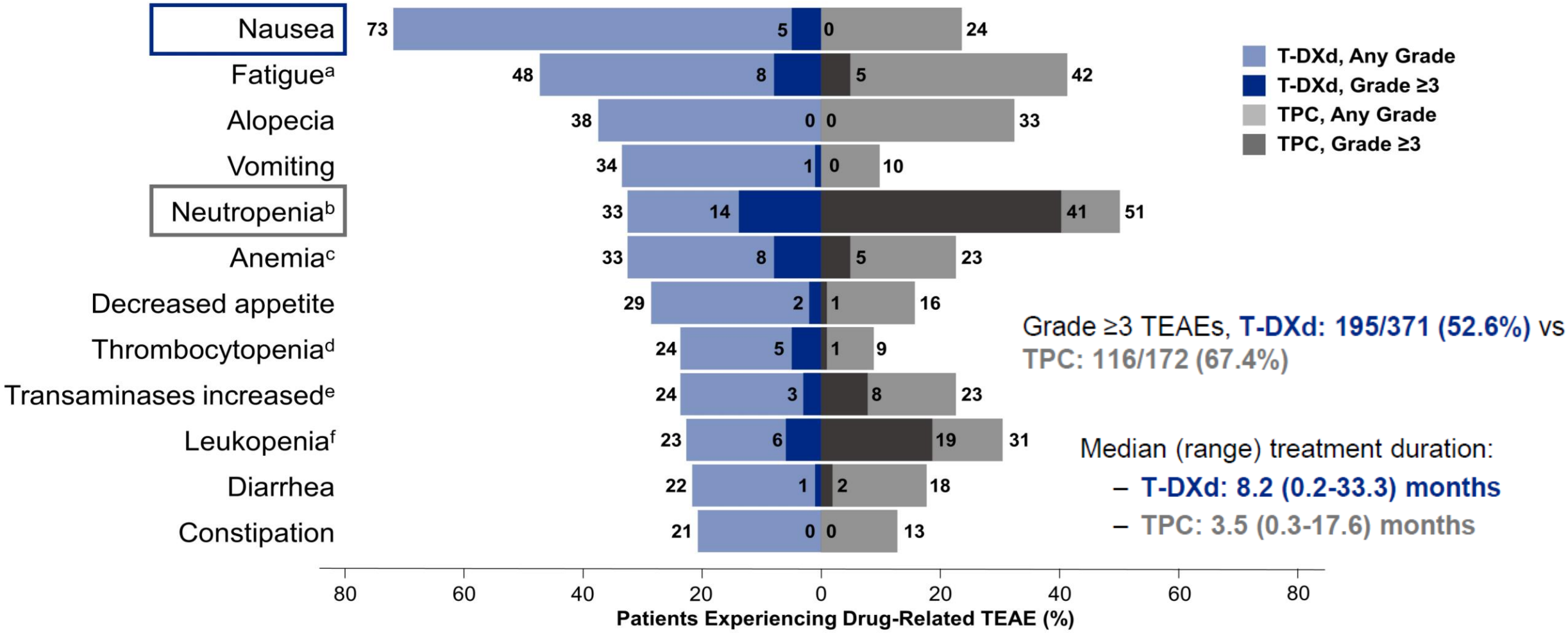


	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

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

Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04: Safety



Grade ≥3 TEAEs, **T-DXd: 195/371 (52.6%)** vs TPC: 116/172 (67.4%)

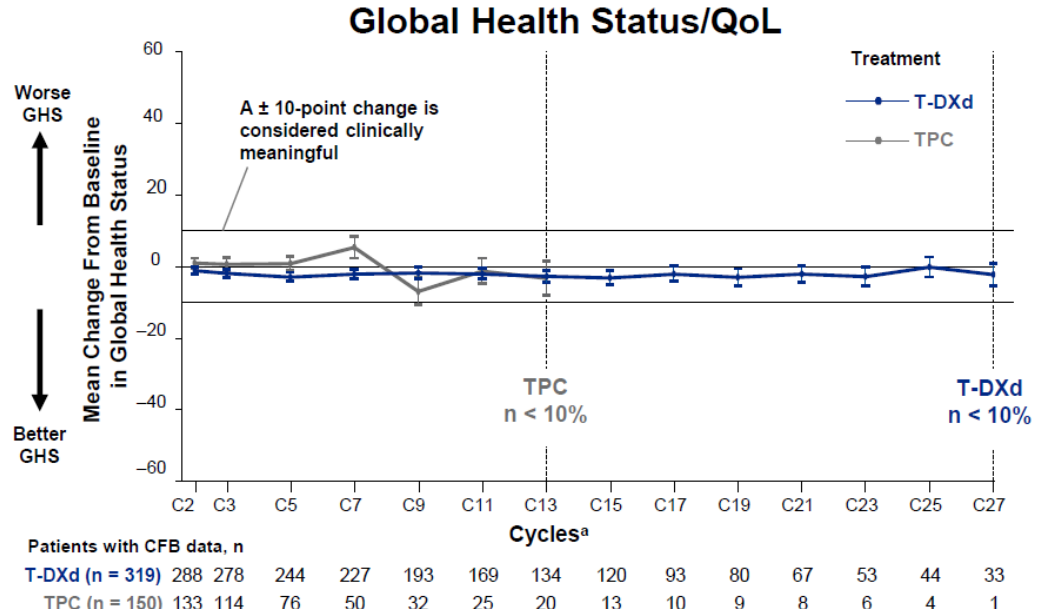
Median (range) treatment duration:
- **T-DXd: 8.2 (0.2-33.3) months**
- TPC: 3.5 (0.3-17.6) months

Adjudicated as drug-related ILD/pneumonitis[a]

