New Directions in Chemotherapy and Immunotherapy in HR+ Breast Cancer

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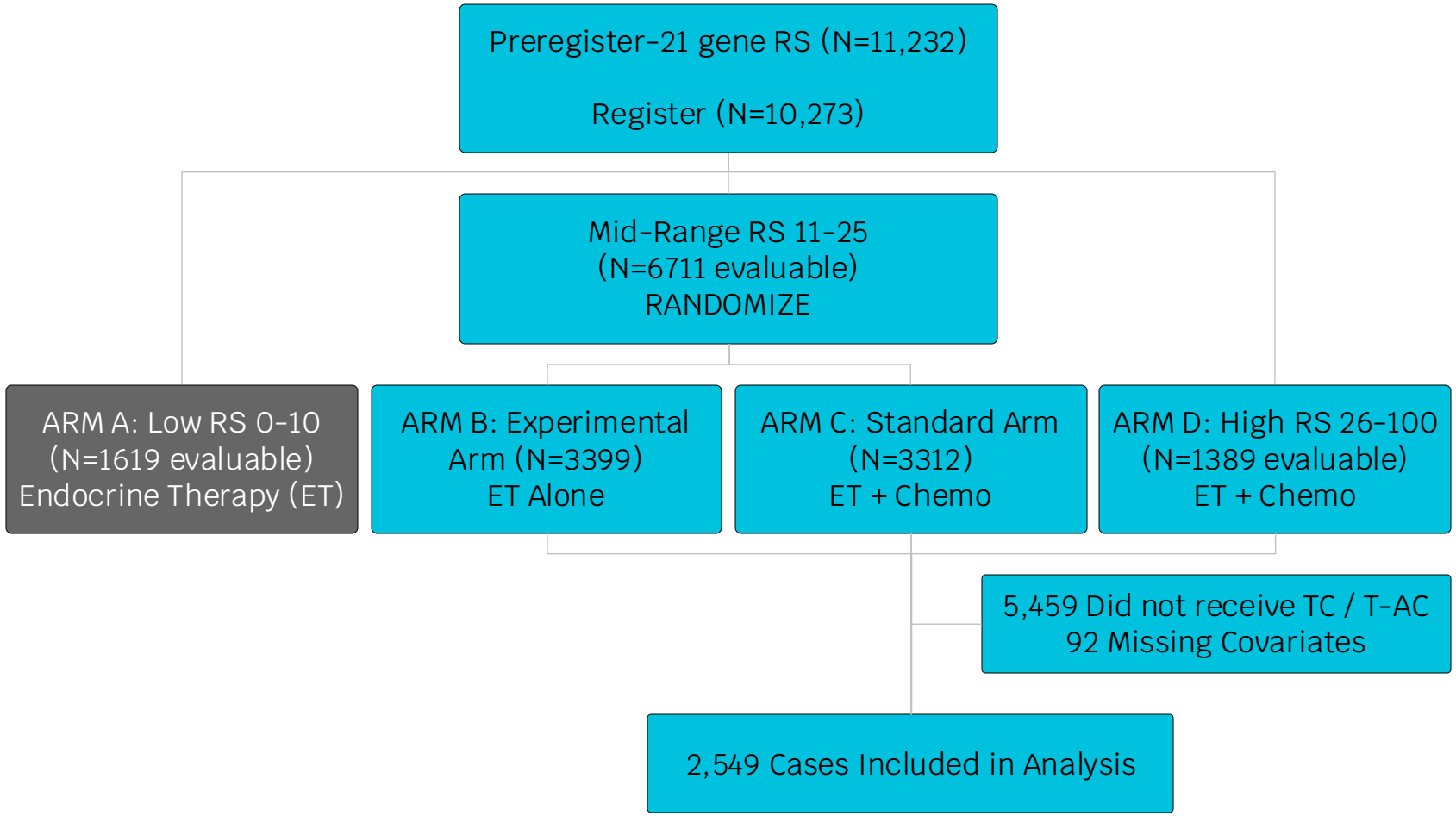
What We'll Cover Today

- Early HR+ HER2- Breast Cancer
  - Who needs chemotherapy
  - Who needs an anthracycline
  - Who benefits from preoperative immunotherapy
- Metastatic HR+ HER2- Breast Cancer
  - Update on approved ADCs
  - What's coming?

