Trastuzumab Deruxtecan nel carcinoma mammario metastatico HER2-low

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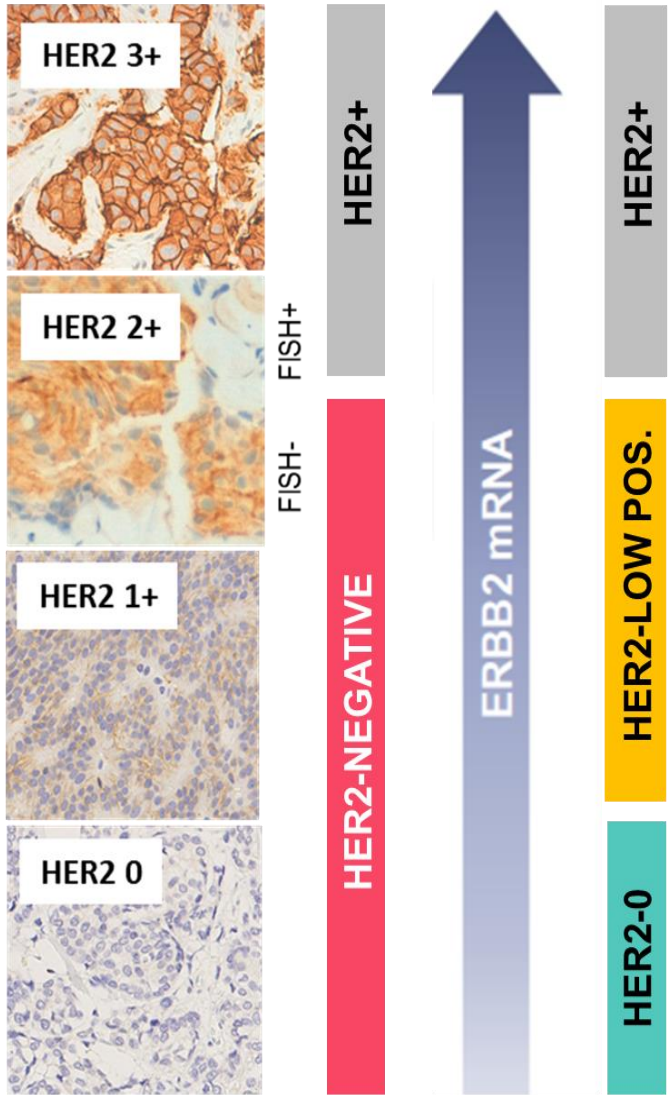
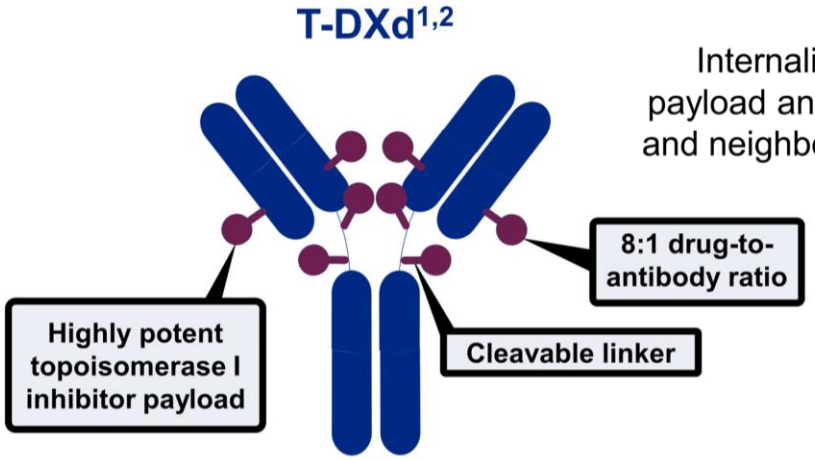
Conflict of interest

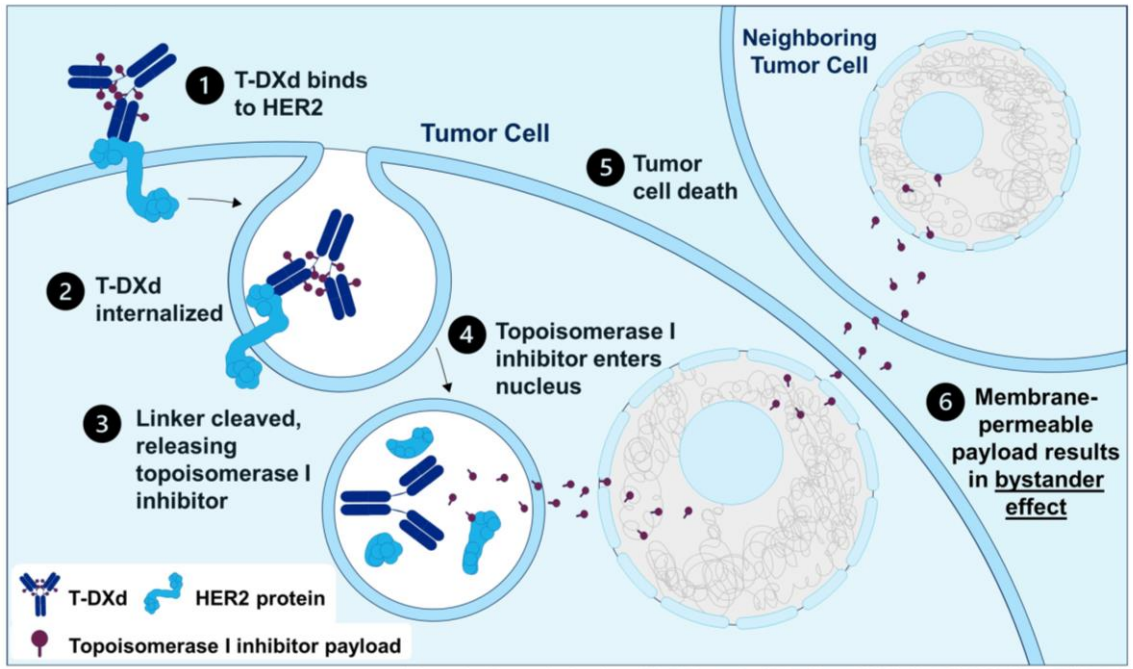
- PF Roche
- PF Gilead
- PF Novartis
- PF Pfizer
- PF Menarini
- PF Astrazeneca
- PF MSD
- PF Lilly

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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Courtesy of *Dr M. Lo Mele, MD*, Pathology Unit Padova Hospital, Italy

Destiny-Breast04 trial

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−

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

Hierarchical testing

PFS in HR+ → PFS in all patients → OS in HR+ → OS in all patients

Primary endpoint

Secondary endpoints

Modi S et al., ASCO 2022, NEJM 2022

Destiny-Breast04 trial: population

Baseline features

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
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)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes misstratified patients.

