Nuove opzioni terapeutiche nel carcinoma mammario metastatico HER2-low

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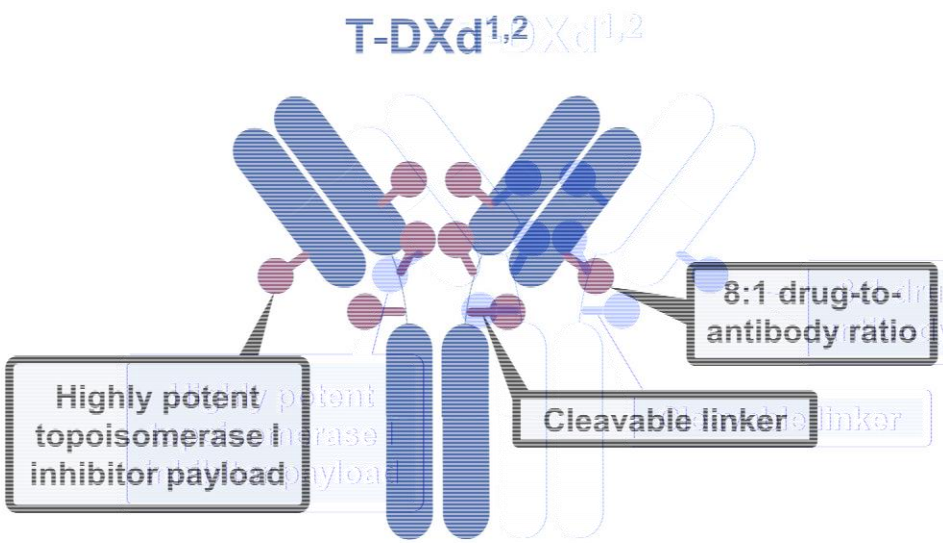
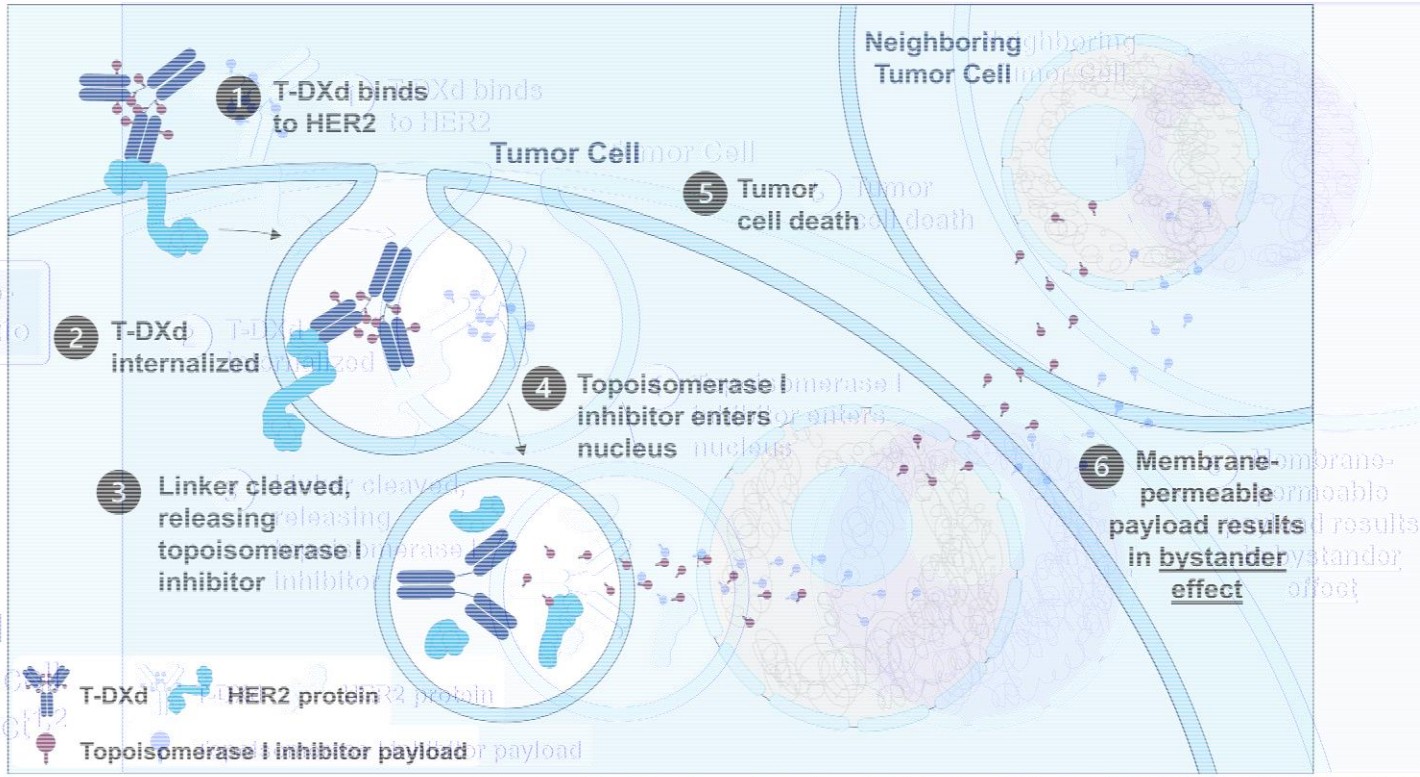
DISCLOSURES

Advisory Board:
EliLilly, Novartis, MSD, Gilead, Eisai, Sanofi, Merck Serono, Exact Sciences, Pfizer, Olema Oncology
Speaker’s Bureau:
EliLilly, Novartis, GSK, Amgen

Trastuzumab Deruxtecan



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[1,2]



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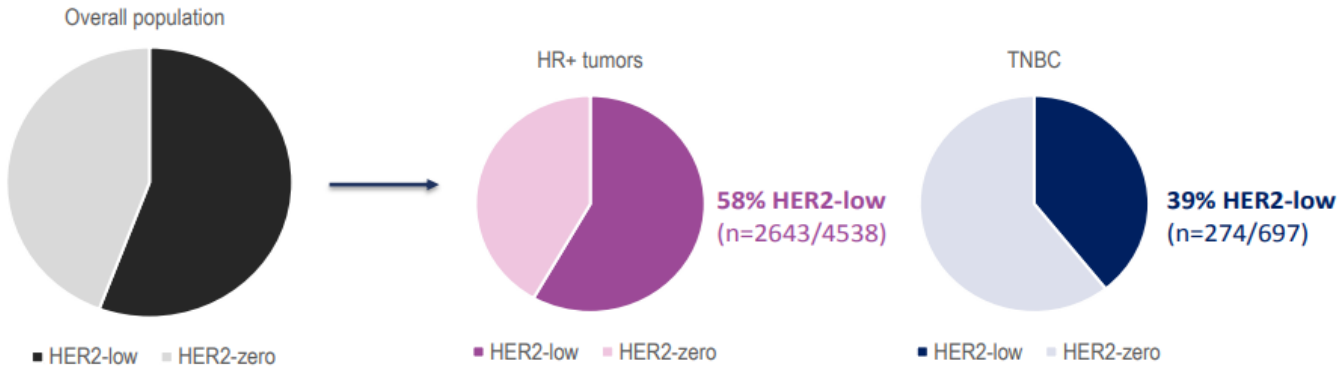
Modi S et al., ASCO 2022, NEJM 2022

HER2-low enriched in HR+ BC

HER2-low in early BC



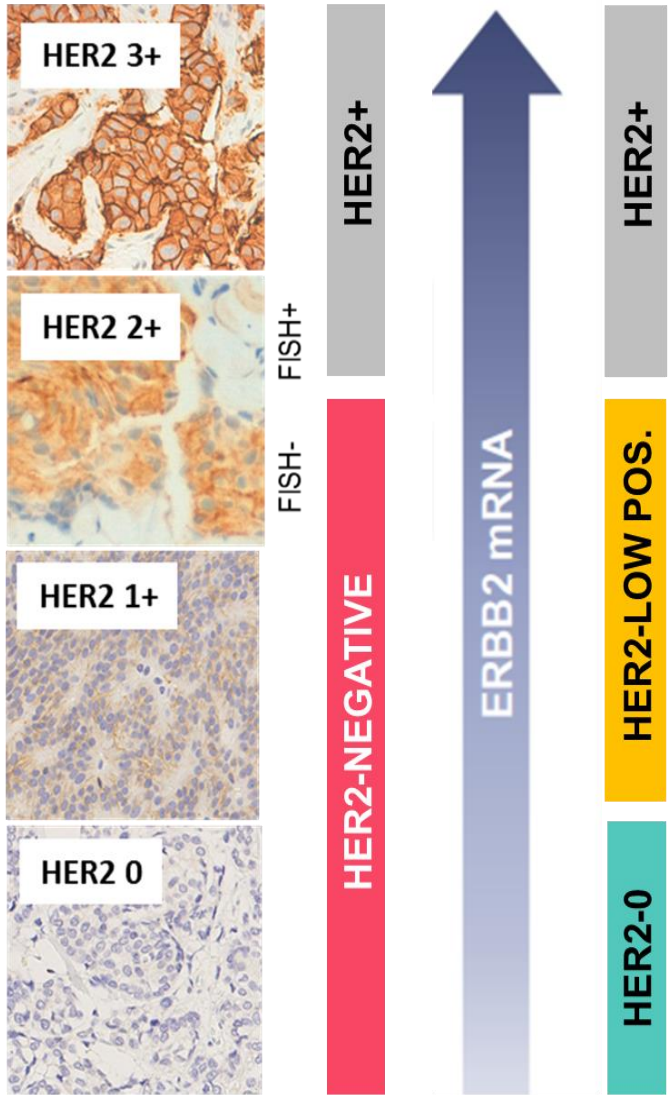
Primary BC phenotype	HER2-0	HER2-LOW	p
HR+/HER2-	33 (31.4%)	72 (68.6%)	0.001
TN	83 (53.2%)	73(46.8%)	