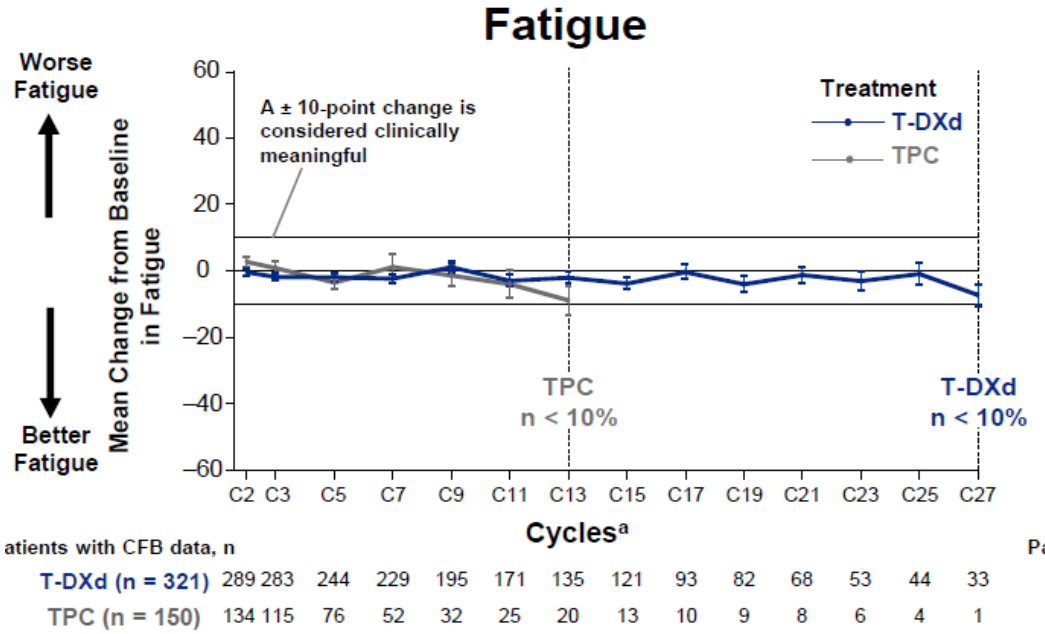
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

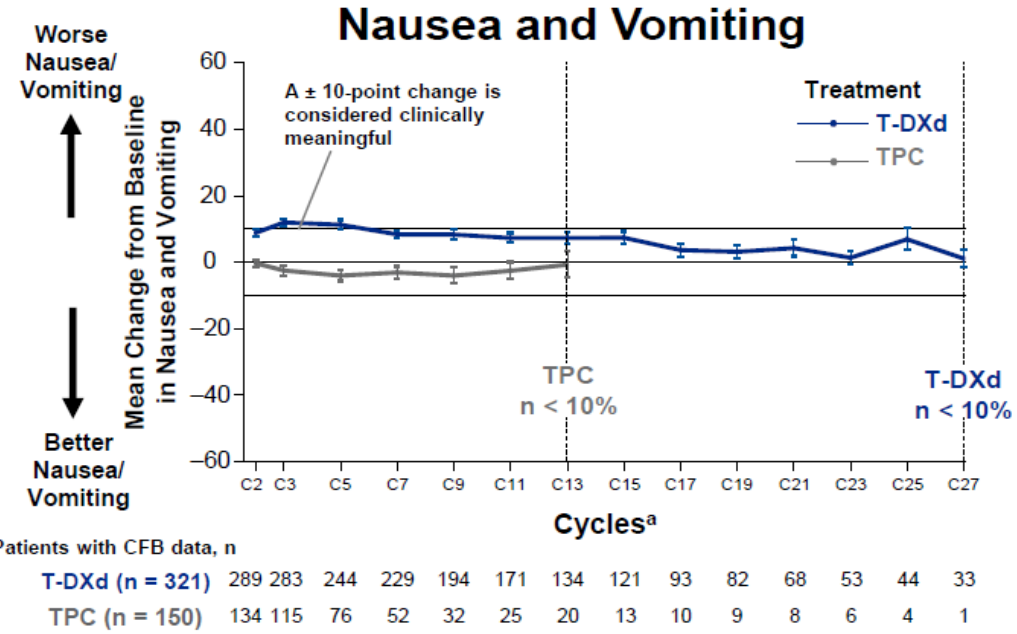
Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04:PROs



- GHS/QoL was maintainted with T-Dxd and TPC (QLQ-C30).
- Fatigue scores remained stable over time in both treatment arms.
- **With T-DXd, an increase in nausea and vomiting scores was only clinically relevant in early cycles,** after which scores decreased and remained stable over time.