Modi S et al., ASCO 2022, NEJM 2022

Destiny-Breast04 trial: population

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 trial: results

Hierarchical testing

PFS in HR+ ✓

↓

PFS in all patients

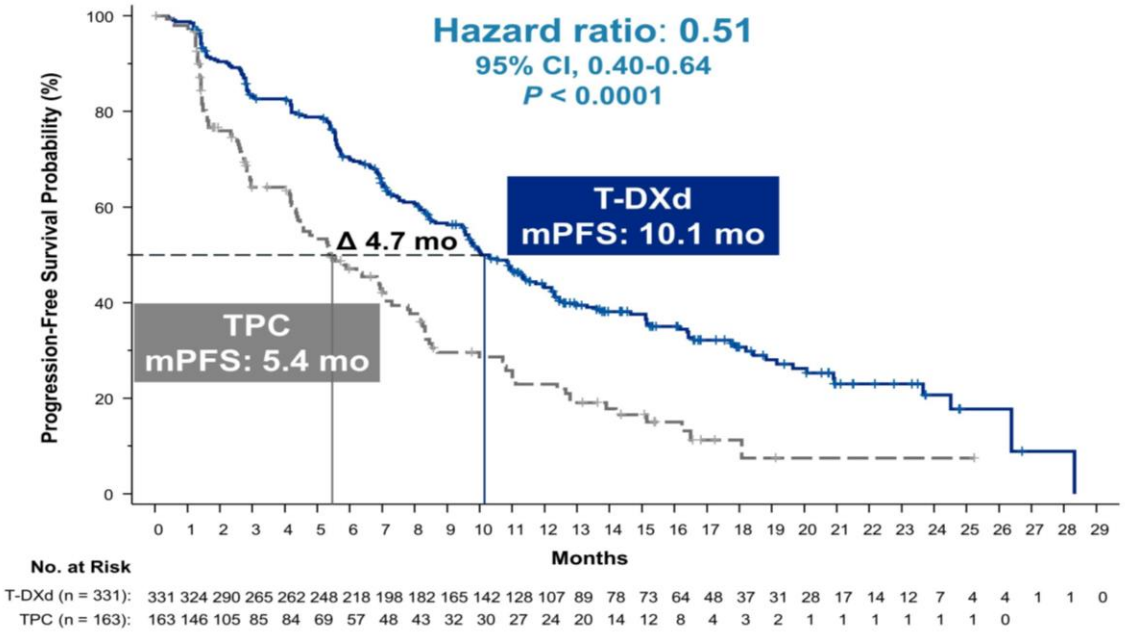
↓

OS in HR+

↓

OS in all patients

Hormone receptor–positive



Primary endpoint met

Updated PFS analysis (32-mos follow up)
median PFS was consistent with results from the primary analysis

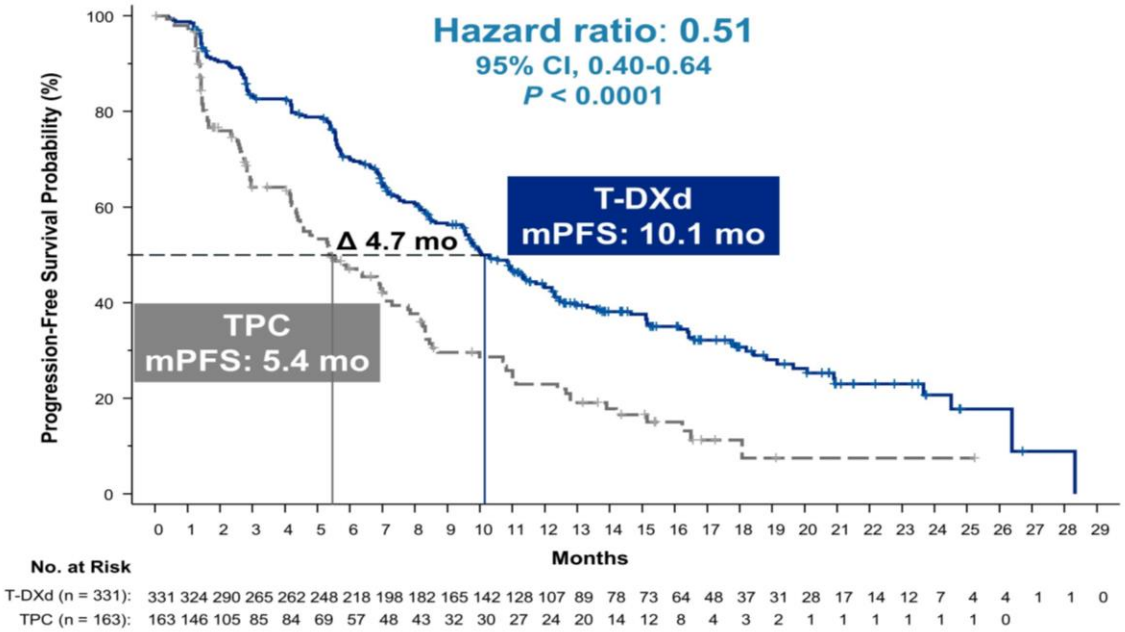
Modi S et al., ASCO 2022, NEJM 2022, ESMO 2023