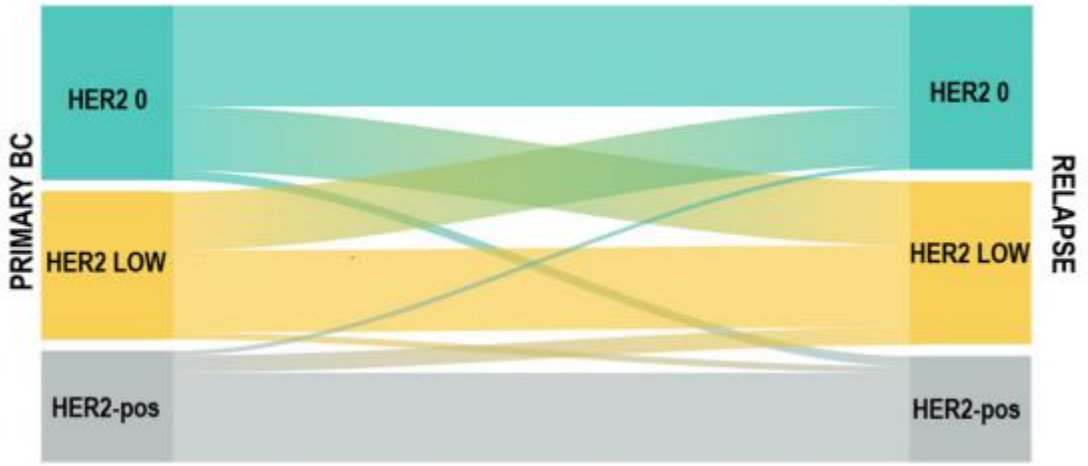
HER2-low in advanced BC

BC phenotype	HER2-LOW %	p
HR+/HER2-neg	54%	*0.001*
TN	36%	
Overall HER2-neg cohort	49%	

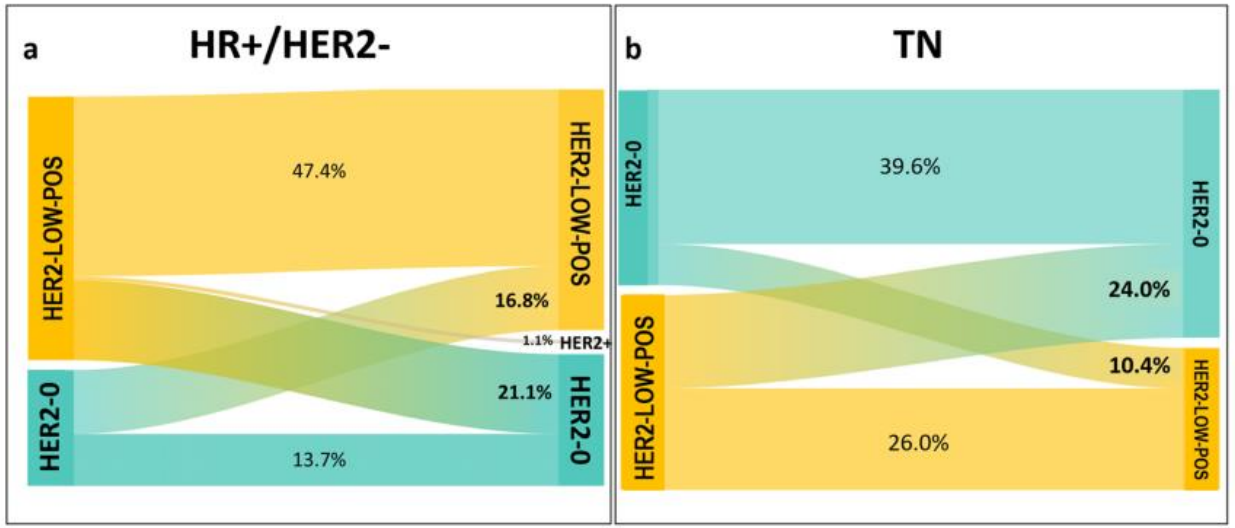
Tarantino P et al, ESMO Breast Cancer 2022; Miglietta et al NPJ Breast Cancer 2021; Miglietta et al NPJ Breast Cancer 2022

HER2-low positive BC: evolution over time





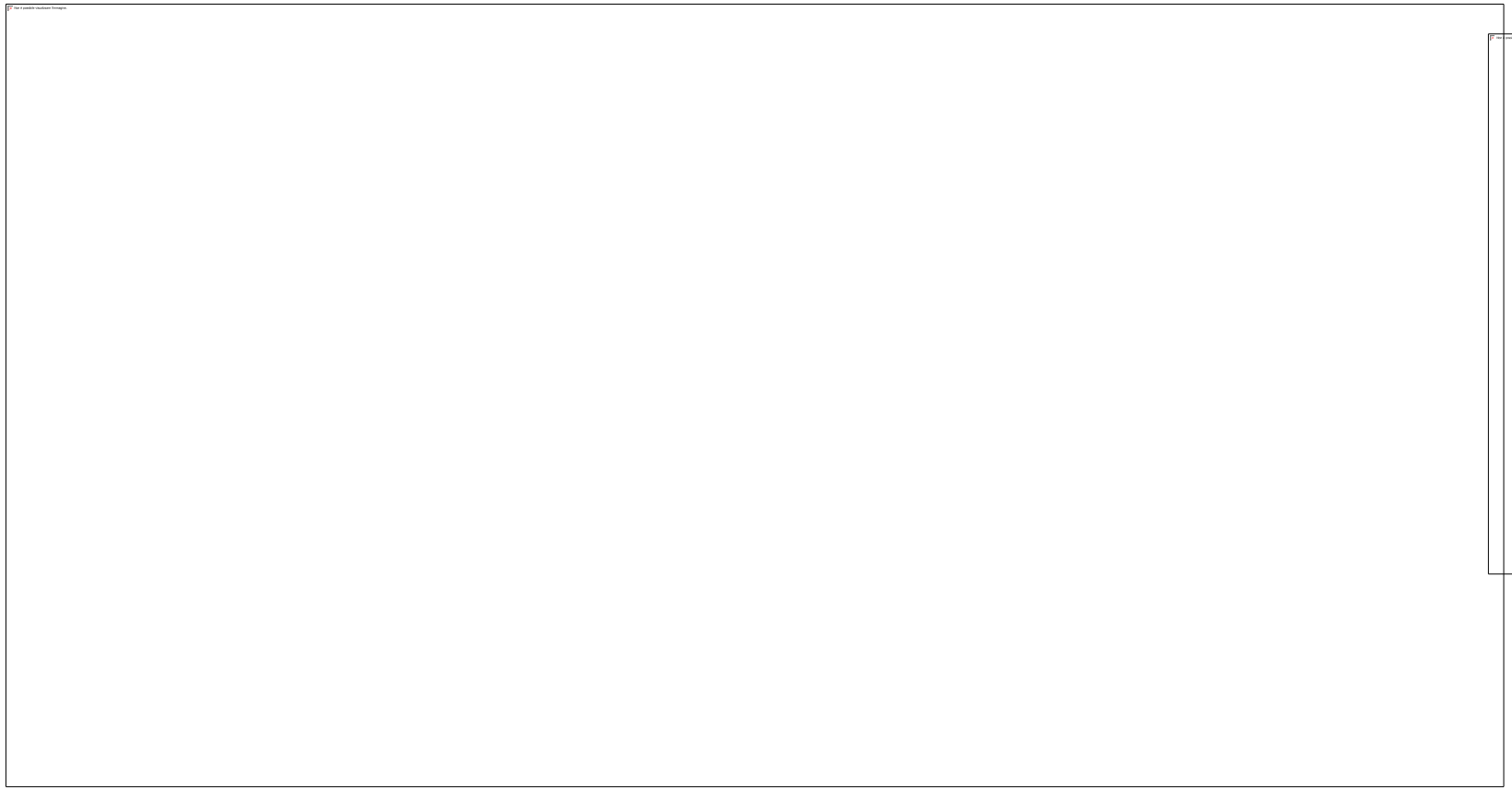
Miglietta F, NPJ Breast Cancer 2021

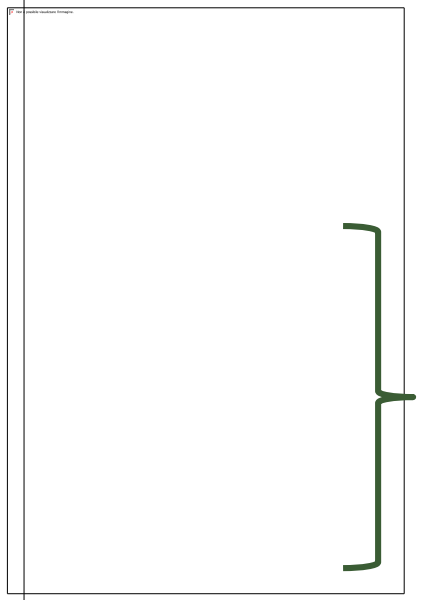


RD post neoadjuvant CT

Miglietta F, NPJ Breast Cancer 2022

DESTINY-Breast04 phase III Trial: T-Dxd vs Chemo in HER2-low





Primary endpoint

Secondary endpoints

89% HR+
Median previous lines for mBC: 3 (1-9)
Median previous chemo lines for mBC:1 (0-3)
70% of HR+ BC pts pretreated with CdK4/6 inh
HER2 1+ 58%, HER2 2+/ISH- 42%