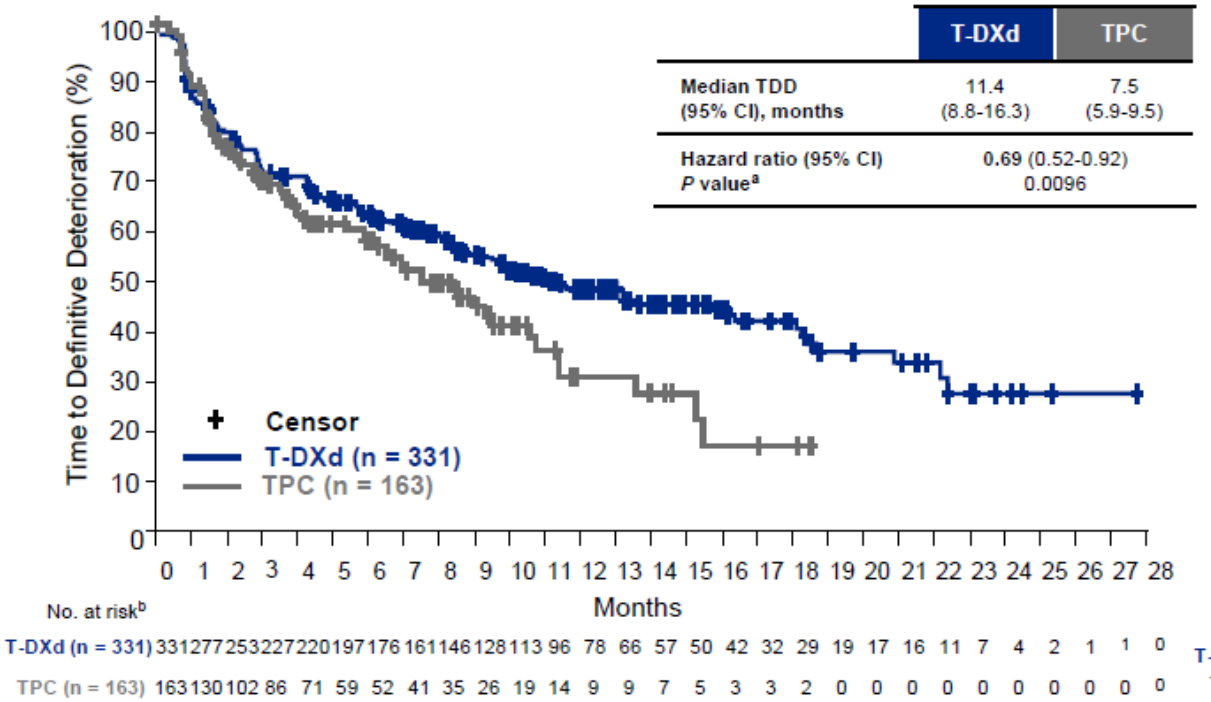




Naoto T. Ueno et al., ESMO 2022

DESTINY-Breast04:PROs

GHS/QoL

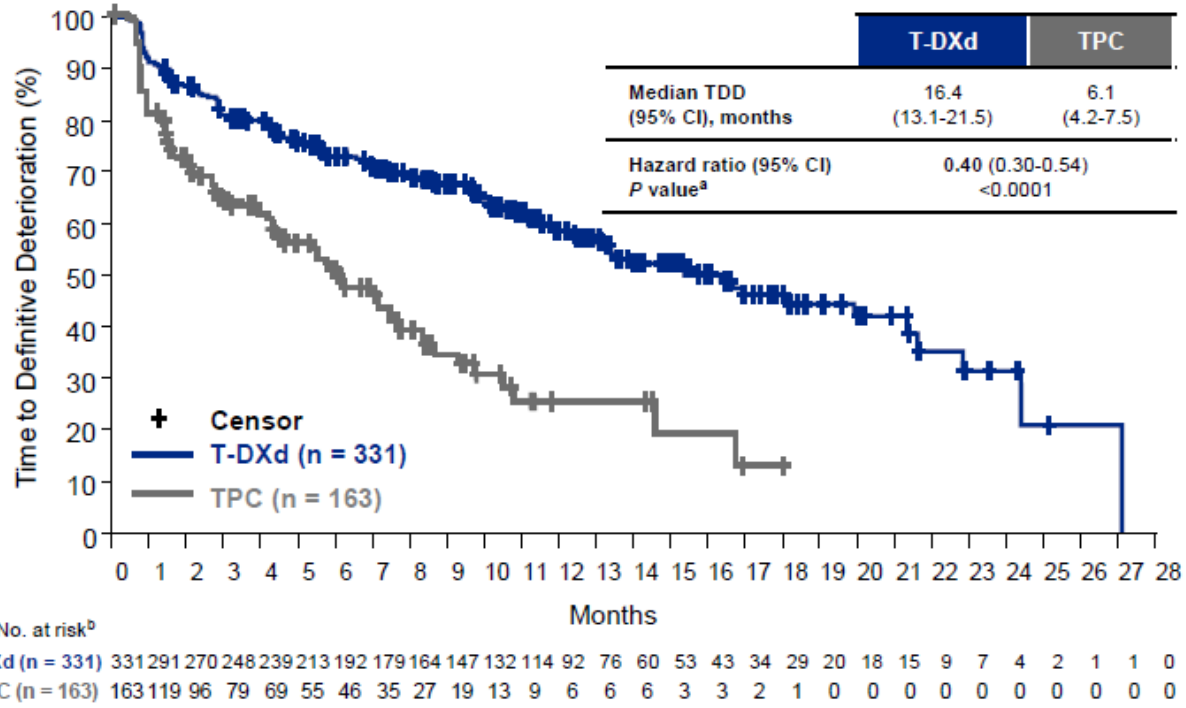


	T-DXd	TPC
Median TDD (95% CI), months	11.4 (8.8-16.3)	7.5 (5.9-9.5)
Hazard ratio (95% CI)	0.69 (0.52-0.92)	
P value[a]	0.0096	

No. at risk[b]

T-DXd (n = 331)	331	277	253	227	220	197	176	161	146	128	113	96	78	66	57	50	42	32	29	19	17	16	11	7	4	2	1	1	0
TPC (n = 163)	163	130	102	86	71	59	52	41	35	26	19	14	9	9	7	5	3	3	2	0	0	0	0	0	0	0	0	0	0

Pain Symptoms



	T-DXd	TPC
Median TDD (95% CI), months	16.4 (13.1-21.5)	6.1 (4.2-7.5)
Hazard ratio (95% CI)	0.40 (0.30-0.54)	
P value[a]	<0.0001	

No. at risk[b]

T-DXd (n = 331)	331	291	270	248	239	213	192	179	164	147	132	114	92	76	60	53	43	34	29	20	18	15	9	7	4	2	1	1	0
TPC (n = 163)	163	119	96	79	69	55	46	35	27	19	13	9	6	6	6	3	3	2	1	0	0	0	0	0	0	0	0	0	0

- **Time to definitive deterioration of GHS/QoL and pain was longer among patients who received T-DXd vs TPC (QLQ-C30)**
- T-DXd treatment delays the deterioration of GHS/QoL and shows a QoL benefit of T-DXd vs TPC in patients with HR+/HER2-low mBC

Naoto T. Ueno et al., ESMO 2022

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
- Safely

[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

PRESENTED BY: Hope S. Rugo, MD

Demographics and Baseline Characteristics

	SG (n=272)	TPC (n=271)
Female, n (%)	270 (99)	268 (99)
Median age, y (range)	57 (29-86)	55 (27-78)
<65 y, n (%)	199 (73)	204 (75)
≥65 y, n (%)	73 (27)	67 (25)
Race or ethnic group, n (%)		
White	184 (68)	178 (66)
Black	8 (3)	13 (5)
Asian	11 (4)	5 (2)
Other[a] / Not reported[b]	69 (25)	75 (28)
ECOG PS, n (%)		
0	116 (43)	126 (46)
1	156 (57)	145 (54)
Visceral metastases at baseline, n (%)	259 (95)	258 (95)
Liver metastases,[c] n (%)	229 (84)	237 (87)
De novo metastatic breast cancer, n (%)	78 (29)	60 (22)