TAILORx: Study Design

Impact of Anthracyclines in High Genomic Risk Node-Negative HR+/HER2- Breast Cancer



Limitations

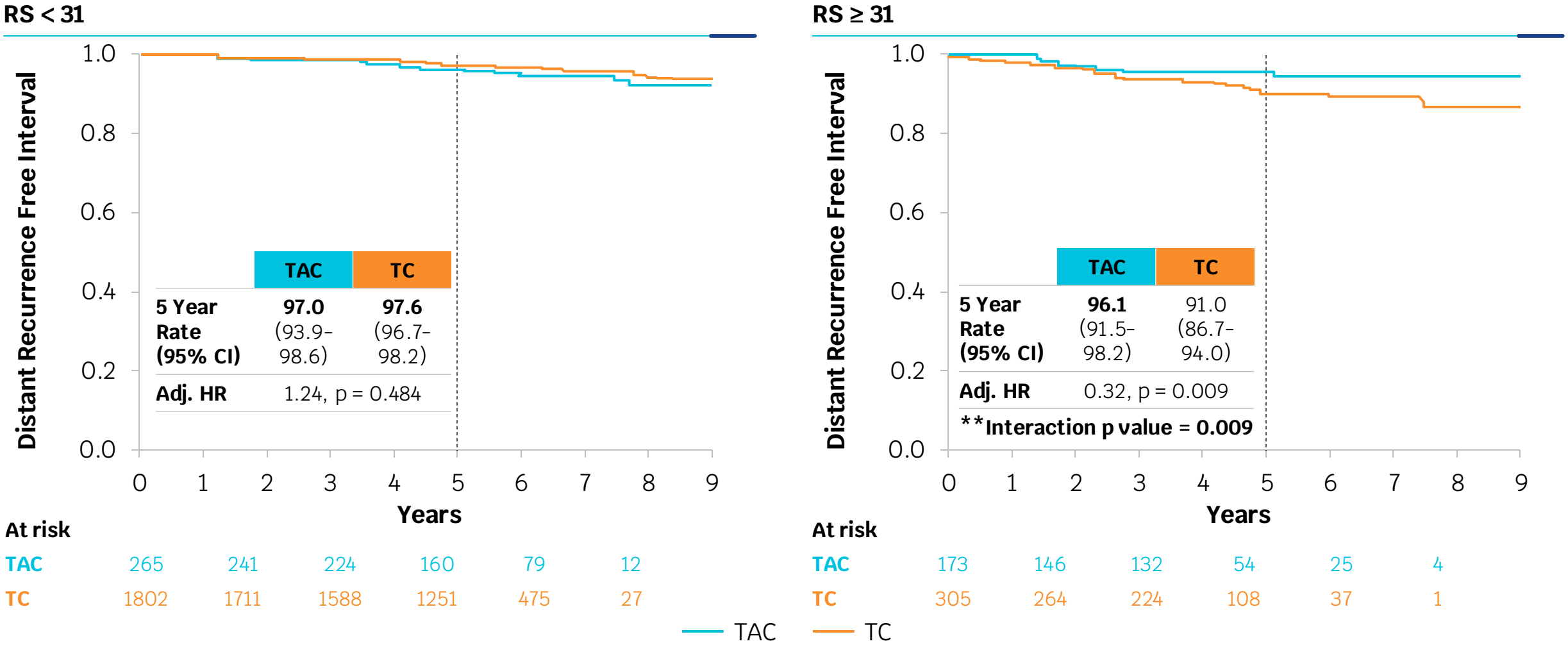
- Post-hoc analysis not designed to evaluate endpoint
- Chemotherapy choice not randomized
- Late effects of anthracycline usage

Despite the bias of higher risk patients receiving anthracyclines, this analysis still noted a benefit in high genomic risk patients.

**Analysis from study database as of March 2, 2018 Reference: Sparano et al. NEJM 2018

Chen, N et al SABCS 2024

TAILORx: Primary Survival Outcome: Distant Recurrence-Free Interval at 5 years



*Adjusted hazard ratios controlling for age, ER/PR status, RS, tumor size, treatment received, and interaction of treatment with RS