Destiny-Breast04 trial: results

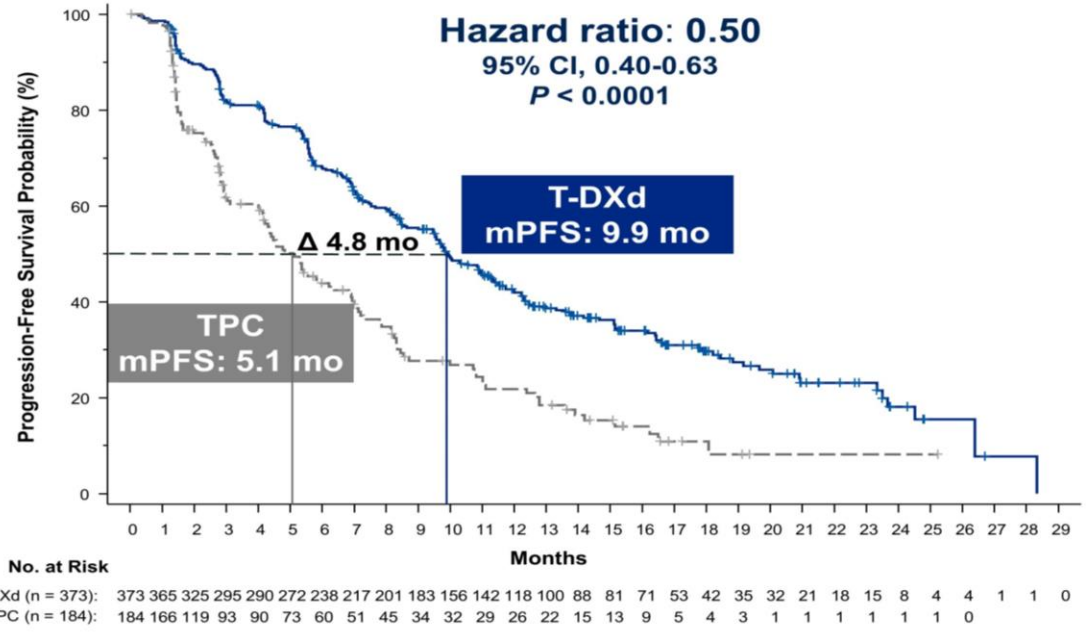
Hierarchical testing

- 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

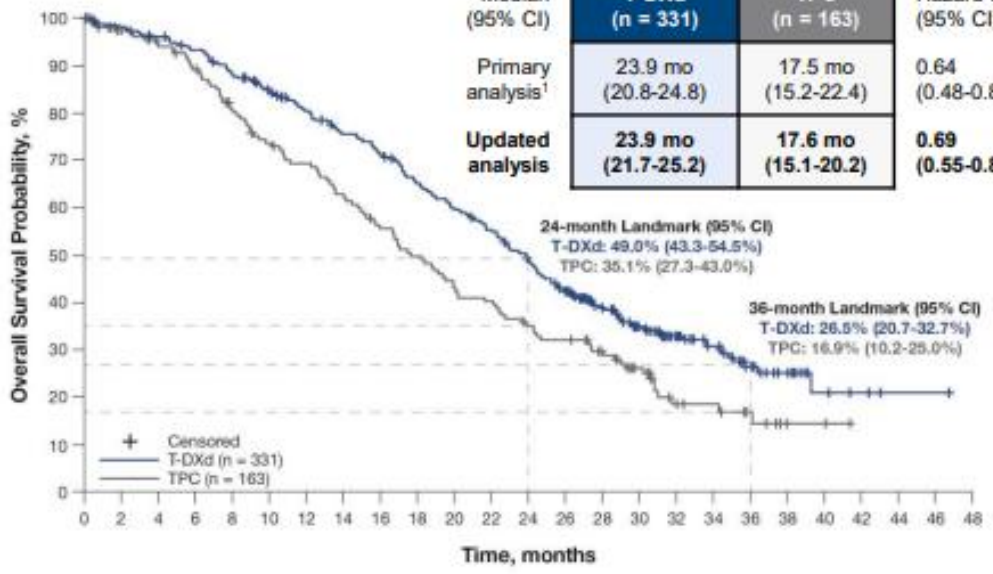
Destiny-Breast04 trial: results

Hierarchical testing

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

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)**



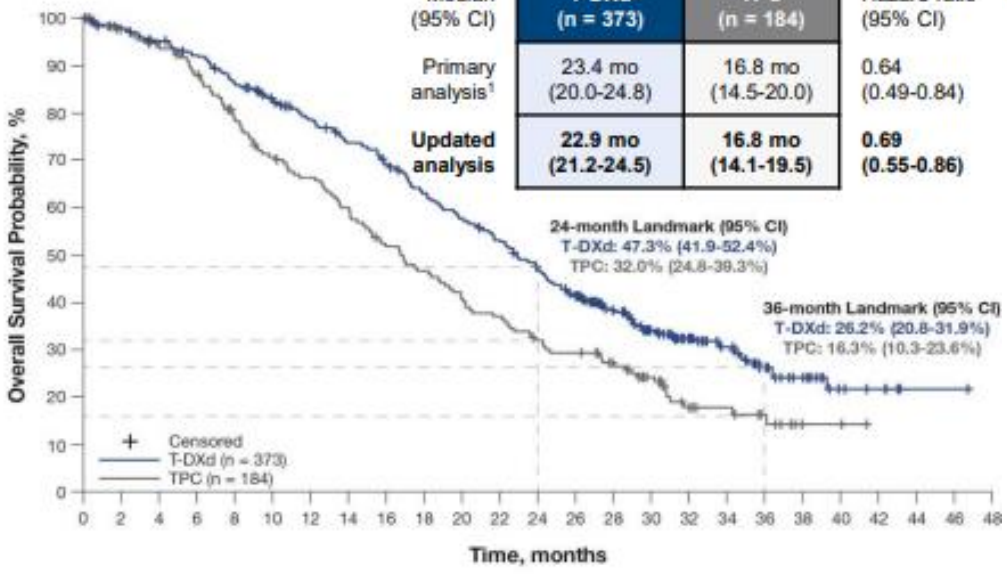
Patients still at risk:

T-DXd (n = 331)

TPC (n = 163)

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)

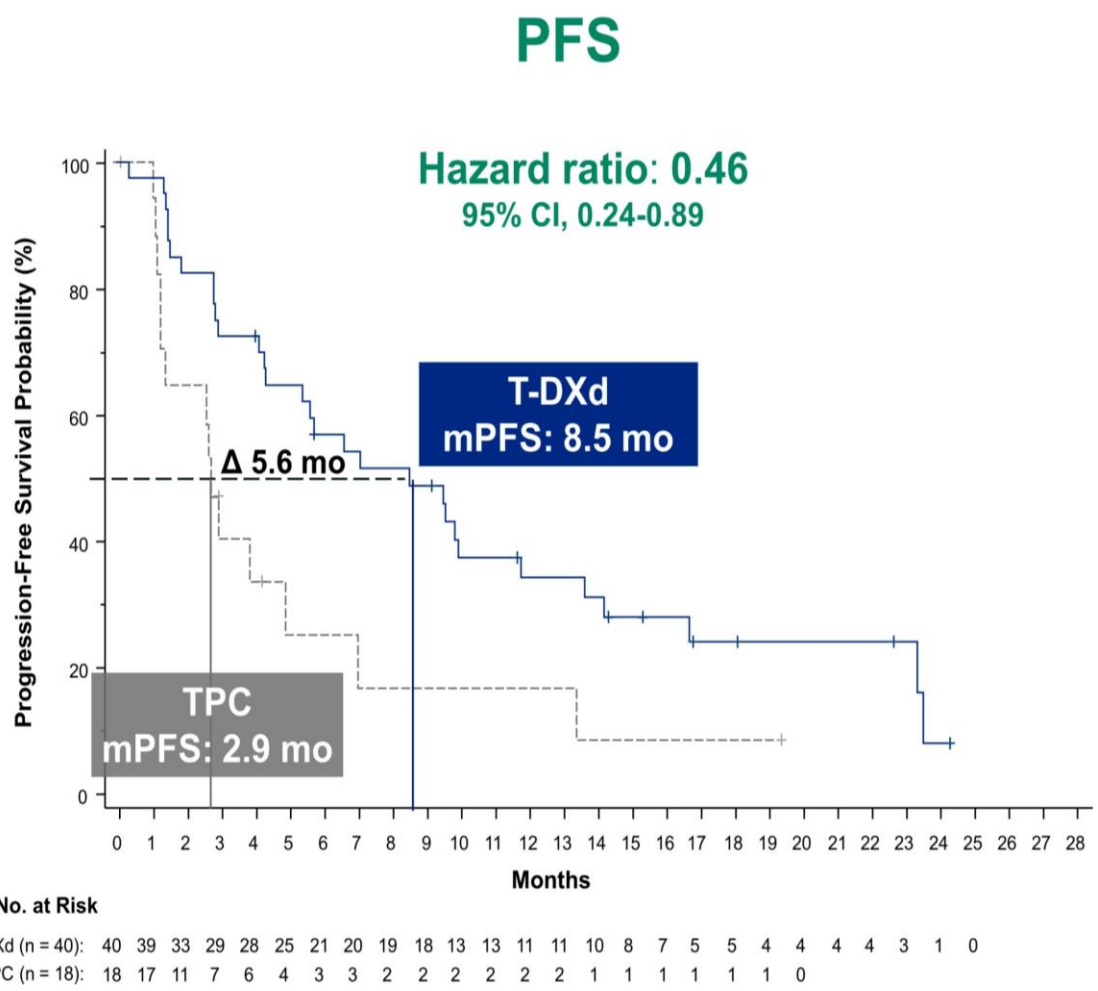
TPC (n = 184)

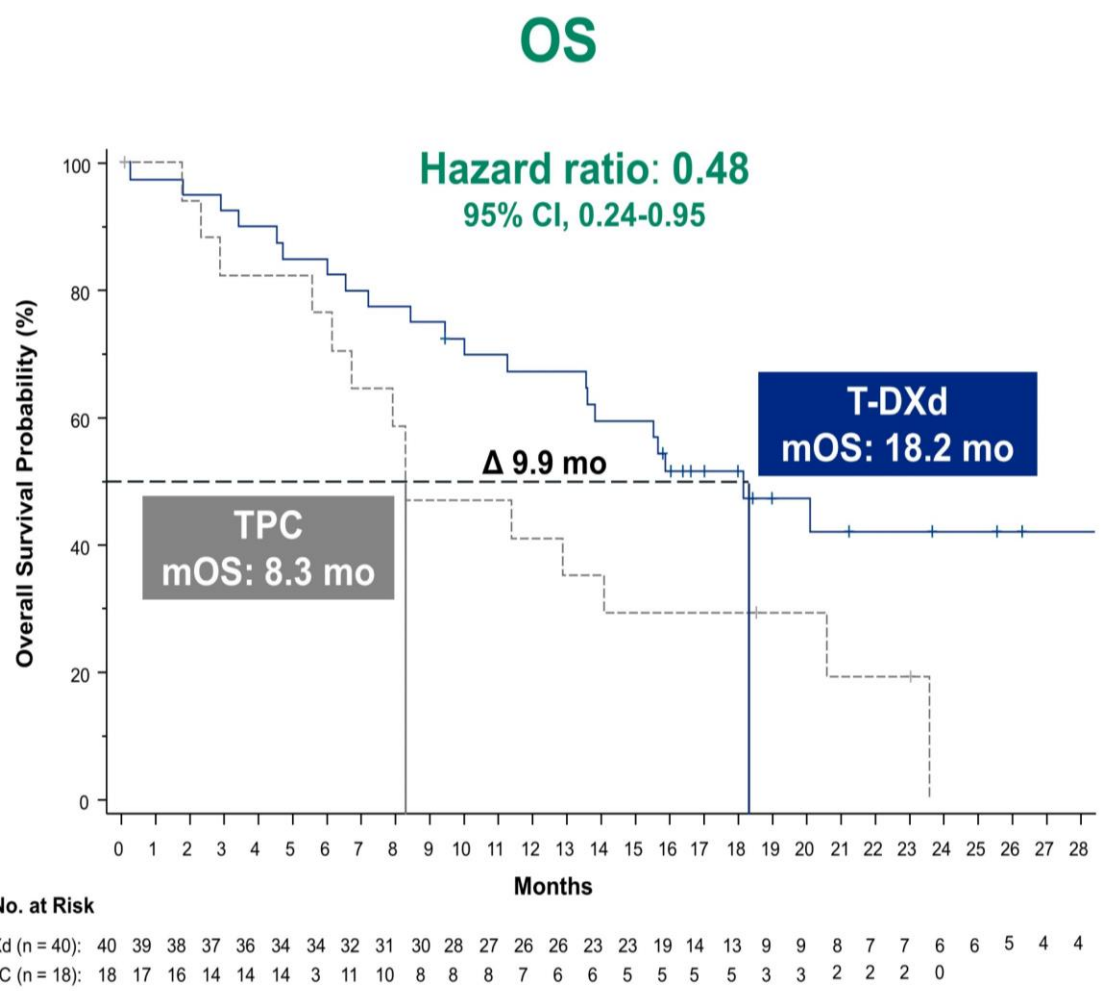
- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