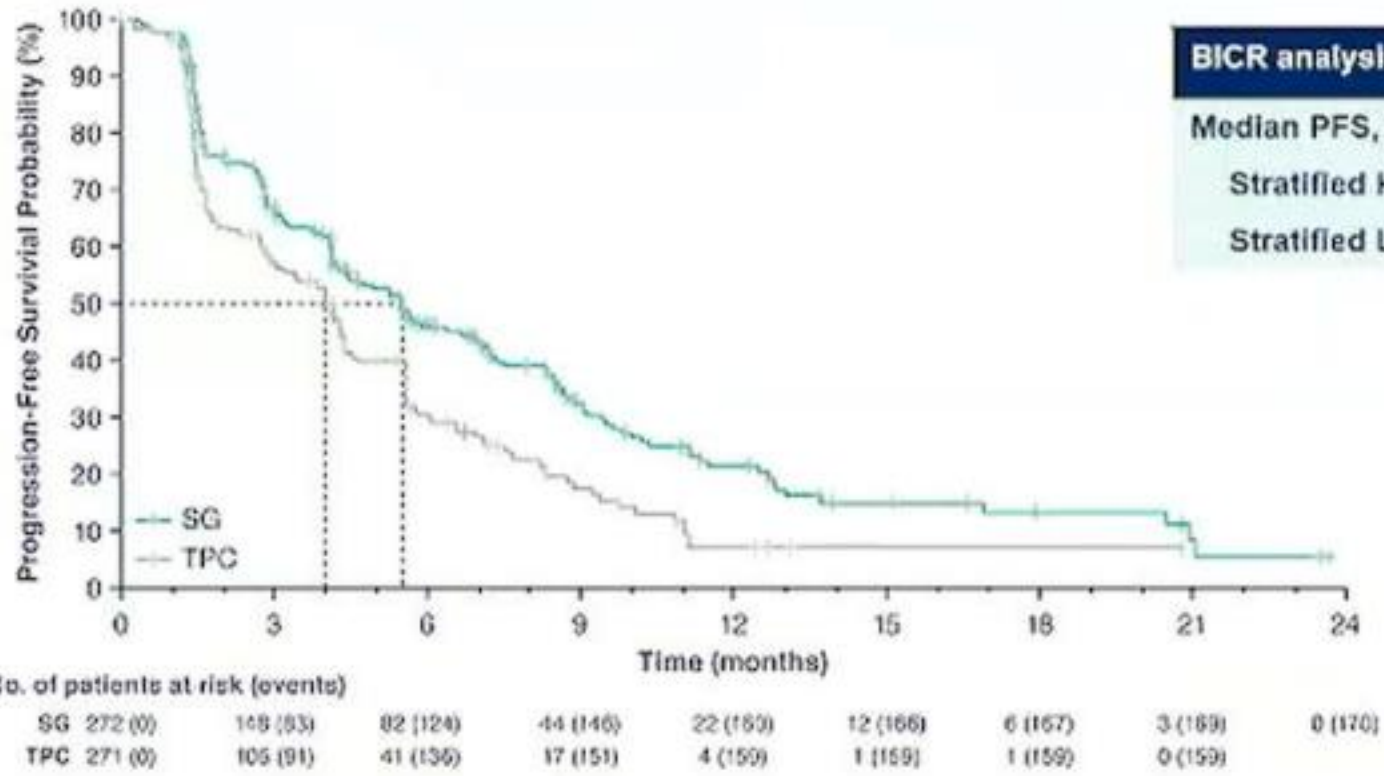
	SG (n=272)	TPC (n=271)
Median time from initial metastatic diagnosis to randomization, mo (range)	48.5 (1.2- 243.8)	46.6 (3.0- 248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)	173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 inhibitor use, n (%)		
≤12 months	161 (59)	166 (61)
>12 months	106 (39)	102 (38)
Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting, n (range)[d]	3 (0-8)	3 (1-5)

[a]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander. [b]Not reported indicates local regulations did not allow collection of race or ethnicity information. [c]Presence of baseline target/non-target liver metastases per RECIST 1.1 by local investigator review. [d]The reported number of prior therapies were miscounted at screening for some patients; 9 patients received prior chemotherapy regimens in the metastatic setting outside the per protocol range for inclusion criteria and were included in the intent-to-treat population.
CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; (neo)adjuvant, neoadjuvant or adjuvant; PR, progesterone receptor; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

PRESENTED BY: Hope S. Rugo, MD

Primary Endpoint: BICR-Assessed PFS per RECIST v1.1 in the ITT Population

SG demonstrated a statistically significant improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death; a higher proportion of patients were alive and progression-free at all landmark timepoints



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	0.0003	

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Primary Endpoint: BICR-Assessed PFS per RECIST v1.1 in the ITT Population