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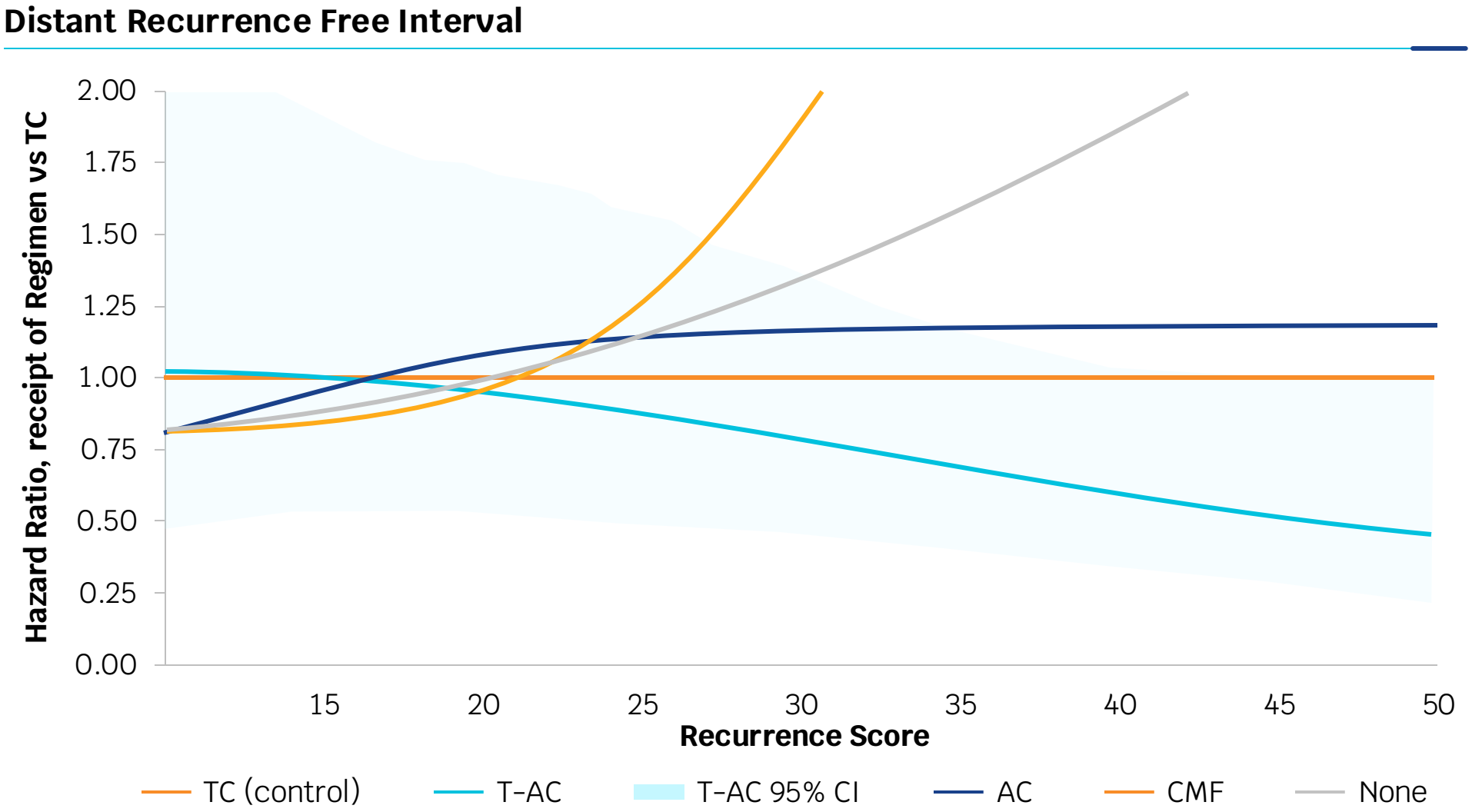
TAILORx: Alternative Chemotherapy Regimens Have Decreased Benefit with Increasing RS

RS	Adj HR, DRFI
15	1.00 (0.51-1.95)
20	0.96 (0.53-1.75)
25	0.89 (0.49-1.61)
30	0.79 (0.45-1.39)
35	0.69 (0.40-1.18)
40	0.60 (0.34-1.05)
45	0.52 (0.27-0.98)
50	0.45 (0.21-0.96)