Efficacy boundary for superiority: $P < 0.0075$

Modi S et al., ASCO 2022, NEJM 2022

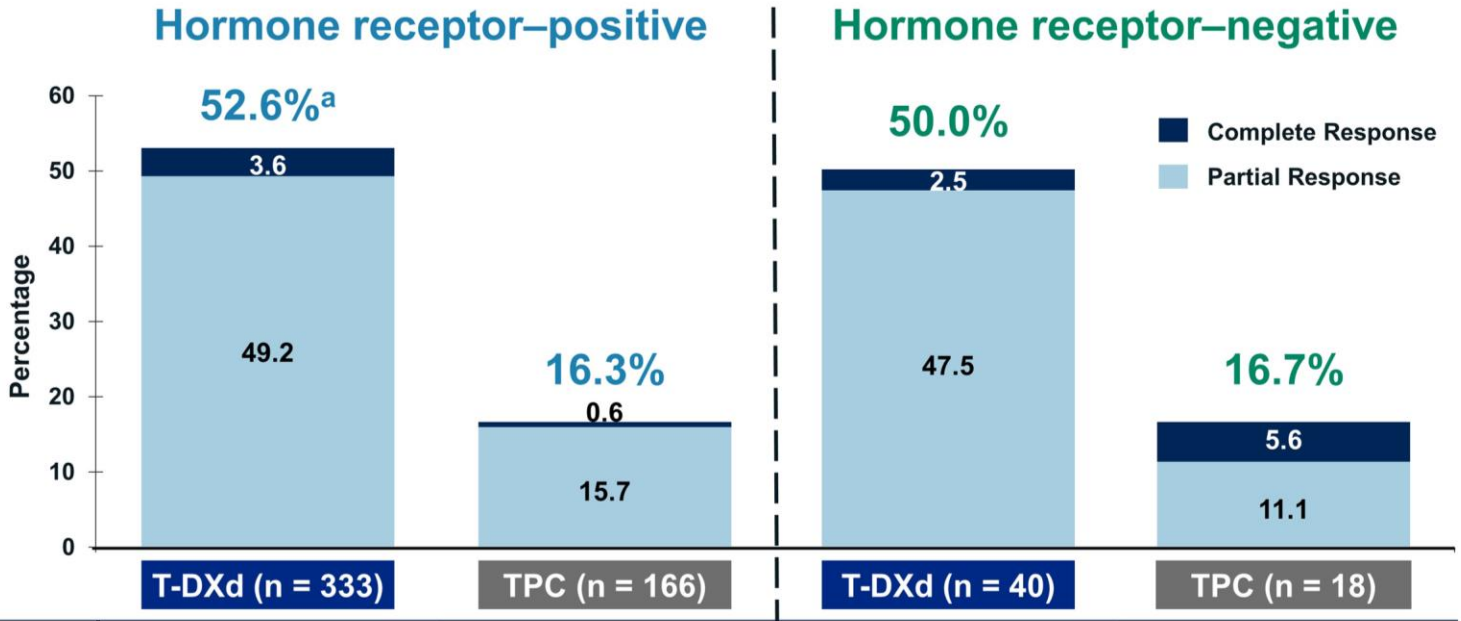
Destiny-Breast04 trial: results





Modi S et al., ASCO 2022, NEJM 2022

Destiny-Breast04 trial: ORR

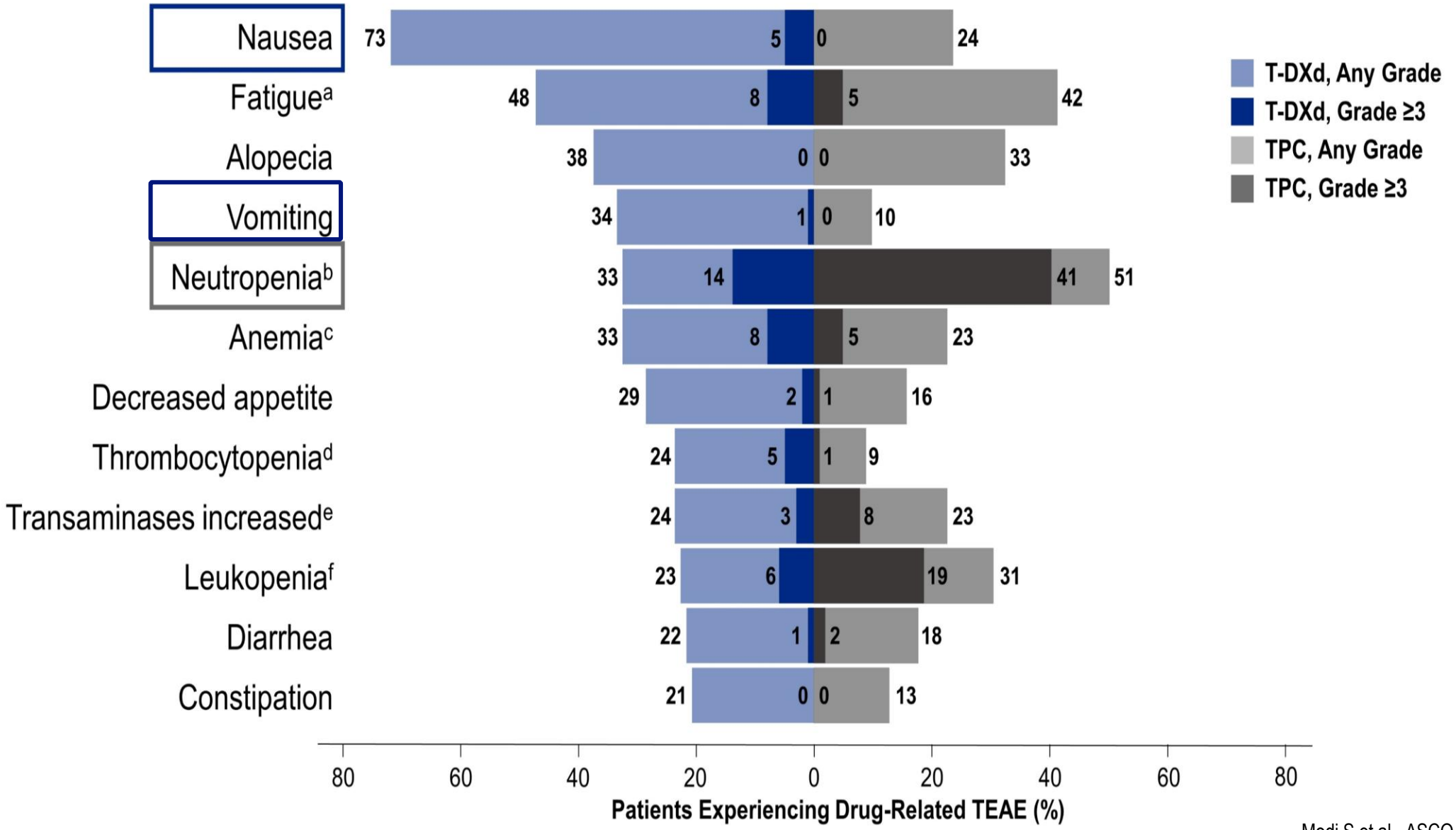


	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

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 trial: safety



Modi S et al., ASCO 2022, NEJM 2022

Destiny-Breast04 trial: safety

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%

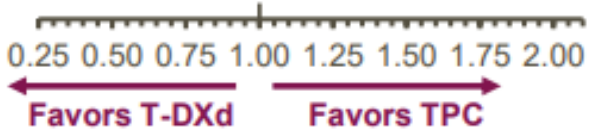
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]Patient-years of exposure are the treatment duration with year as unit. [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 trial: QoL