Modi S et al., NEJM 2022

DESTINY-Breast04 phase III Trial: clinicopathologic features

Baseline features

DESTINY-Breast04 phase III Trial: clinicopathologic features

Prior therapies

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

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

Modi S et al., ASCO 2022, NEJM 2022

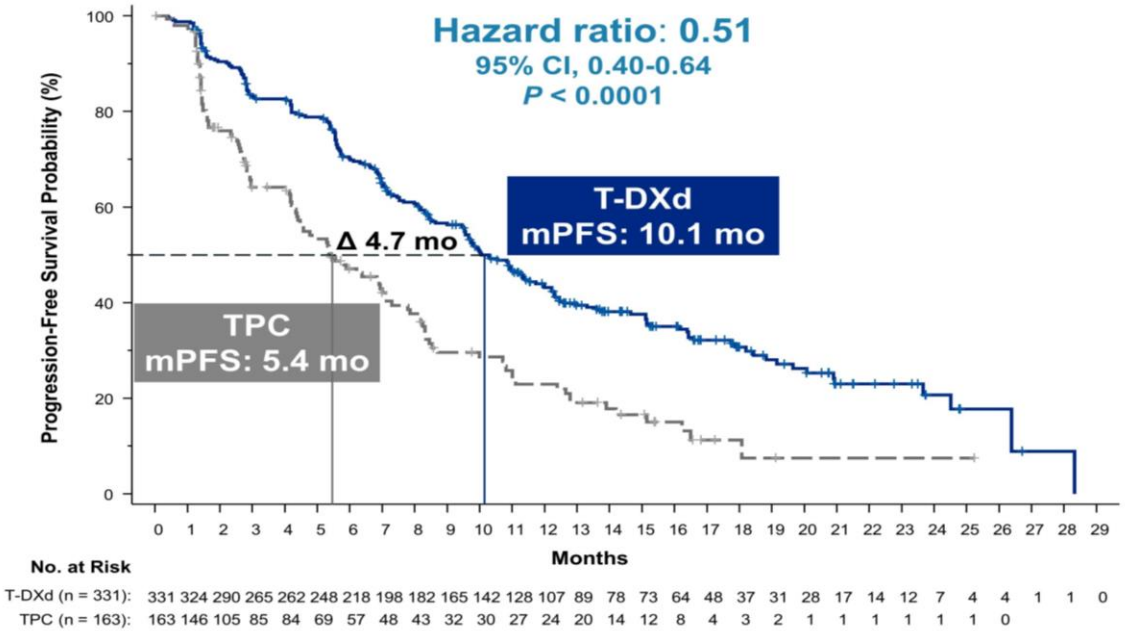
DESTINY-Breast04 phase III Trial: efficacy results

PFS in HR+ *(primary endpoint)* and all patients

Hierarchical testing

- PFS in HR+ ✓
- PFS in all patients
- OS in HR+
- OS in all patients

Hormone receptor–positive



Primary endpoint met

Modi S et al., ASCO 2022, NEJM 2022

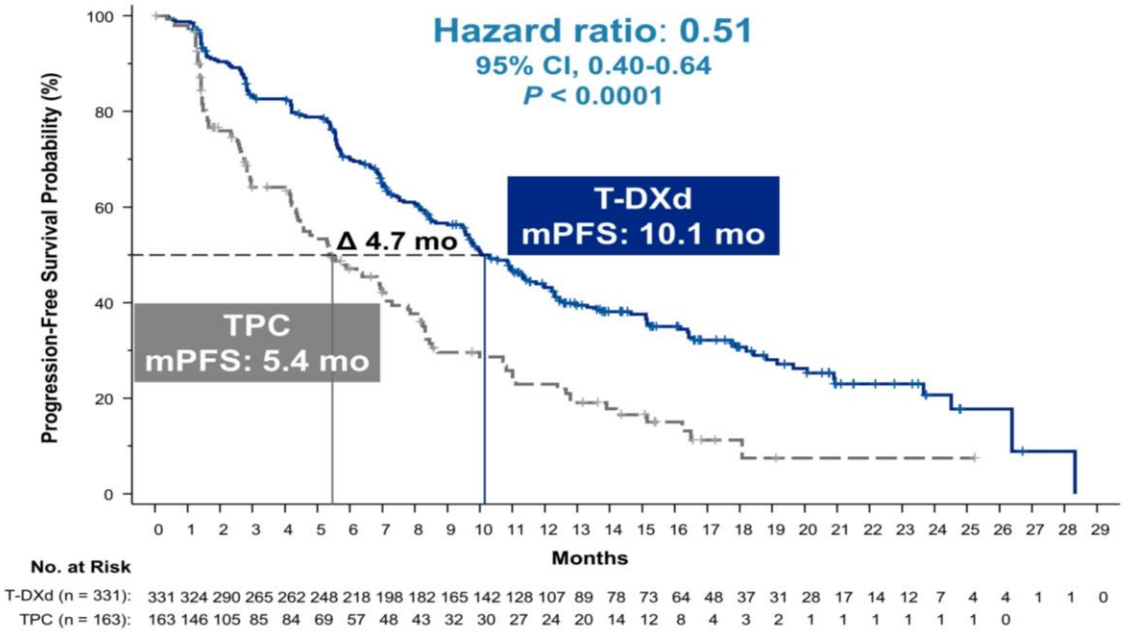
DESTINY-Breast04 phase III Trial: efficacy results