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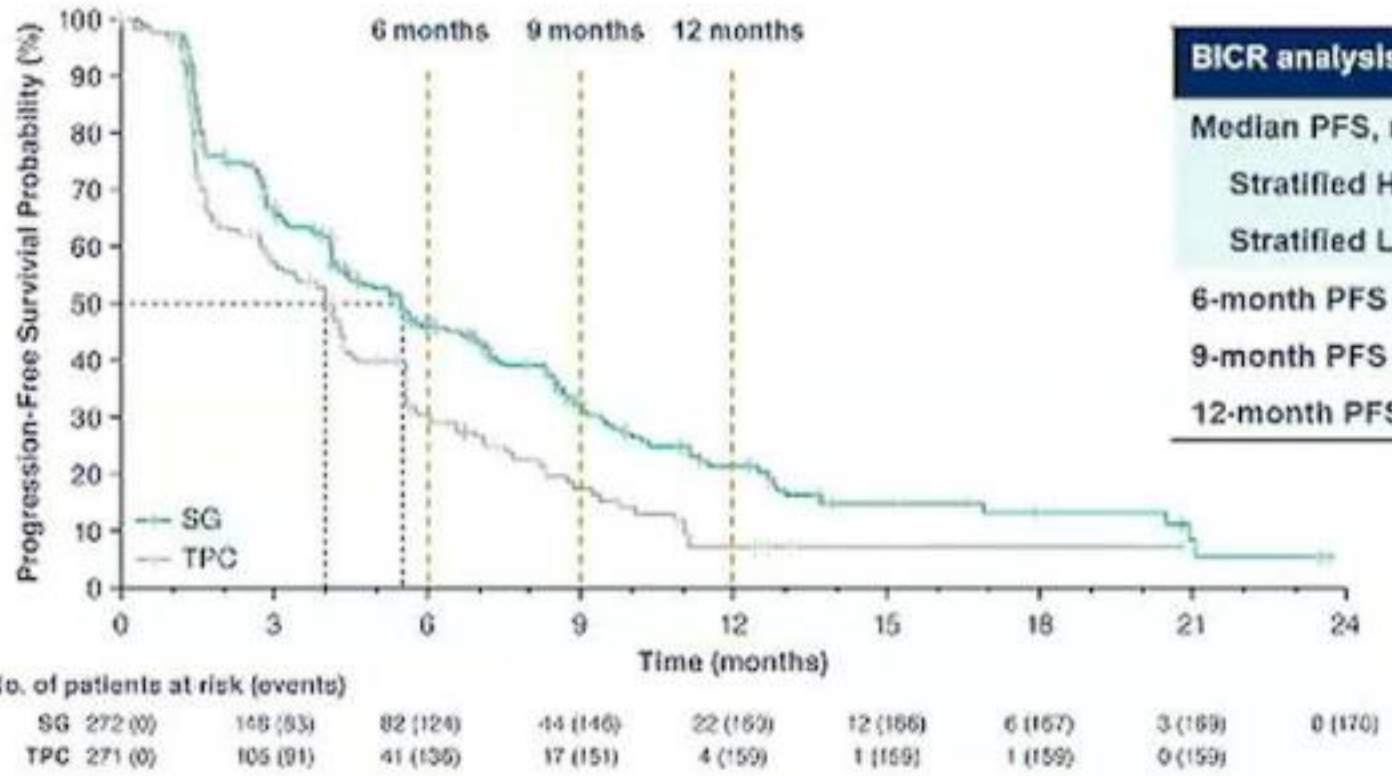
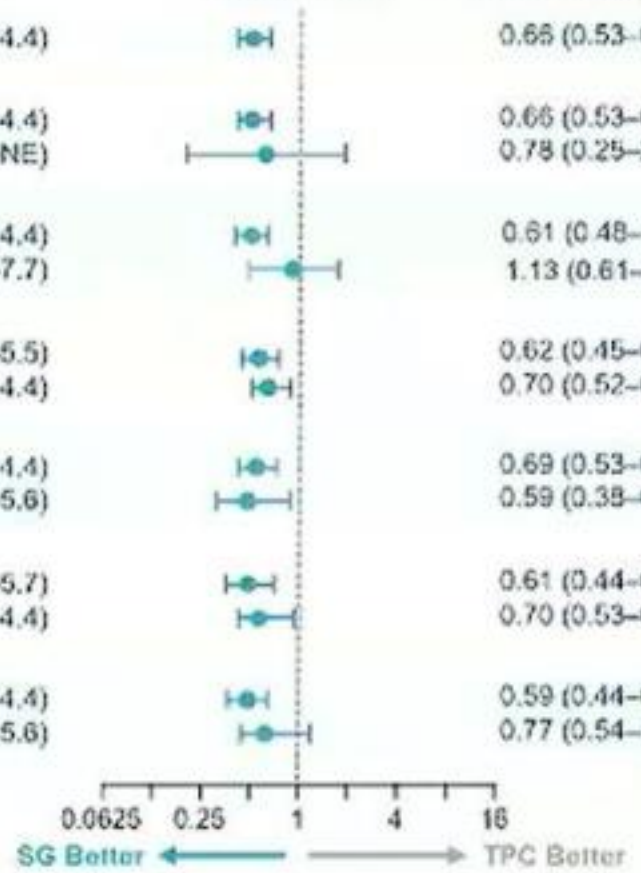


BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	0.66 (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