TIME TO DEFINITIVE DETERIORATION IN PRO MEASURES OF INTEREST WAS OVERALL PROLONGED IN PATIENTS RECEIVING T-DXd vs TPC

		Median (95% CI) TDD, months		Hazard Ratio (95% CI)	*P* Value[d]
		T-DXd (n = 331)	TPC (n = 163)		
EORTC QLQ-C30	Global health status/QoL[a]	11.4 (8.8-16.3)	7.5 (5.9-9.5)	0.69 (0.52-0.92)	0.0096
	Pain symptoms	16.4 (13.1-21.5)	6.1 (4.2-7.5)	0.40 (0.30-0.54)	<0.0001
	Physical functioning[b]	16.6 (11.3-21.5)	7.5 (4.9-9.5)	0.53 (0.40-0.70)	<0.0001
	Emotional functioning[b]	19.2 (16.3-24.5)	10.5 (7.1-NE)	0.69 (0.50-0.96)	0.0266
	Social functioning[b]	12.8 (10.4-15.2)	6.0 (4.4-7.7)	0.59 (0.45-0.77)	0.0001
	Fatigue[c]	11.1 (7.2-12.4)	4.5 (3.1-6.2)	0.61 (0.47-0.79)	0.0002
	Nausea and vomiting[c]	5.7 (3.8-8.4)	9.3 (7.5-17.1)	1.46 (1.09-1.96)	0.0128
EORTC QLQ-BR23	Arm symptoms[b]	14.4 (11.9-23.0)	8.7 (5.6-NE)	0.62 (0.45-0.85)	0.0027
	Breast symptoms[b]	NE (24.7-NE)	NE (NE-NE)	0.71 (0.50-1.01)	0.1008
EQ-5D-5L	VAS[b,c]	12.0 (9.9-15.2)	6.8 (4.9-11.4)	0.73 (0.54-0.97)	0.0288

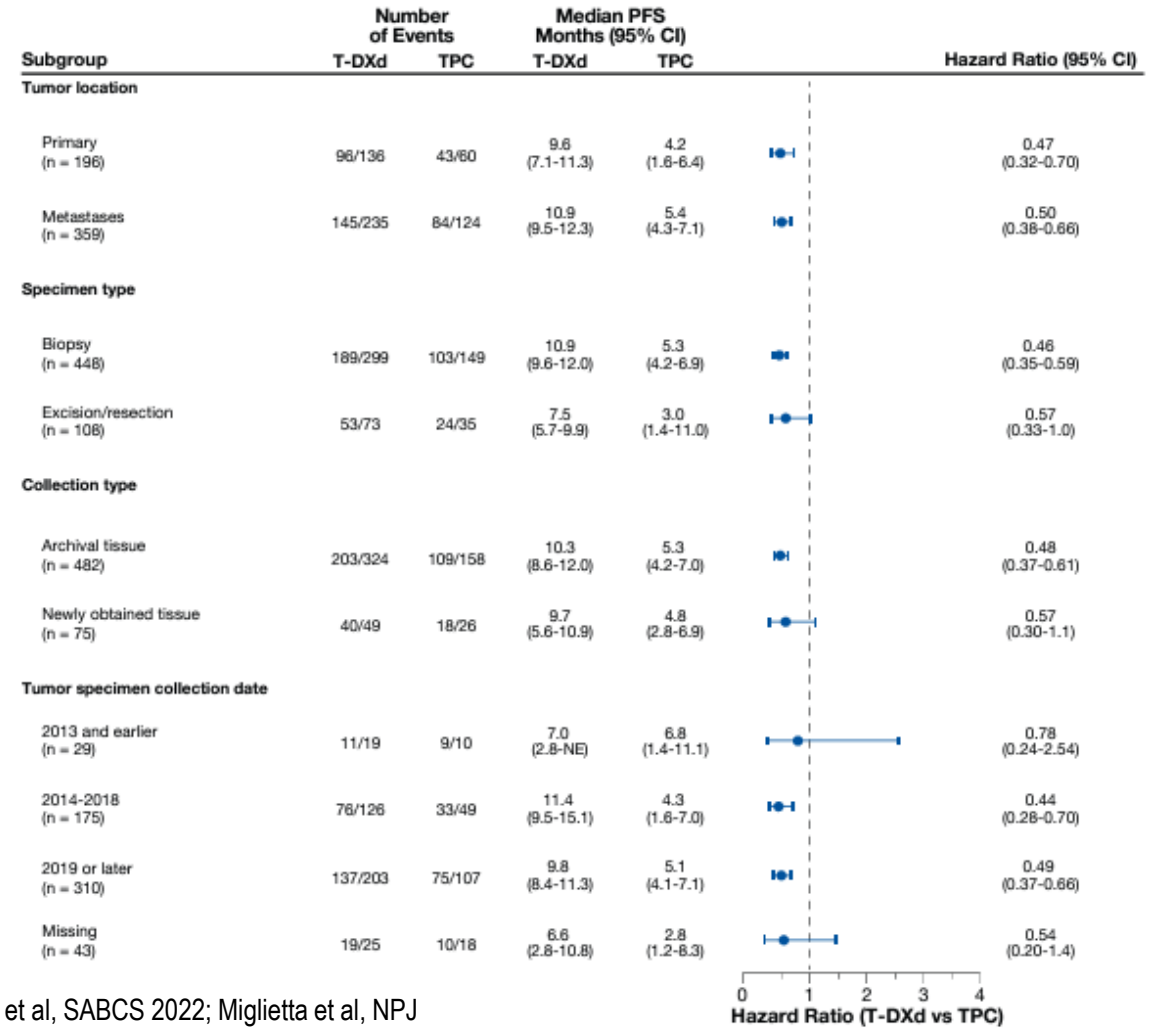


- **Similar TDD results were observed among the all-patient cohort in PRO measures of interest**