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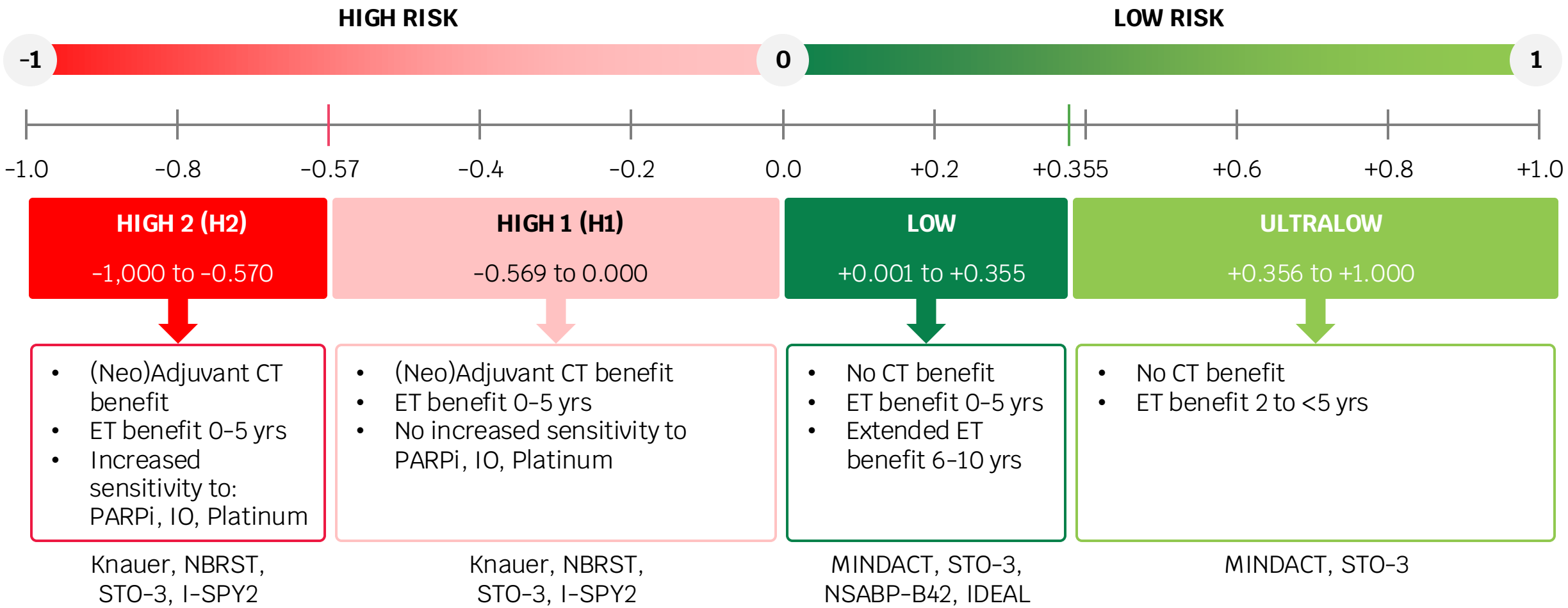
70-gene MammaPrint test: Implications for ET and CT Decisions

MammaPrint classifies patients with HR+HER2- EBC as having an Ultra Low, Low, High 1, or High 2 risk of distant recurrence



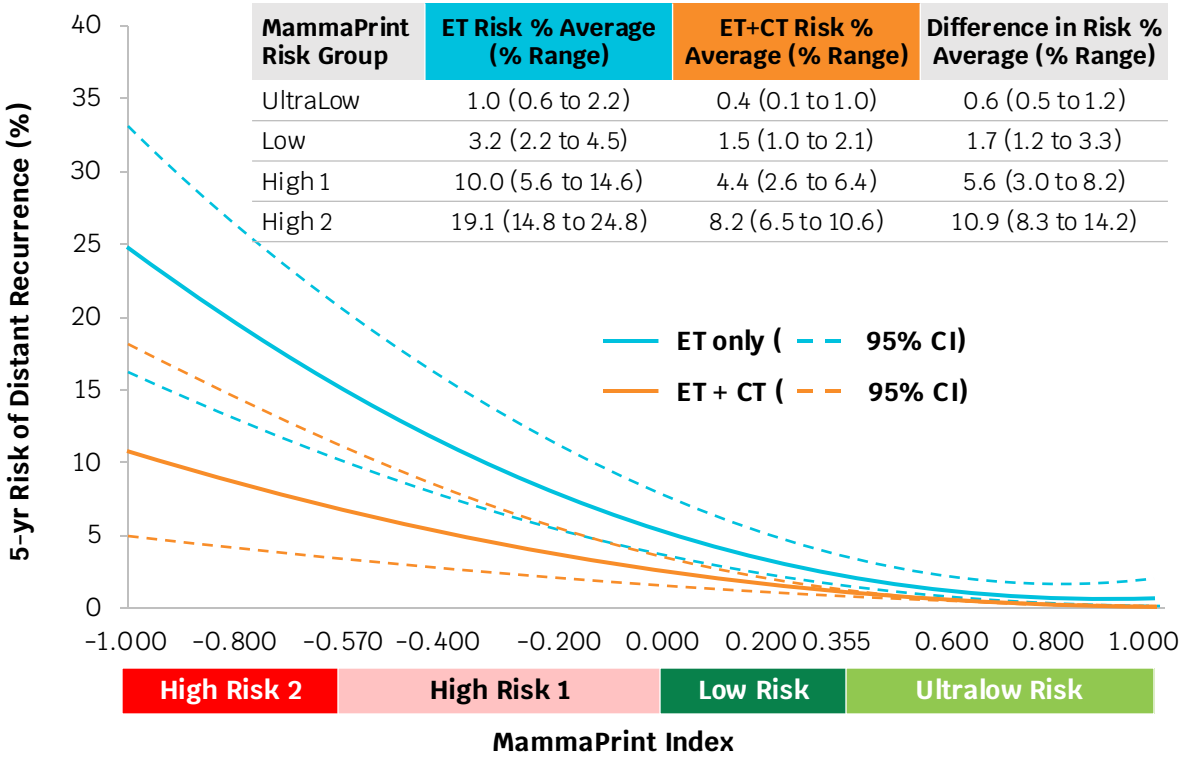
References: **Knauer** (Breast Cancer Res Treat 2010), **NBRST** (Whitworth, Ann Surg Oncol 2022), **STO-3** (van't Veer, Breast Cancer Res Treat, 2017; Esserman, JAMA Onc, 2017), **I-SPY2** (https://www.ispytrials.org/i-spy-platform/i-spy2; Pusztai, Cancer Cell 2021). **MINDACT** (Piccart, Lancet Oncol, 2021; Lopes Cardozo, JCO, 2022). **NSABP-B42** (Rastogi, ASCO, 2021). **IDEAL** (Liefers, SABCS, 2022)