PFS in HR+ *(primary endpoint)* and all patients

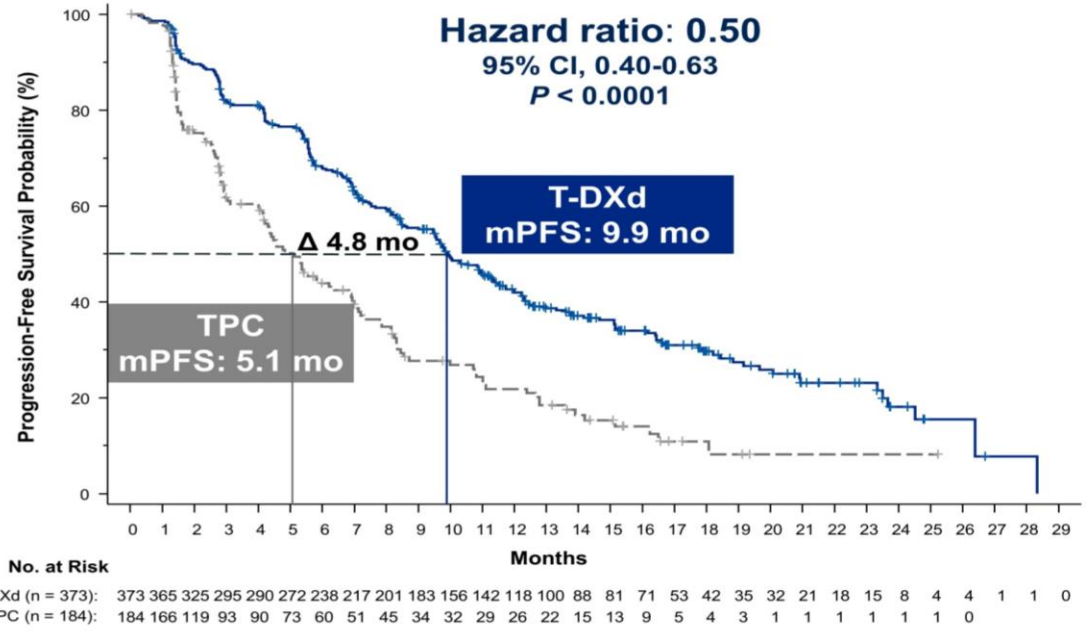
Hierarchical testing

- PFS in HR+ ✓
- PFS in all patients ✓
- OS in HR+
- OS in all patients

Hormone receptor–positive



All patients



Modi S et al., ASCO 2022, NEJM 2022

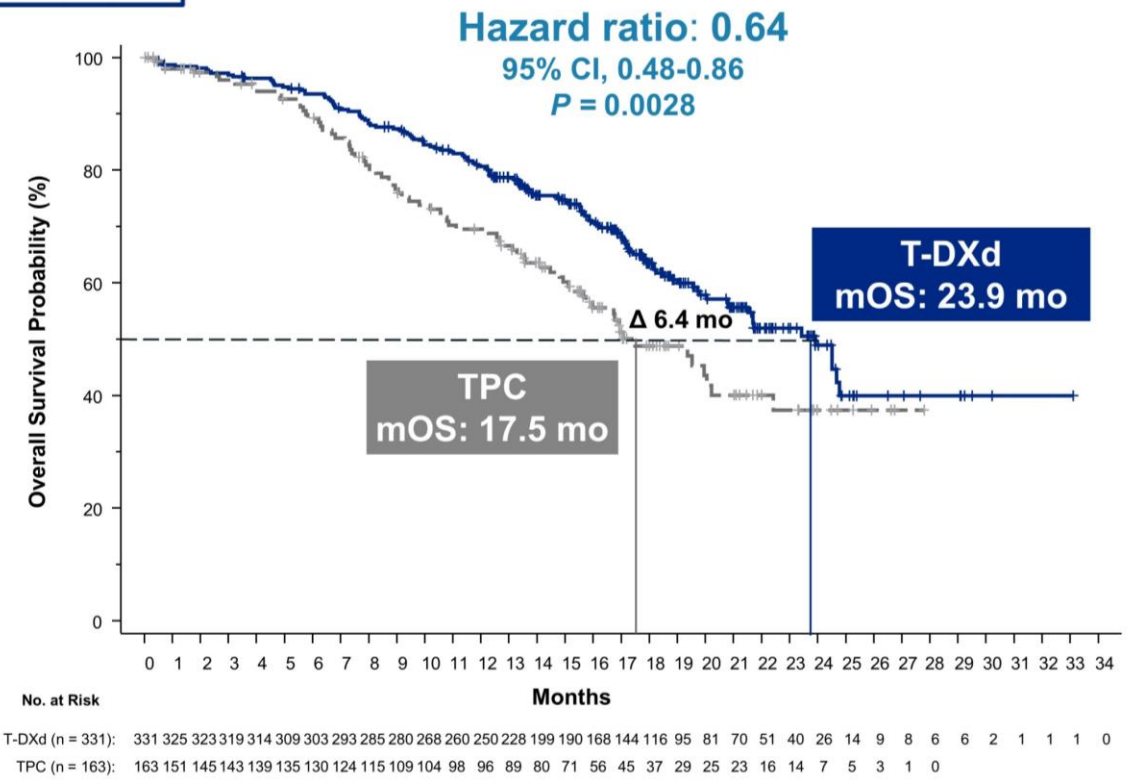
DESTINY-Breast04 phase III Trial: efficacy results

OS in HR+ and all patients

Hierarchical testing

- PFS in HR+ ✓
- PFS in all patients ✓
- OS in HR+ ✓
- OS in all patients

Hormone receptor–positive



Modi S et al., ASCO 2022, NEJM 2022

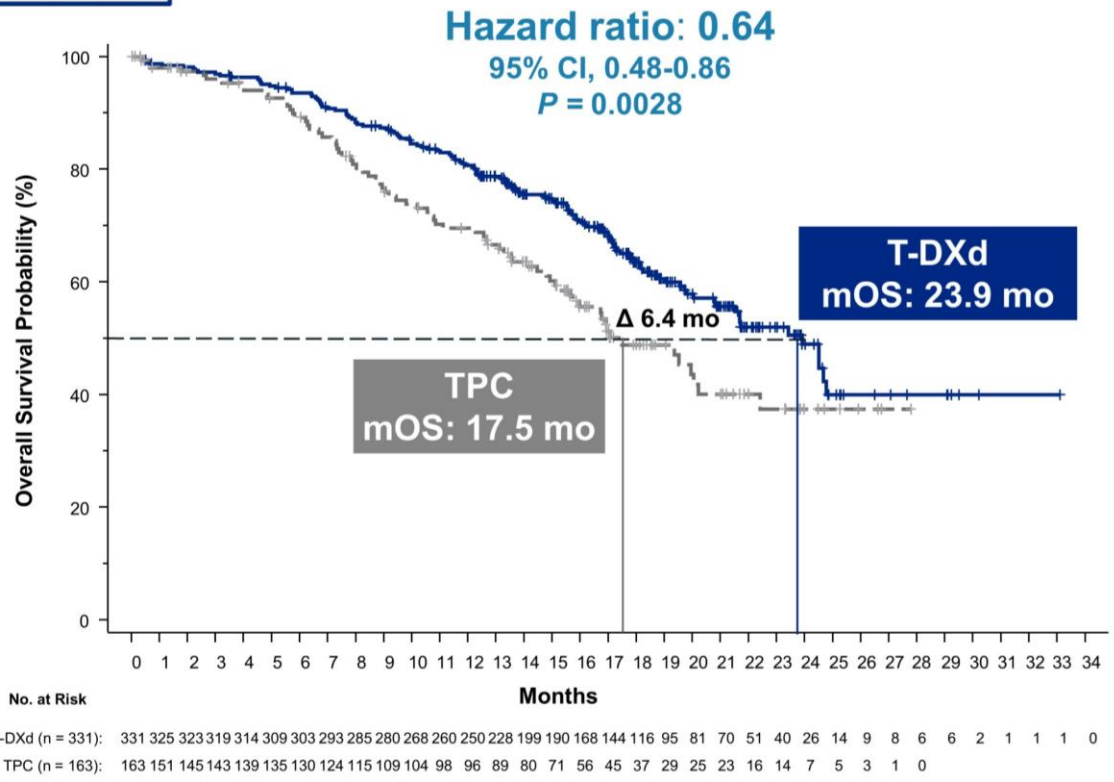
DESTINY-Breast04 phase III Trial: efficacy results