Ueno et al, ESMO 2022

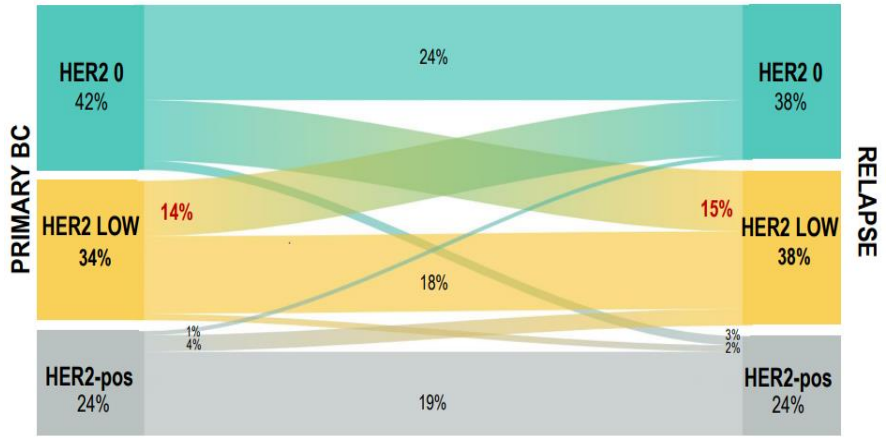
Patient selection

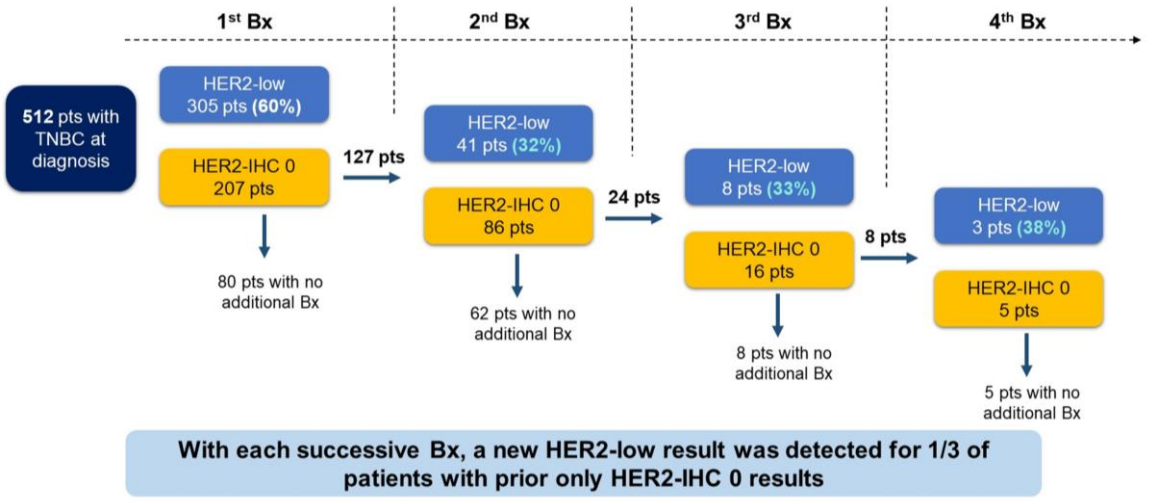
Within the DB04 trial, patients' inclusion was based on the **most recent available tumor tissue** to centrally determine HER2-low status. Efficacy of T-DXd was consistent regardless of tumor sample characteristics.



Prat et al, SABCS 2022; Miglietta et al, NPJ BC 2021; Bar et al, ASCO 2023

HER2-low expression is highly unstable during disease evolution, possibly due to temporal heterogeneity, spatial heterogeneity, (pre-) analytical factors, and/or other factors.



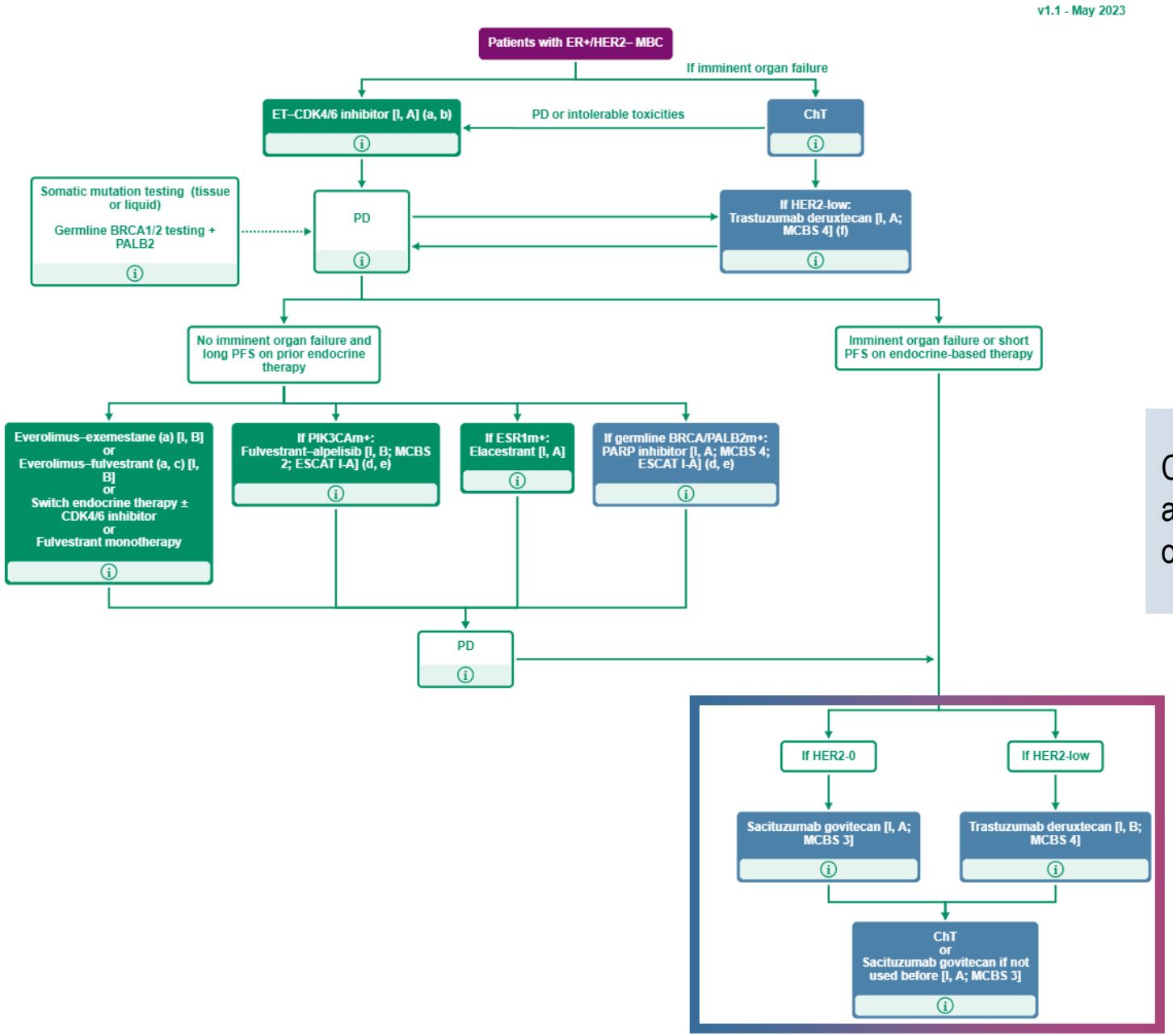


Patient selection

Treatment with T-DXd can be based on HER2-low status from the primary or the metastatic tumor tissue, at any timepoint of disease course

In case of HER2-0-only status throughout the disease history, a repeated biopsy is suggested to re-evaluate the HER2 status

Contextualization: HR+/HER2- MBC



Consider CT-based options after exhaustion of ET-based tx or expected benefit from ET.