Median follow-up was 19.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

PFS Subgroup Analyses

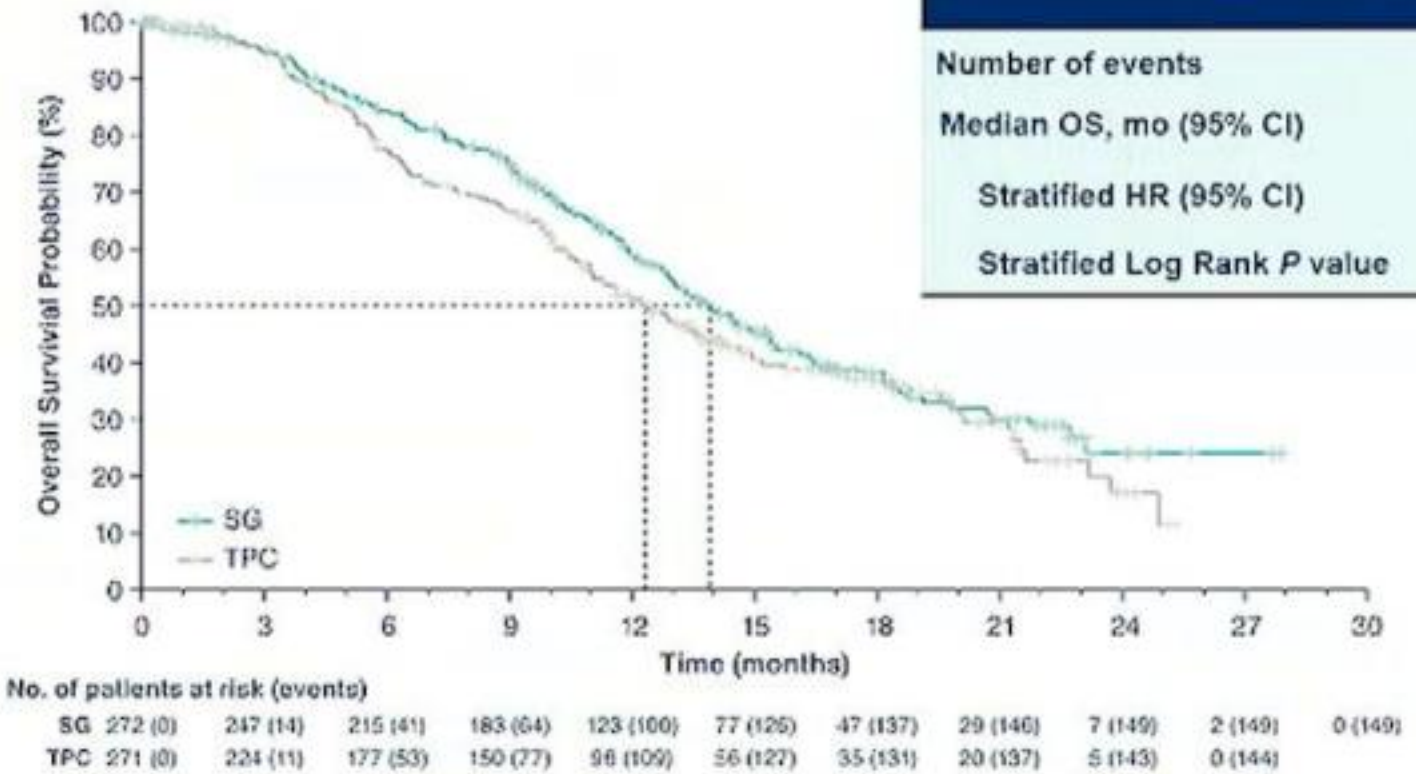
Subgroup	Median PFS, months (95% CI) SG	TPC	Hazard Ratio (95% CI)
Overall (N=543)	5.5 (4.2–7.0)	4.0 (3.1–4.4)	0.66 (0.53–0.82)
Visceral Metastasis			
Yes (n=517)	5.5 (4.2–7.0)	4.0 (3.1–4.4)	0.66 (0.53–0.83)
No (n=26)	9.1 (1.3–NE)	5.6 (1.6–NE)	0.78 (0.25–2.40)
ET for mBC ≥6 Months			
Yes (n=469)	5.6 (4.4–7.4)	4.1 (3.1–4.4)	0.61 (0.48–0.78)
No (n=74)	3.9 (2.5–5.8)	3.5 (1.6–7.7)	1.13 (0.61–2.07)
# of Prior Chemos for mBC			
≤2 (n=233)	5.7 (4.2–8.3)	4.2 (2.8–5.5)	0.62 (0.45–0.85)
≥3 (n=310)	5.3 (4.0–6.9)	3.7 (2.7–4.4)	0.70 (0.52–0.95)
Age Group			
<65 years (n=403)	5.5 (4.1–6.9)	4.1 (3.0–4.4)	0.69 (0.53–0.89)
≥65 years (n=140)	6.7 (4.2–9.0)	3.5 (1.7–5.6)	0.59 (0.38–0.93)
ECOG Performance Score			
0 (n=242)	5.7 (4.2–8.5)	4.1 (2.7–5.7)	0.61 (0.44–0.86)
1 (n=301)	5.0 (4.0–7.1)	4.0 (2.8–4.4)	0.70 (0.53–0.94)
Prior CDK4/6i Duration			
≤12 months (n=327)	6.0 (4.6–8.3)	4.0 (2.8–4.4)	0.59 (0.44–0.78)
>12 months (=208)	4.4 (3.3–7.0)	4.2 (2.7–5.6)	0.77 (0.54–1.10)



- PFS benefit for SG vs TPC was consistent across predefined subgroups, including patients with
  - ≥3 prior chemotherapy regimens in the metastatic setting
  - Visceral metastases
  - Age ≥65 years

PFS subgroup analyses by race, geographic region, TPC arm agents, and early relapse were assessed but not included in this figure
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; mBC, metastatic breast cancer; NE, not evaluable; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice

OS in the ITT Population (First Planned Interim Analysis)



	SG (n=272)	TPC (n=271)
Number of events	149	144
Median OS, mo (95% CI)	13.9 (12.7-15.4)	12.3 (10.8-14.2)
Stratified HR (95% CI)	0.84 (0.67-1.06)	
Stratified Log Rank *P* value	*P*=0.14	

- **OS data is not yet mature at the first of three planned OS analyses**
- **Further follow-up is ongoing**

ITT, intent-to-treat; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice

Response Rates

BICR analysis	SG (n=272)	TPC (n=271)
ORR, n (%)	57 (21)	38 (14)
Odds ratio, nominal *P* value[a]	1.63, *P*=0.03	
Best overall response, n (%)		
CR	2 (1)	0
PR	55 (20)	38 (14)
SD	142 (52)	106 (39)
SD ≥6 mo	35 (13)	21 (8)
PD	58 (21)	76 (28)
NE	15 (6)	51 (19)
CBR,[b] n (%)	92 (34)	59 (22)
Odds ratio, nominal *P* value[a]	1.84, *P*=0.002	
Median DOR, mo (95% CI)	7.4 (6.5-8.6)	5.6 (3.8-7.9)

ORR (21% vs 14%) and CBR (34% vs 22%) were higher with SG vs TPC

[a]Not formally tested because CS at IA1 was not statistically significant.
[b]CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR, and SD ≥6 months.
BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; DCR, duration of response; IA1, interim analysis 1; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

PRESENTED BY: Hope S. Rugo, MD

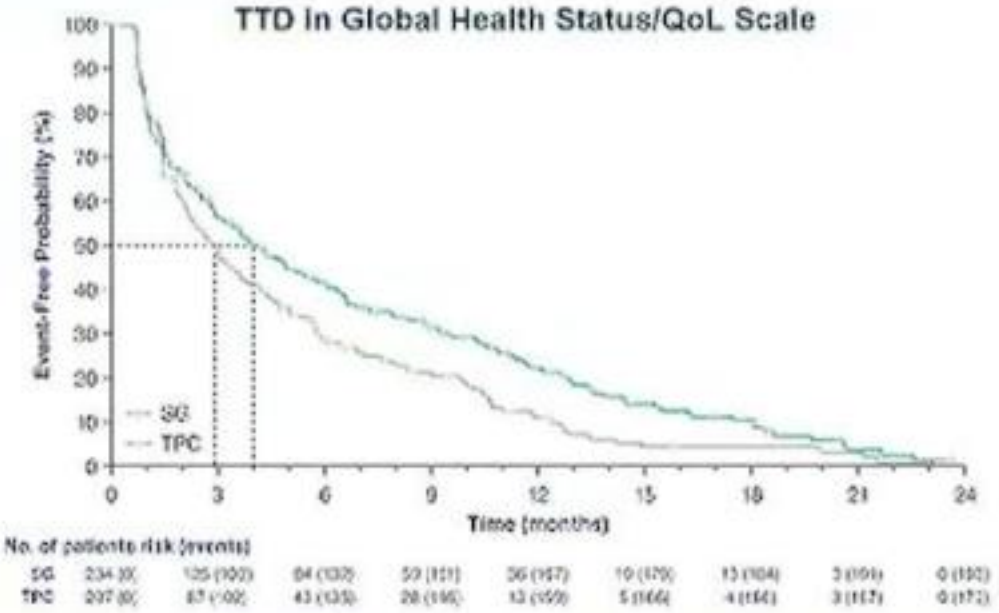
Key All Grade and Grade ≥3 Treatment-Related Adverse Events[a]