OS in HR+ and all patients

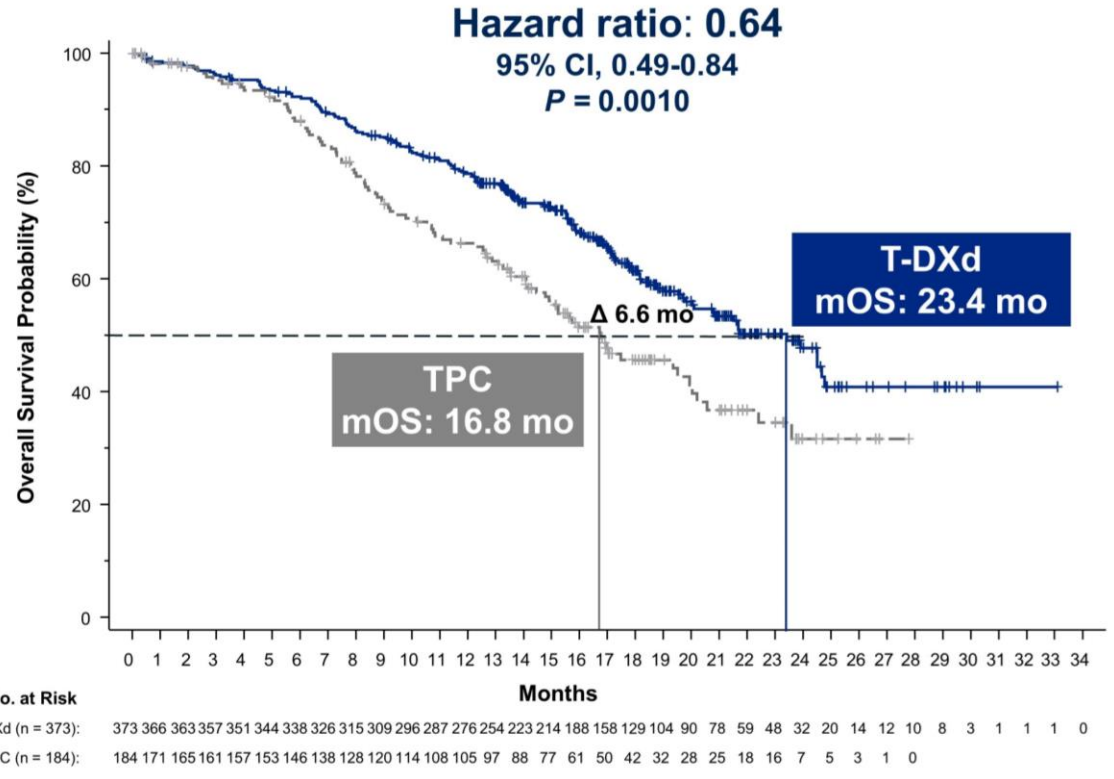
Hierarchical testing

- PFS in HR+ ✓
- PFS in all patients ✓
- OS in HR+ ✓
- OS in all patients ✓

Hormone receptor–positive



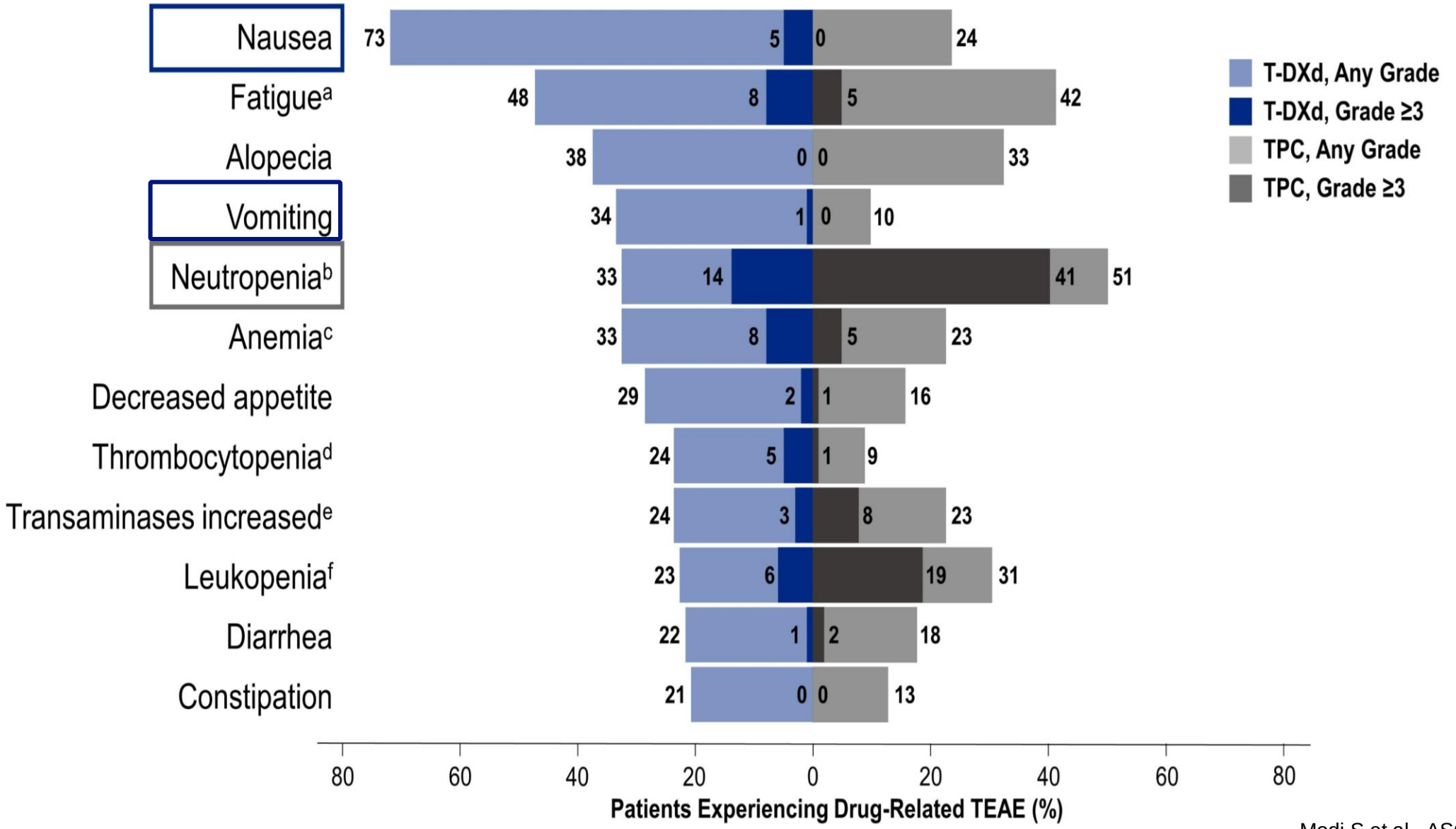
All patients



Modi S et al., ASCO 2022, NEJM 2022

DESTINY-Breast04 phase III Trial: safety results

Drug related TEAEs in ≥20% of patients



Modi S et al., ASCO 2022, NEJM 2022

DESTINY-Breast04 phase III Trial: safety results

Overall safety summary

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

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

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

Modi S et al., ASCO 2022, NEJM 2022

DESTINY-Breast04 phase III Trial: safety results

Adverse Events of Special Interest

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)

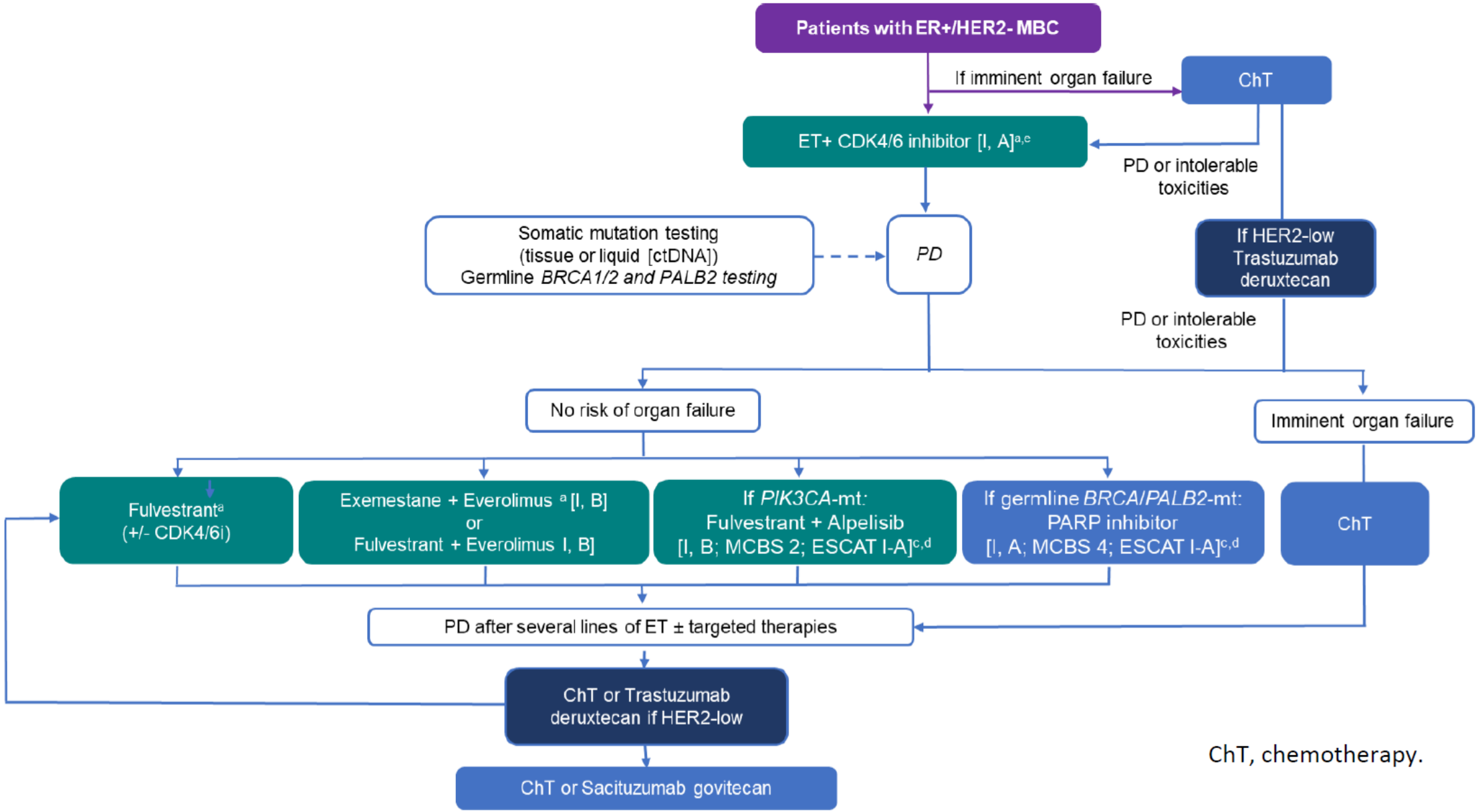
Median time to onset of ILD/pneumonitis during T-DXd = 129 days

Left ventricular dysfunction[b]

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

Modi S et al., ASCO 2022, NEJM 2022

HR+/HER2- metastatic breast cancer: treatment algorithm



ChT, chemotherapy.