O'Shaughnessy, J et al. ASCO 2024

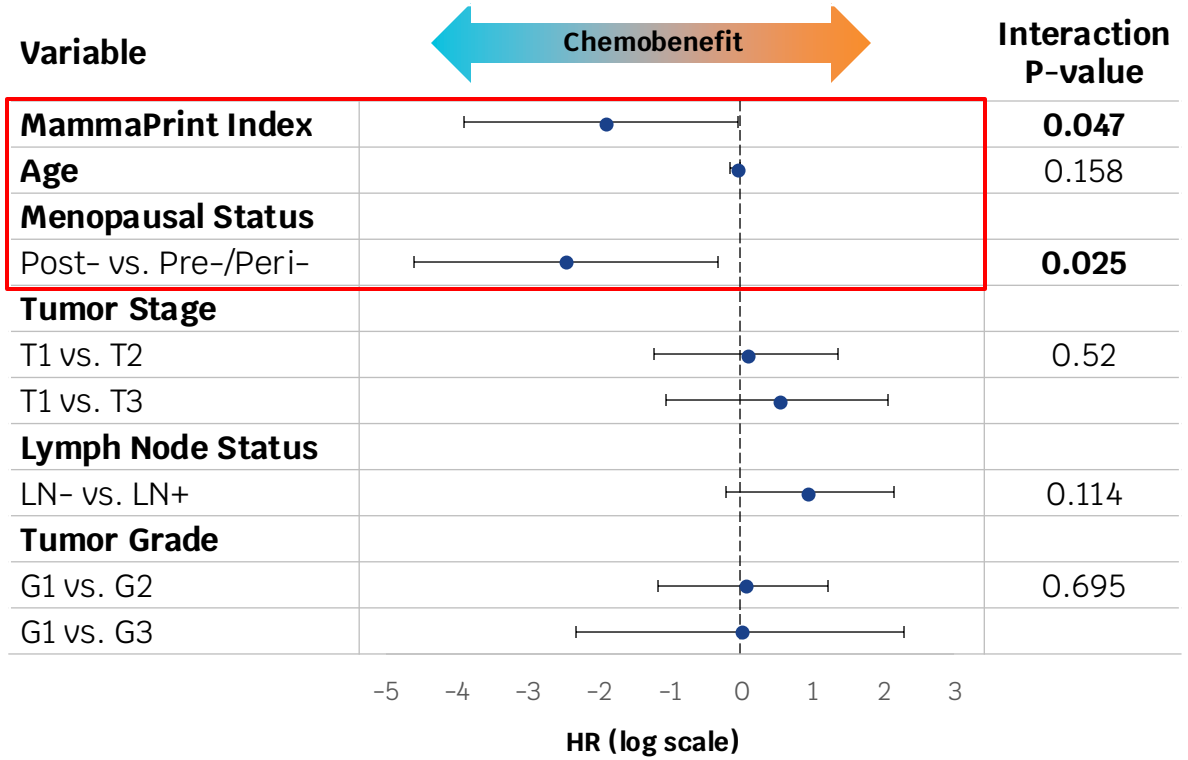
Prediction of Chemotherapy Benefit by MammaPrint® in HR+HER2- Early-Stage Breast Cancer Revealed by the FLEX Registry of Real-World Data