ESMO living guidelines

Competing scenario: TROPIC02 trial

Rugo et al, JCO 2022;
Rugo et al, Lancet Oncol 2023;
Rugo et al, ESMO 2022

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

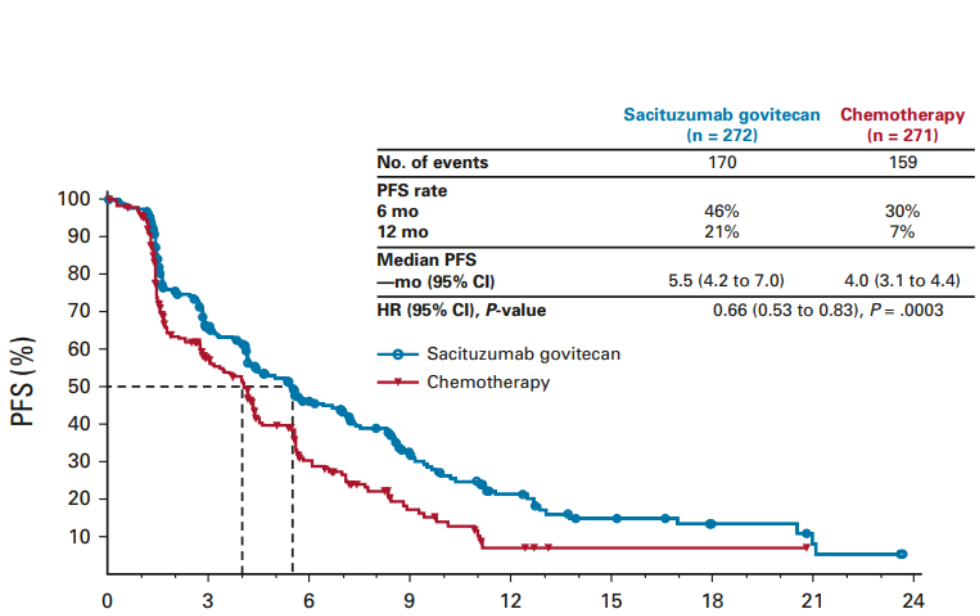
Endpoints

Primary
- PFS by BICR

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

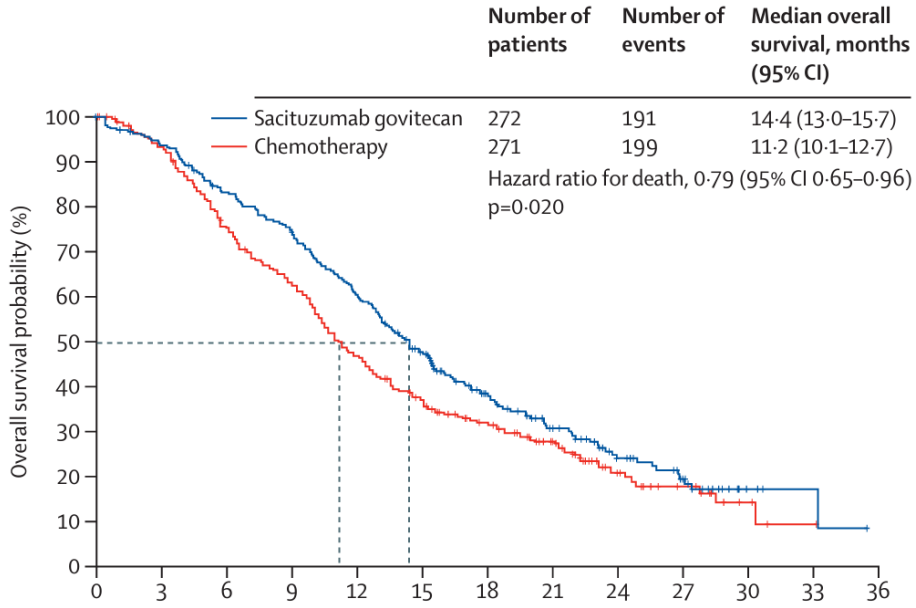
Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

SG arm:
- Median **prior tx lines**: 3 (2, 38%; ≥3, 58%)
- **Prior CDK 4/6i use**: ≤12 mos 58%



	Sacituzumab govitecan (n = 272)	Chemotherapy (n = 271)
No. of events	170	159
PFS rate		
6 mo	46%	30%
12 mo	21%	7%
Median PFS —mo (95% CI)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)
HR (95% CI), *P*-value	0.66 (0.53 to 0.83), *P* = .0003	

Sacituzumab govitecan
Chemotherapy



	Number of patients	Number of events	Median overall survival, months (95% CI)
Sacituzumab govitecan	272	191	14·4 (13·0–15·7)
Chemotherapy	271	199	11·2 (10·1–12·7)

Hazard ratio for death, 0·79 (95% CI 0·65–0·96)
p=0·020

TROPIC02 trial: more heavily pre-treated population compared to DB04 trial.

SG efficacy confirmed regardless of HER2 IHC groups → confirmed also in HER2-low BC

Evolving scenario

D9670C00001 - A Phase 3, Randomized, Multicenter, Open-label, Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting (DESTINY-Breast06)