Study Design

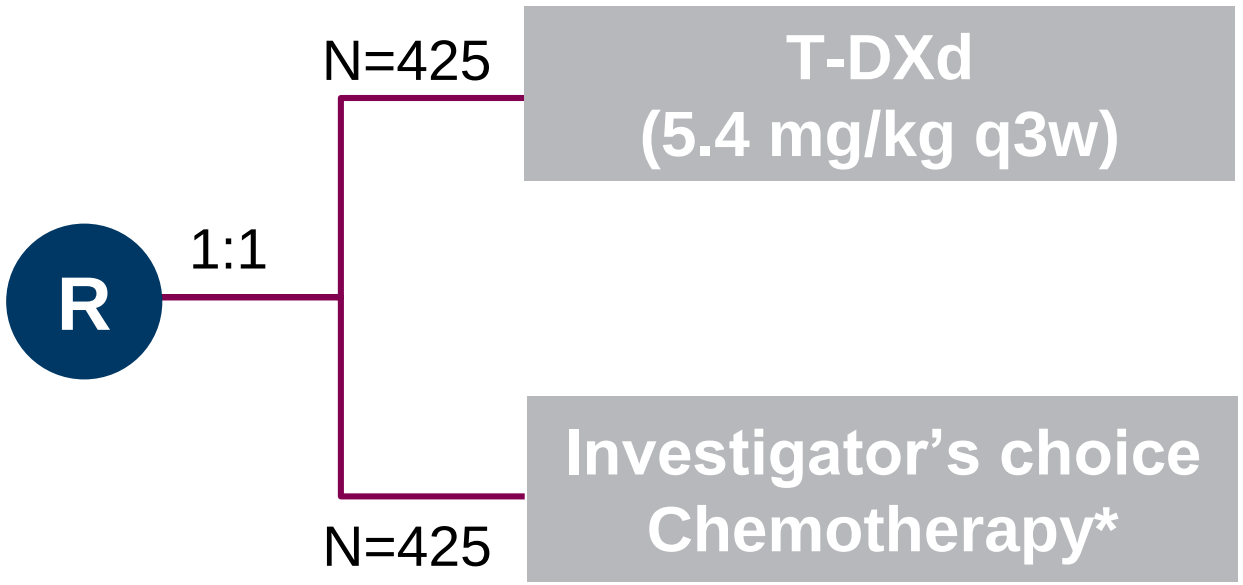
DESTINY BREAST-06

Patient Population

- Advanced/Metastatic HR+ Breast cancer after progression on ≥2 prior ETs
- No prior chemotherapy in the metastatic setting
- Low HER2: IHC>0<1+ or 1+ or 2+ (determined based on central IHC assessment of archival tissue collected at time of diagnosis of metastatic disease or later)

Stratification

- Prior CDK4/6 inhibitor use
- HER2 IHC 2+ vs. 1+ vs. >0<1+
- Prior taxane in the nonmetastatic setting



* Chemotherapy options: capecitabine, paclitaxel, nAb-paclitaxel

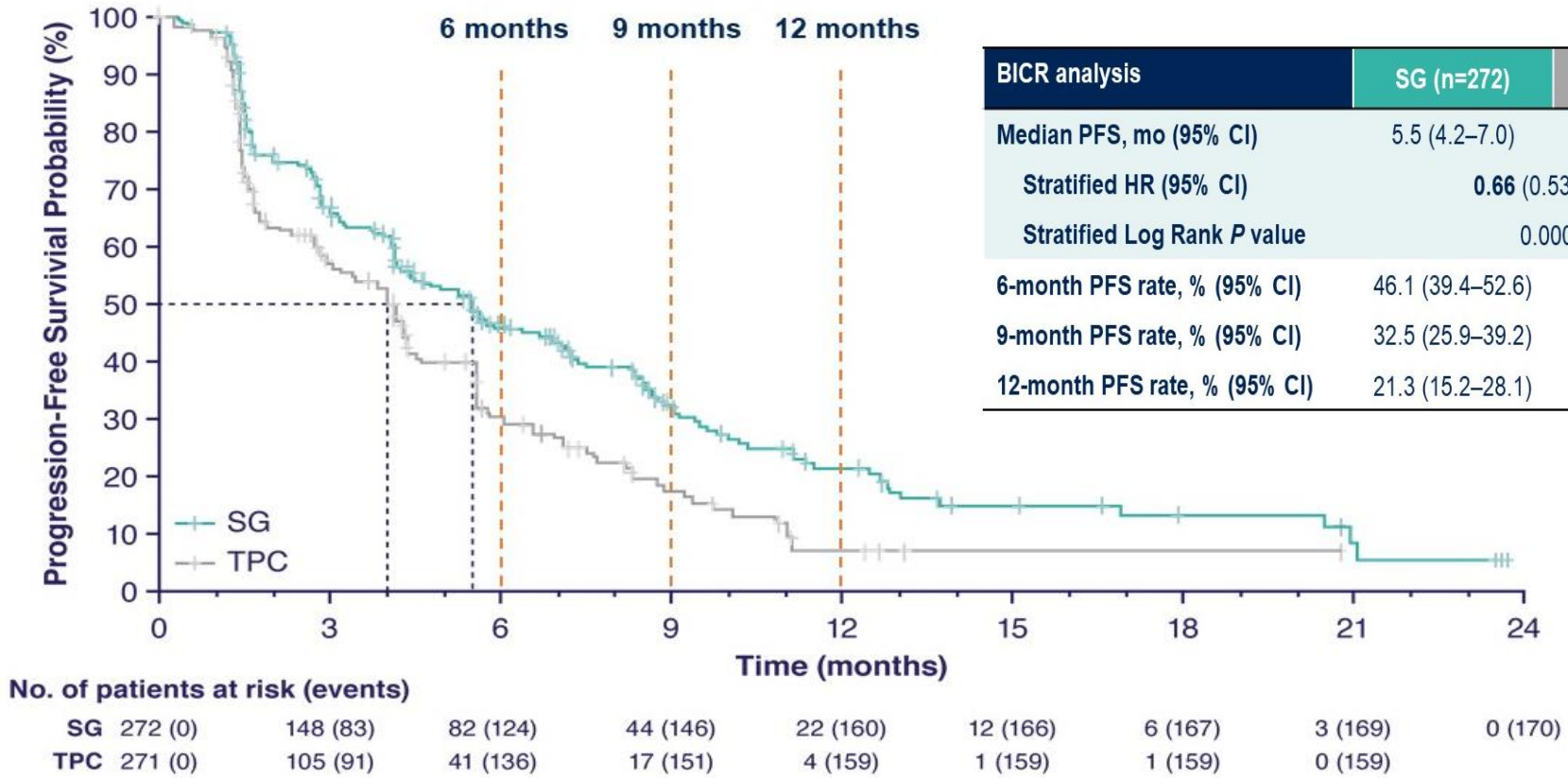
- Treatment continues until progressive disease or toxicity
- HER2 IHC >0 <1+ defined by tumor membrane expression characterized as faint or barely perceptible and incomplete membrane staining that is seen in 10% or fewer tumor cells (HER2 IHC >0 <1+ population N=150)
- Futility analysis in HER2 IHC >0 <1+ cohort will be done at 70 patients
- Target at least 51% of patient population with prior CDK4/6 inhibitor use

TROPiCS-02 trial: SG in HR+/HER2- ABC

mBC previously treated with ET, CDK 4/6 inh and CT

Rugo et al, ASCO 2022

TROPICS-02 (SG in pretreated HR+/HER2- mBC): PFS



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)

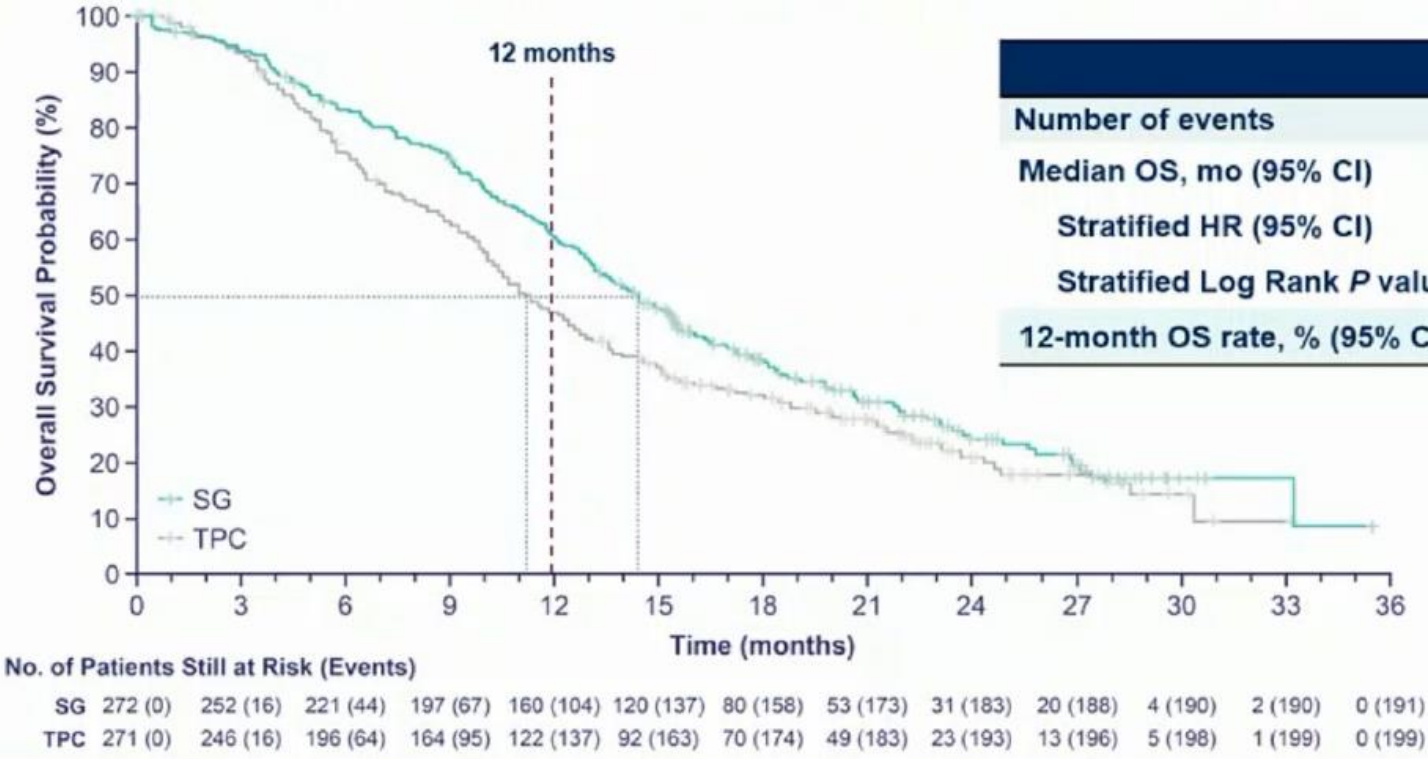
PFS benefit was consisted across predefined subgroups, including:

- ≥3 prior chemo regimens in metastatic setting
- Visceral metastases

Exploratory analysis: similar effect according to HER20/low
Marmé F et al., ESMO 2022

Rugo H et al., ASCO 2022, J Clin Oncol 2022

TROPICS-02: OS at second interim analysis



	SG (n=272)	TPC (n=271)
Number of events	191	199
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	
12-month OS rate, % (95% CI)	61 (55–66)	47 (41–53)

No. of Patients Still at Risk (Events)

SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)
TPC	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)

- SG demonstrated a statistically significant improvement in OS vs TPC with 21% reduction in the risk of death; having met statistical significance, no further formal statistical testing of OS will occur
- Patients who received SG survived a median of ***3.2 months longer*** than those who received TPC

Rugo H et al., ESMO 2022

TROPiCS-02 trial: efficacy by HER2 immunohistochemistry status

PARIS 2022 ESMO congress

Sacituzumab govitecan efficacy in HR+/HER2– metastatic breast cancer by HER2 immunohistochemistry status in the phase 3 TROPiCS-02 study

Peter Schmid,[1] Javier Cortes,[2] Frederik Marmé,[3] Hope S. Rugo,[4] Sara M. Tolaney,[5] Mafalda Oliveira,[6] Delphine Loirat,[7] Komal Jhaveri,[8] Oh Kyu Yoon,[9] Monica Motwani,[9] Hao Wang,[9] Rosemary Delaney,[10] Aditya Bardia[11]

[1]Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; [2]International Breast Cancer Center (IBCC), Quiron Group, Madrid & Barcelona, Spain; [3]Heidelberg University, University Hospital Mannheim, Heidelberg, Germany; [4]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]Institut Curie, Paris, France; [8]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [9]Gilead Sciences, Inc, Foster City, CA, USA; [10]Gilead Sciences, Inc, Morris Plains, NJ, USA; [11]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

Presenter: Dr. Frederik Marmé

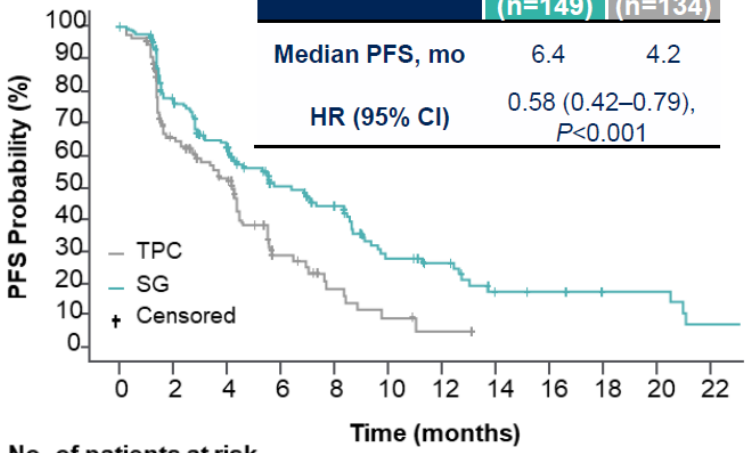
Saturday, September 10, 15:40 - 15:45
FPN 214MO

TROPiCS-02 trial: efficacy by HER2 immunohistochemistry status

SG Improved PFS vs TPC in HER2-Low and HER2 IHC0 Groups, Consistent with Outcomes in the ITT Population

HER2-Low[a]

	SG (n=149)	TPC (n=134)
Median PFS, mo	6.4	4.2
HR (95% CI)	0.58 (0.42–0.79), *P*<0.001	

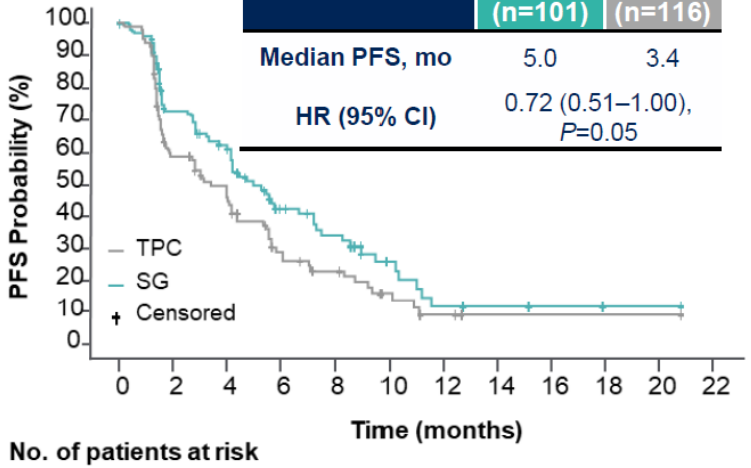


No. of patients at risk

TPC	134	65	43	16	8	4	1	0	0	0	0	0
SG	149	99	77	50	38	22	16	8	7	5	5	2

HER2 IHC0

	SG (n=101)	TPC (n=116)
Median PFS, mo	5.0	3.4
HR (95% CI)	0.72 (0.51–1.00), *P*=0.05	

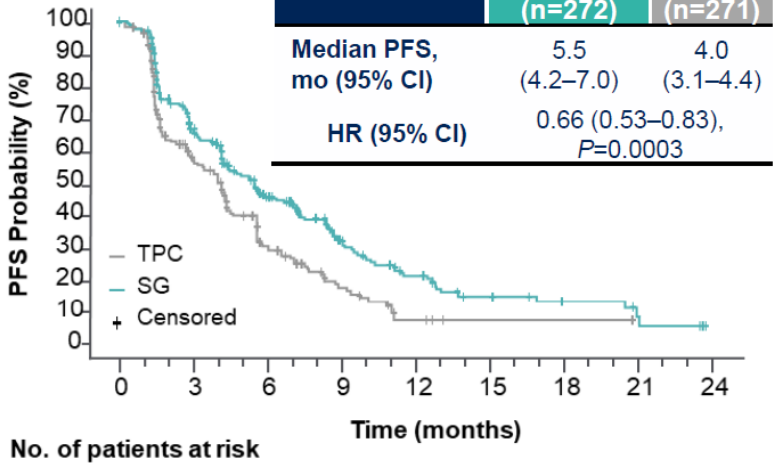


No. of patients at risk

TPC	116	53	39	20	14	7	3	1	1	1	1	0
SG	101	64	50	27	20	9	4	3	2	1	1	0

ITT[1]

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



No. of patients at risk

TPC	271	105	41	17	4	1	1	0
SG	272	148	82	44	22	12	6	3	0

- Within the HER2-Low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- The hazard ratio for median PFS in a sensitivity analysis of the HER2-Low subgroup (excluding ISH-unverified[b]) was similar (HR, 0.53)

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.
[b]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-low, consistent with the trial eligibility criteria to enroll HER2-negative patients.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology.