Risk of 5-year DRFI for patients receiving ET vs ET+CT across the MammaPrint Index

MammaPrint Risk Group	ET Risk % Average (% Range)	ET+CT Risk % Average (% Range)	Difference in Risk % Average (% Range)
UltraLow	1.0 (0.6 to 2.2)	0.4 (0.1 to 1.0)	0.6 (0.5 to 1.2)
Low	3.2 (2.2 to 4.5)	1.5 (1.0 to 2.1)	1.7 (1.2 to 3.3)
High 1	10.0 (5.6 to 14.6)	4.4 (2.6 to 6.4)	5.6 (3.0 to 8.2)
High 2	19.1 (14.8 to 24.8)	8.2 (6.5 to 10.6)	10.9 (8.3 to 14.2)



Association of MammaPrint Index and 5-year chemotherapy benefit



- In this Real World Evidence prospective, propensity score matched study of 1002 patients, patients with increasing MPI risk (High Risk) had significantly lower risk of DRFI events when treated with ET+CT compared to ET alone.
- Consistent with findings from MINDACT, patients with MammaPrint indices within Low and UltraLow Risk ranges did not derive significant CT benefit.

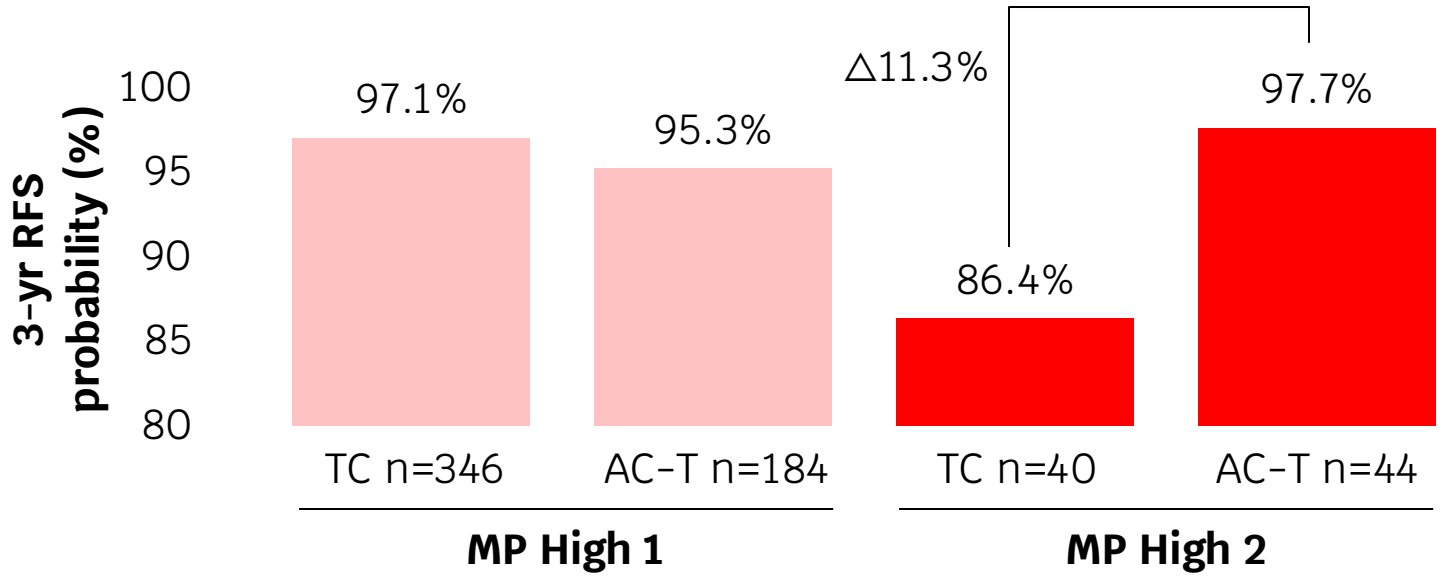
Brufsky A et al. SABCS 2024 P02-08-12

MammaPrint High 2 may be associated with benefit from anthracycline therapy

Chemotherapy Regimen	High 1	High 2
TC (N=386)	97.1% (95.1-99.2)	86.4% (74.2-100.0)
AC-T/TAC (N=228)	95.3% (91.8-98.8)	97.7% (93.4-100.0)
Difference in 3-yr RFS	-1.8%	11.3%