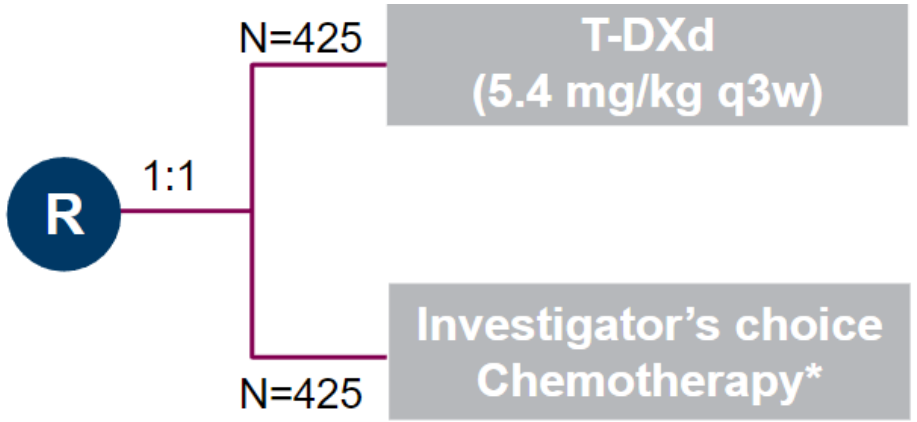
HER2 ULTRA-LOW

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

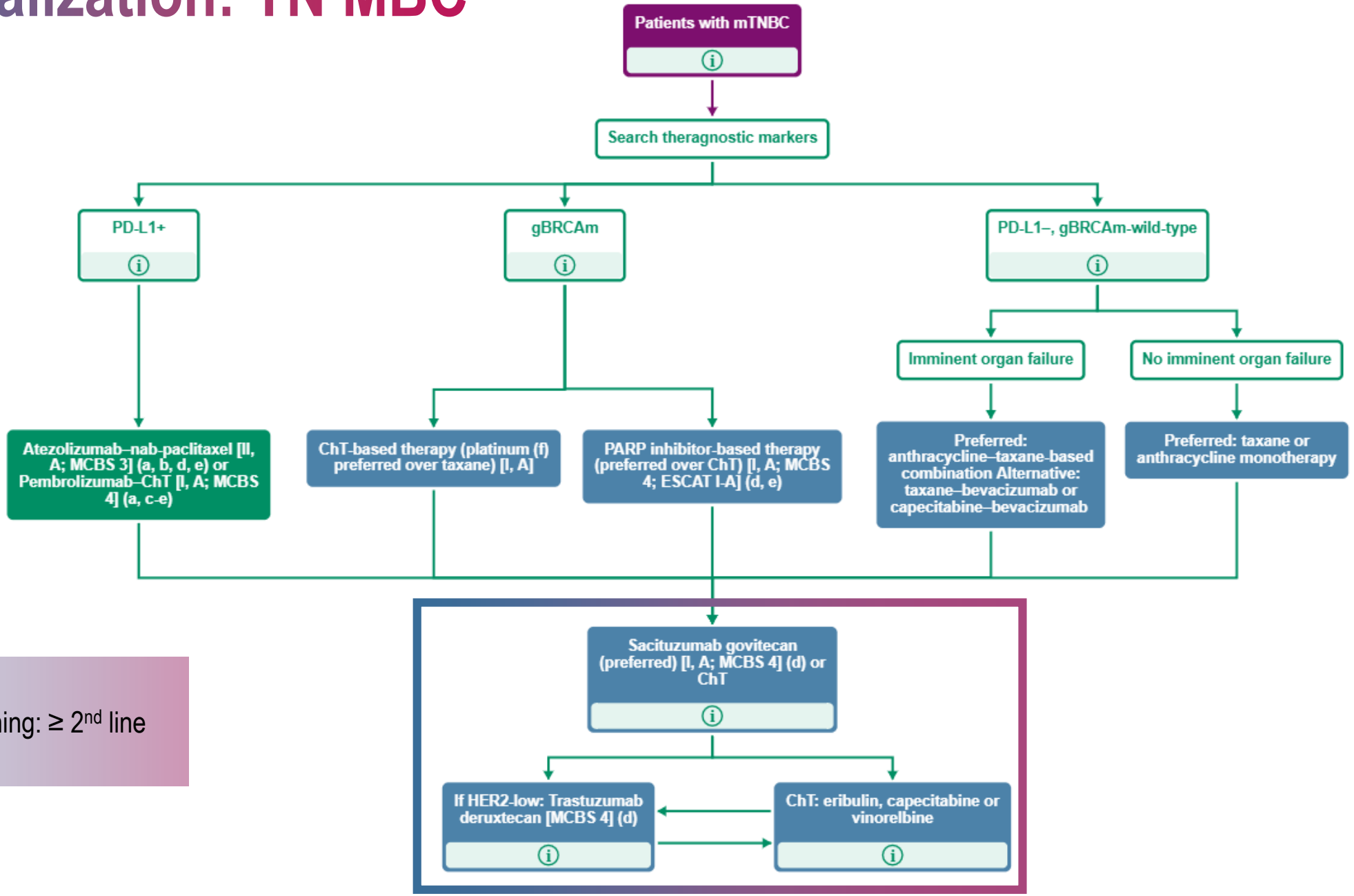


* Chemotherapy options: capecitabine, paclitaxel, nAb-paclitaxel

- 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

Contextualization: TN MBC

v1.1 - May 2023

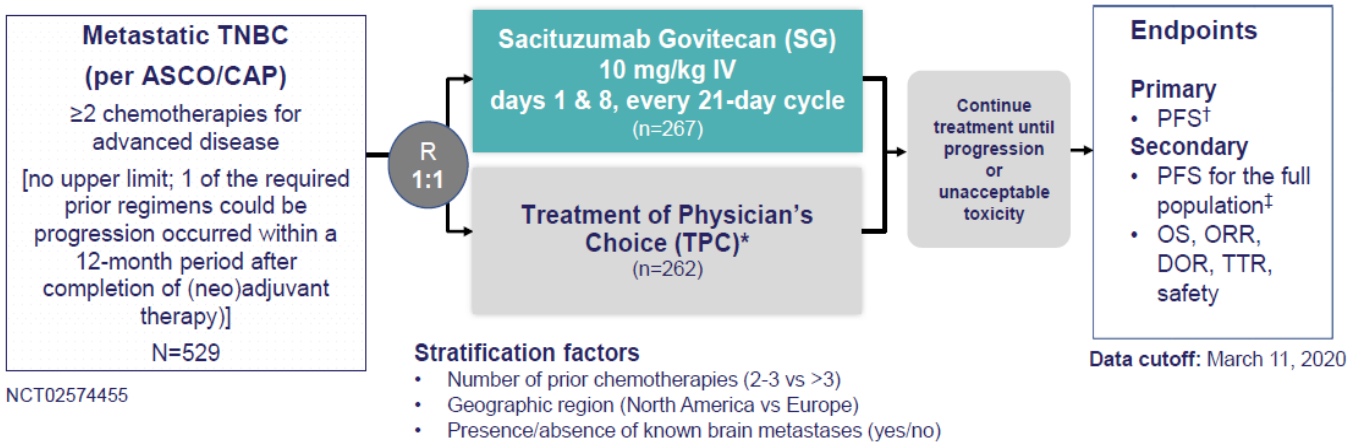


ADC positioning: ≥ 2nd line

ESMO living guidelines

Competing scenario: ASCENT trial

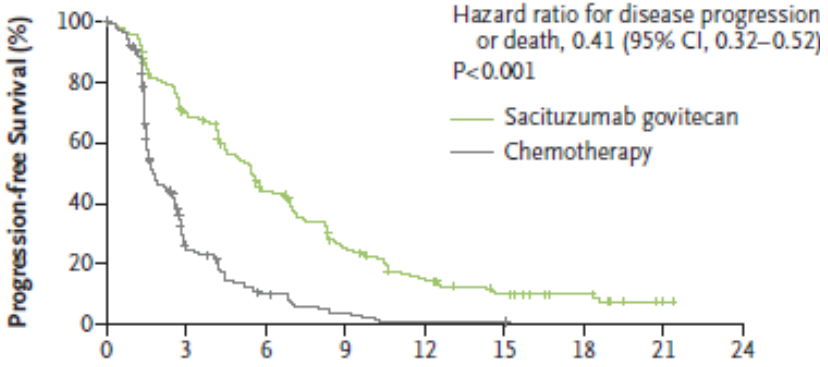
Bardia A et al, ESMO 2020, NEJM 2021; Hurvitz et al, SABCS 2020



- TNBC at initial diagnosis ≈70%
- Median anticancer regimens: 4 (2-17)
- 29-26% previously treated with PD-1/PD-L1 inhibitors
- 17-18% previously treated with PARP inhibitors

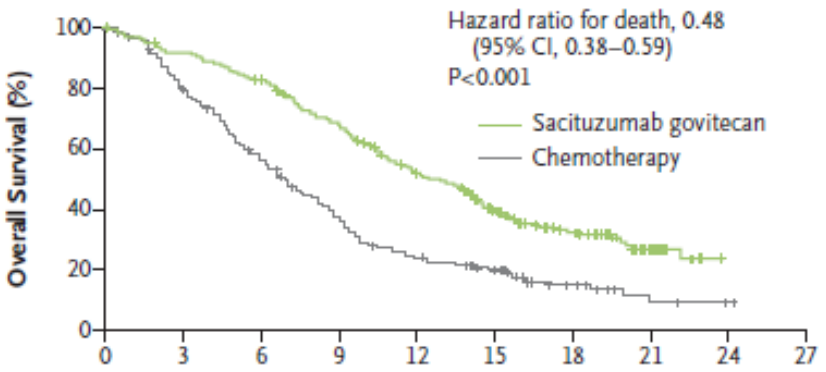
Without BMs

	No. of Patients	No. of Events	Median Progression-free Survival (mo (95% CI))
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)



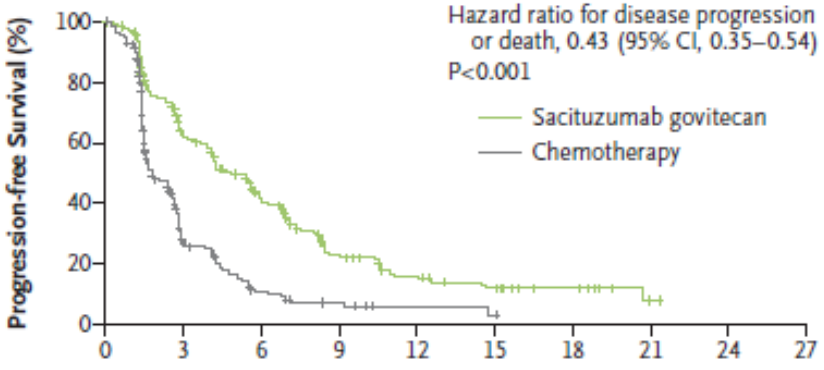
Without BMs

	No. of Patients	No. of Events	Median Overall Survival (mo (95% CI))
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)



Full population

	No. of Patients	No. of Events	Median Progression-free Survival (mo (95% CI))
Sacituzumab Govitecan	267	190	4.8 (4.1–5.8)
Chemotherapy	262	171	1.7 (1.5–2.5)



Remarks

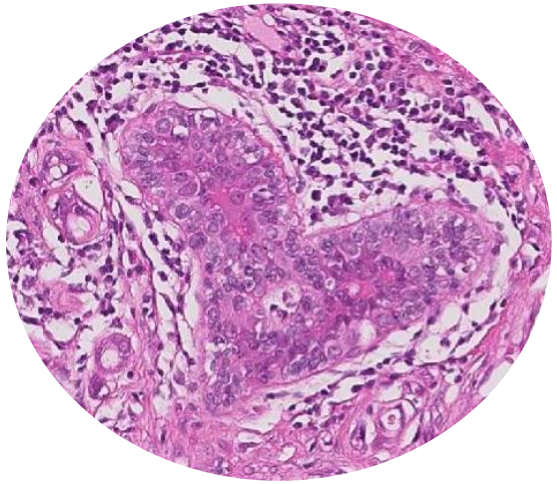
- **HER2-low MBC represents an operational entity** → guidance for determining access to T-DXd

- **T-DXd** currently represents a viable option **for HER2-low MBC pre-treated with 1-2 CT lines**
  - HR+/HER2-: after exhaustion of ET-based lines/expected benefit
  - TNBC: after exhaustion of targeted options (ICI and PARP-i)

- **T-DXd positioning partially overlap with SG both in HR+ and TNBC**:
  - HR+/HER2-: T-DXd to be prioritized over SG
  - TNBC: SG to be prioritized over T-DXd
  - *Solid data regarding safety and activity of SG after T-DXd and viceversa are lacking, however there is no biological rationale to suggest that one, administered after the other would be either inefficient or unsafe*
  - *Need for more data to rationalize ADC sequencing at a single patient level*

Grazie

Federica Miglietta



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