TROPiCS-02 trial: efficacy by HER2 immunohistochemistry status

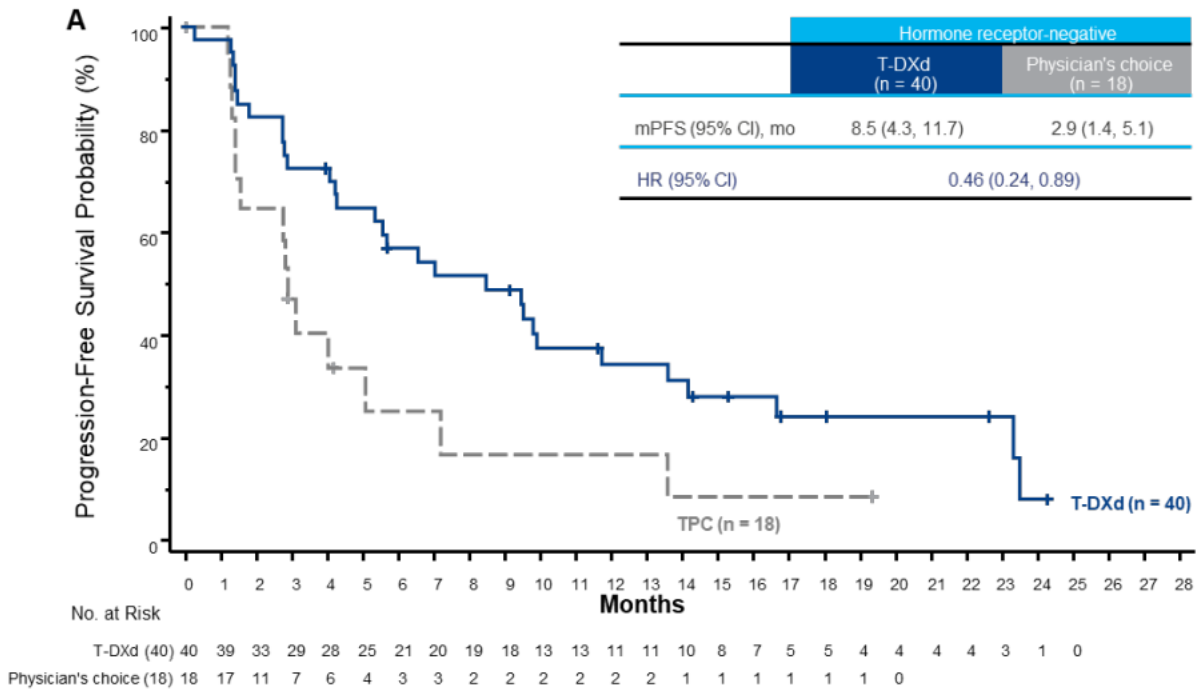
Conclusions

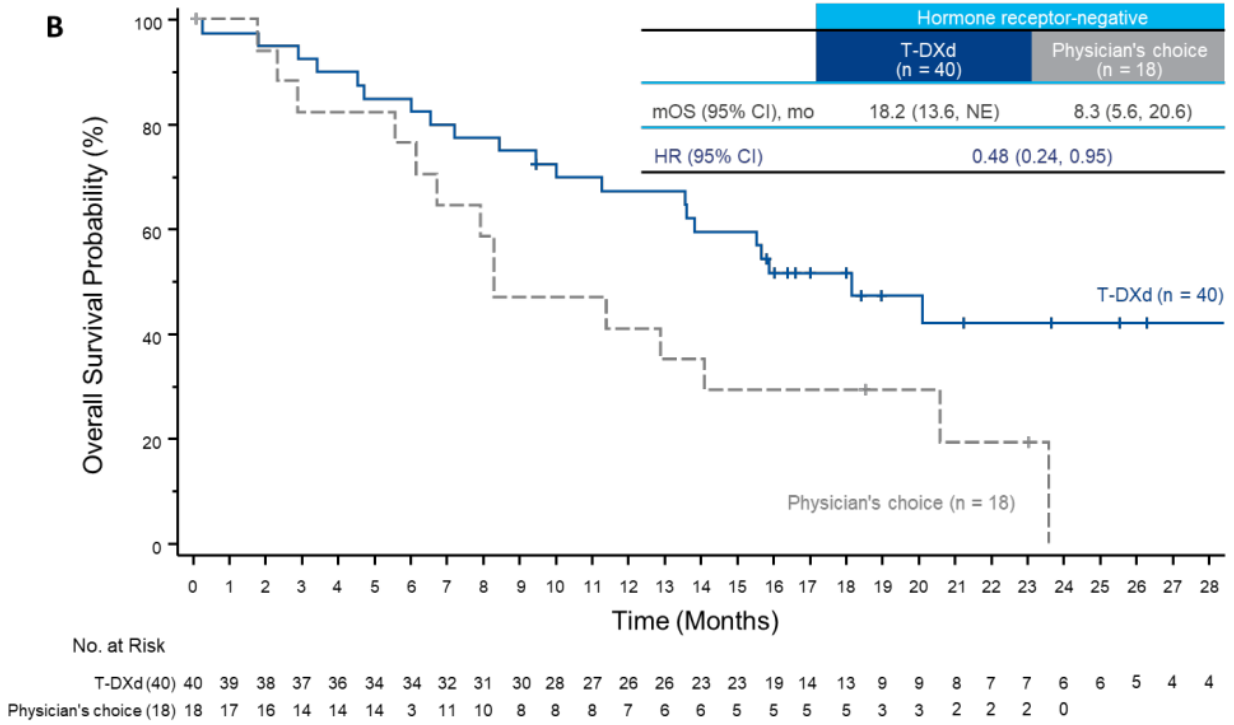
- SG improved efficacy outcomes vs TPC in HER2-Low and HER2 IHC0 HR+/HER2– mBC, consistent with that of the TROPiCS-02 ITT population:
  - Median PFS was 6.4 vs 4.2 mo (HR, 0.58) in the HER2-Low group, and 5.0 vs 3.4 mo (HR, 0.72) in the HER2 IHC0 group
  - ORR was 26% vs 12% in the HER2-Low group, and 16% vs 15% in the HER2 IHC0 group
- The safety profile of SG in the HER2-Low and HER2 IHC0 groups was manageable and consistent with that of the overall TROPiCS-02 safety population and with previous studies[1-3]
- SG should be considered an effective treatment option for patients with HR+/HER2– mBC, regardless of HER2 IHC status

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; mBC, metastatic breast cancer; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). 2. Kalinsky K, et al. *Ann Oncol*. 2020;31(12):1709-1718. 3. Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

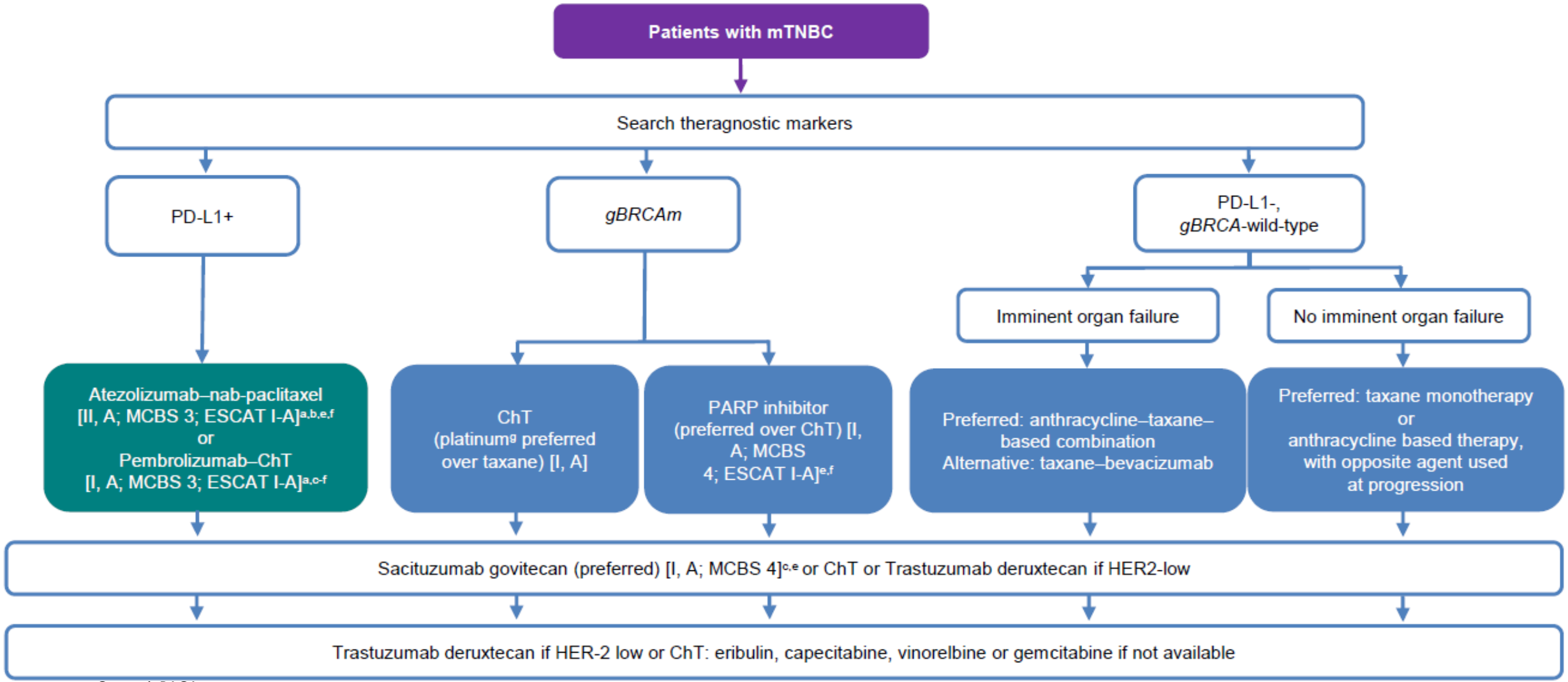
TRASTUZUMAB-DXD VS TPC IN HER2 LOW MBC: EXPLORATORY RESULTS OF DESTINY-BREAST04 IN HR-





Modi S et al., N Engl J Med 2022.

Triple-negative breast cancer: treatment algorithm



- Gennari, PAGA .