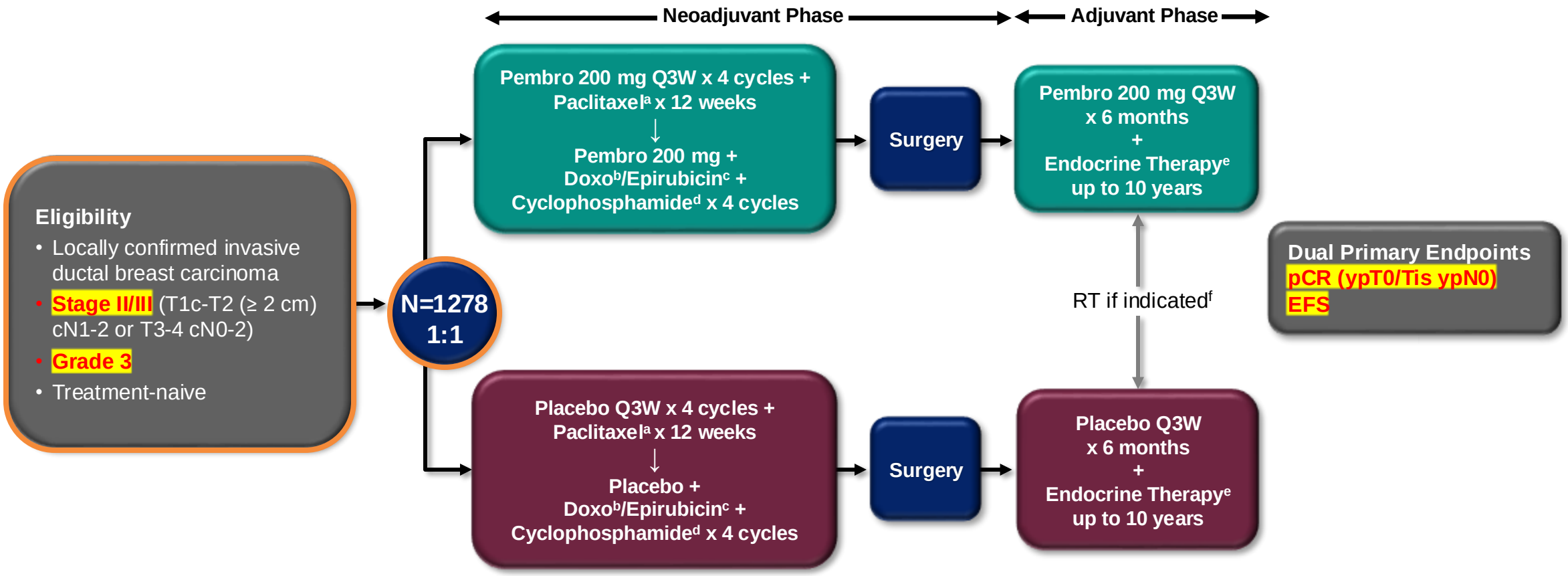
Patients not randomized to TC vs AC-T

- Similar 3-yr RFS rates for High 1 patients treated with AC-T or TC
- Higher 3-yr RFS rate for High 2 patients treated with AC-T than with TC



O'Shaughnessy, J et al. ASCO 2024

KEYNOTE-756 Study Design (NCT03725059)