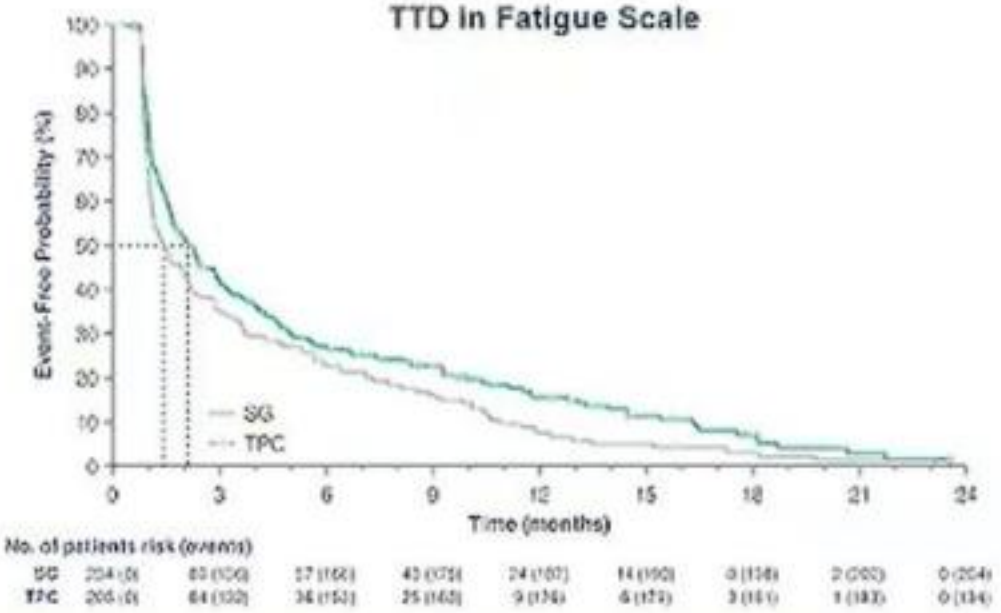
TRAEs, n (%)		SG (n=268)		TPC (n=249)	
		All grade	Grade ≥3	All grade	Grade ≥3
Hematologic	**Neutropenia[b]**	188 (70)	**136 (51)**	134 (54)	**94 (38)**
	Anemia[c]	91 (34)	17 (6)	62 (25)	8 (3)
	Leukopenia[d]	37 (14)	23 (9)	23 (9)	13 (5)
	Lymphopenia[e]	31 (12)	10 (4)	25 (10)	8 (3)
	Febrile neutropenia	14 (5)	14 (5)	11 (4)	11 (4)
Gastrointestinal	**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
Other	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)

- **There were no events of interstitial lung disease in the SG arm (vs 1% in the TPC arm) and no TRAEs of cardiac failure or left ventricular dysfunction in either arm**

Assessed in the safety population of patients who received ≥1 dose of study treatment. Patients may report more than one event per preferred term.
[a]Key All Grade and Grade ≥3 TRAEs defined as those occurring in ≥10% and ≥5% of patients in one arm, respectively. [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 'white blood cell 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'.
SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related adverse event.

EORTC QLQ-C30 Time to Deterioration Endpoints





TTD	Patients SG/TPC, n/n	SG median TTD, mo (95% CI)	TPC median TTD, mo (95% CI)	Stratified HR (95% CI)	Nominal *P* value[a]
Global Health Status/QoL	234/207	4.0 (3.0-5.4)	2.9 (2.2-3.6)	0.74 (0.59-0.91)	0.005
Fatigue	234/205	2.1 (1.6-2.8)	1.4 (1.1-1.9)	0.76 (0.62-0.93)	0.007
Pain	229/202	3.7 (2.8-4.9)	3.4 (2.7-4.6)	0.92 (0.74-1.14)	0.45

Assessed in patients all patients in the intent-to-treat population who had an evaluable assessment of the health-related QoL at baseline and at least one evaluable assessment at post-baseline visits.
[a]Not formally tested because OS at IA1 was not statistically significant.
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; IA1, interim analysis 1; OS, overall survival; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTD, time-to-deterioration.

Topics

- HER2-low BC Definition and Features
- Anti-HER2 Agents in HER2 low BC
  - Monoclonal Antibodies & *'Old'* Antibody Drug Conjugates (ADCs)
  - 'New' ADCs: Trastuzumab-Deruxtecan (T-Dxd)
- **Conclusions & Future Perspectives**

Conclusions (1)

- **HER2-low BC is defined by IHC score 1+ or 2+/ISH-**
  - **Nearly 50% of all BC are HER2-low**
  - **HER2-low are more common among Luminal-Like tumors than TNBC**
  - **HER2-low seems to have no distinct biology/prognosis than HER2 score 0**
- **Negative results in HER2-low with '*Old*' anti-HER2 Abs and ADCs**
- **HER2-low BC emerges as a new druggable entity, through the delivery of payloads**
- **Destiny-Breast04 established T-Dxd as a new standard of care in HER2-low BC**

Conclusions (2)

- **T-Dxd is the first HER2-targeted therapy to demonstrate efficacy in HER2-low BC**
  - **Similar magnitude of benefit across all subgroups**
  - **More data are needed in HER2-low/HR-**
  - **Peculiar toxicity of T-Dxd, management is crucial!**

On August 5, 2022, the FDA approved T-Dxd for HER2-low BC

- **Limited benefit of CT for pts who progress after multiple lines of CT and/or CDK4/6i (mPFS ~ 4 months)**
- **CT could be replaced by novel ADCs (against newer targets, novel payloads), such as Sacituzumab-govitecan (TROPiCS-02 study)**

DESTINY-Breast04

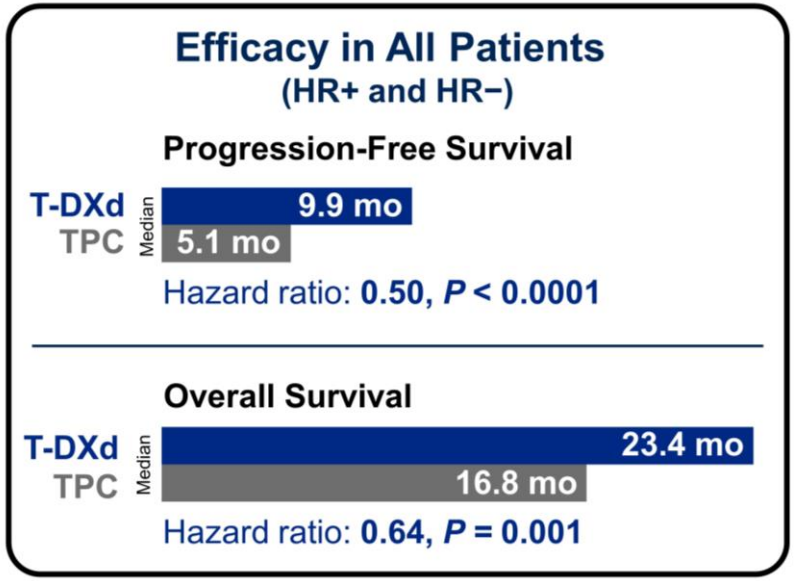


Figure 1. **Study Schema**

ASCENT-07

Key eligibility criteria:

- HR+/HER2 negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced or metastatic breast cancer
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1

Patients must have one of the following:

- Disease progression on ≥2 previous lines of ET with or without a targeted therapy in the metastatic setting
  - Disease recurrence while on the first 24 months of starting adjuvant ET will be considered a line of therapy; these patients will only require 1 line of ET in the metastatic setting
- Disease progression within 6 months of starting first line ET with or without a CDK4/6i in the metastatic setting
- Disease recurrence while on the first 24 months of starting adjuvant ET with CDK4/6i and if the patient is no longer a candidate for additional ET in the metastatic setting as determined by the investigator

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 vs ≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/UK/EU vs ROW)

Primary Endpoint

- PFS by BICR

Key Secondary Endpoints

- OS
- ORR by BICR
- Change from baseline in Physical Functioning and TTD of Global Health Status

Secondary Endpoints

- PFS by investigator
- ORR by investigator
- DOR
- Safety

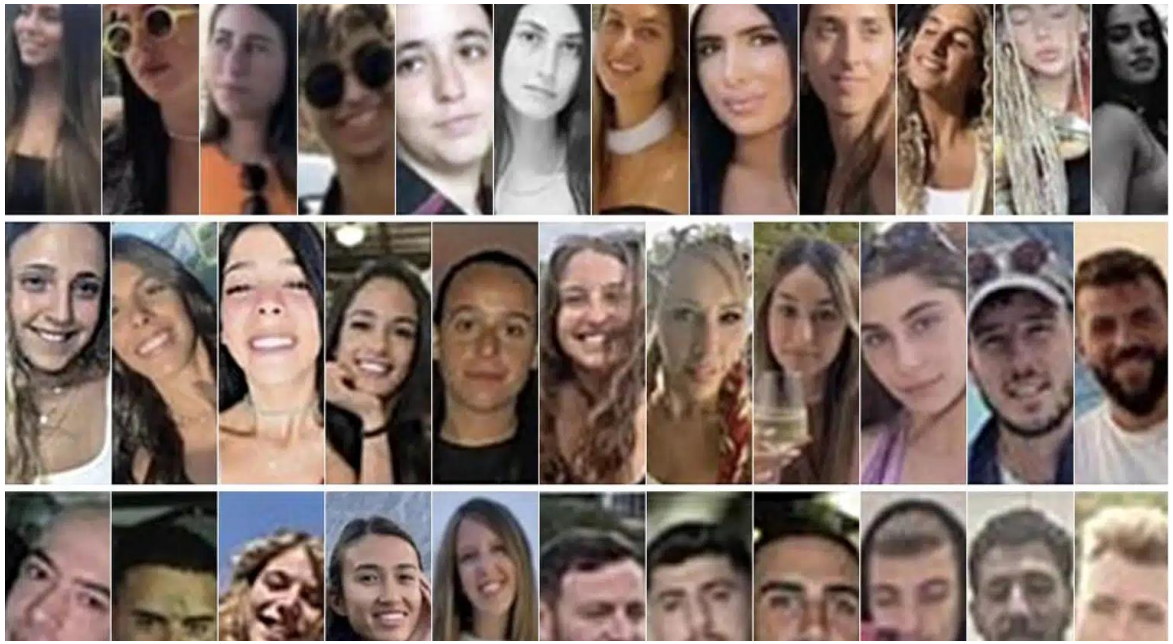
Future Perspective

- **We need to precisely refine HER2 negative disease (distinguishing 'truly' HER2 negative from HER2-low)**

- **HER2 status can change between early and relapsed setting → IHC 0 on the primary often converts to HER2-low upon relapse**

- **Ongoing Phase 3 trial: T-DXd vs TPC in HER2-Low*, HR+ whose disease has progressed on ET (DESTINY-Breast06) [*HER2-low or HER2-ultra low: IHC >0 <1+ expression]**
  - **Role of ADCs in chemo naïve and HER2 Ultra-Low patients? Will ADCs replace CT as first-treatment of choice post-ET?**

- **Novel anti-HER2 agents are currently investigated in HER2-low BC ('*New*' ADC, Vaccines and Bispecific Antibodies)**
  - **T-Duocarmazine showed activity in heavily pretreated HER2-low MBC (ORR 28%-40%)**



Thank you for your attention