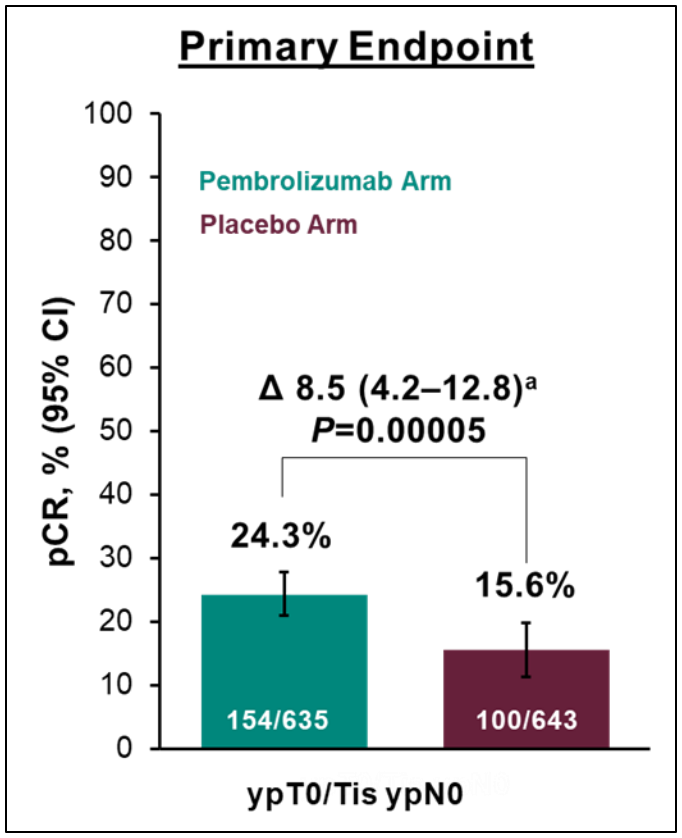


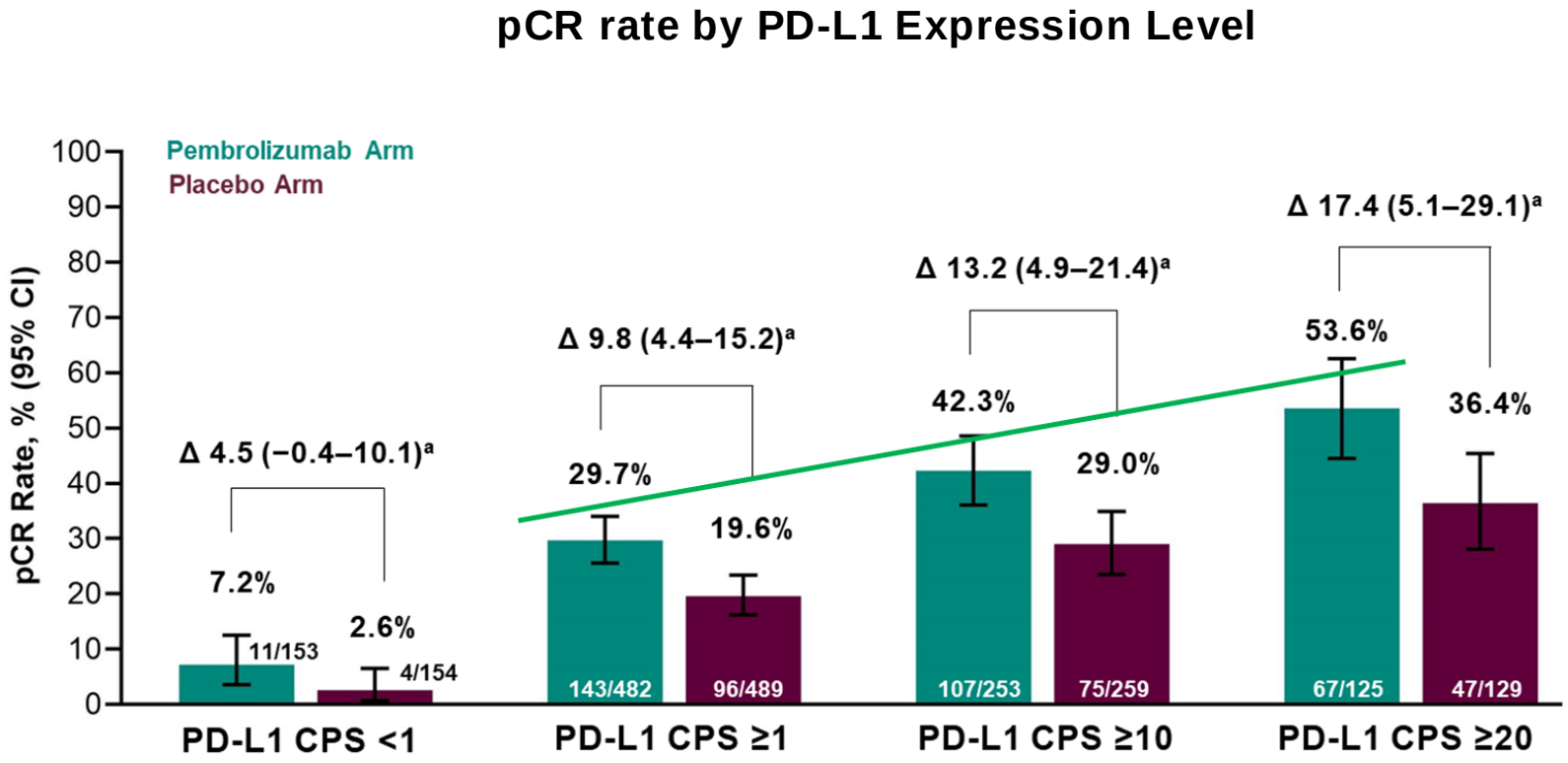
[a]Paclitaxel dose was 80 mg/m^2 QW. [b]Doxorubicin dose was 60 mg/m^2 Q3W. [c]Epirubicin dose was 100 mg/m^2 Q3W. [d]Cyclophosphamide dose was 600 mg/m^2 Q3W or Q2W.

[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

Cardoso F, O'Shaughnessy J et al. SABCS 2023

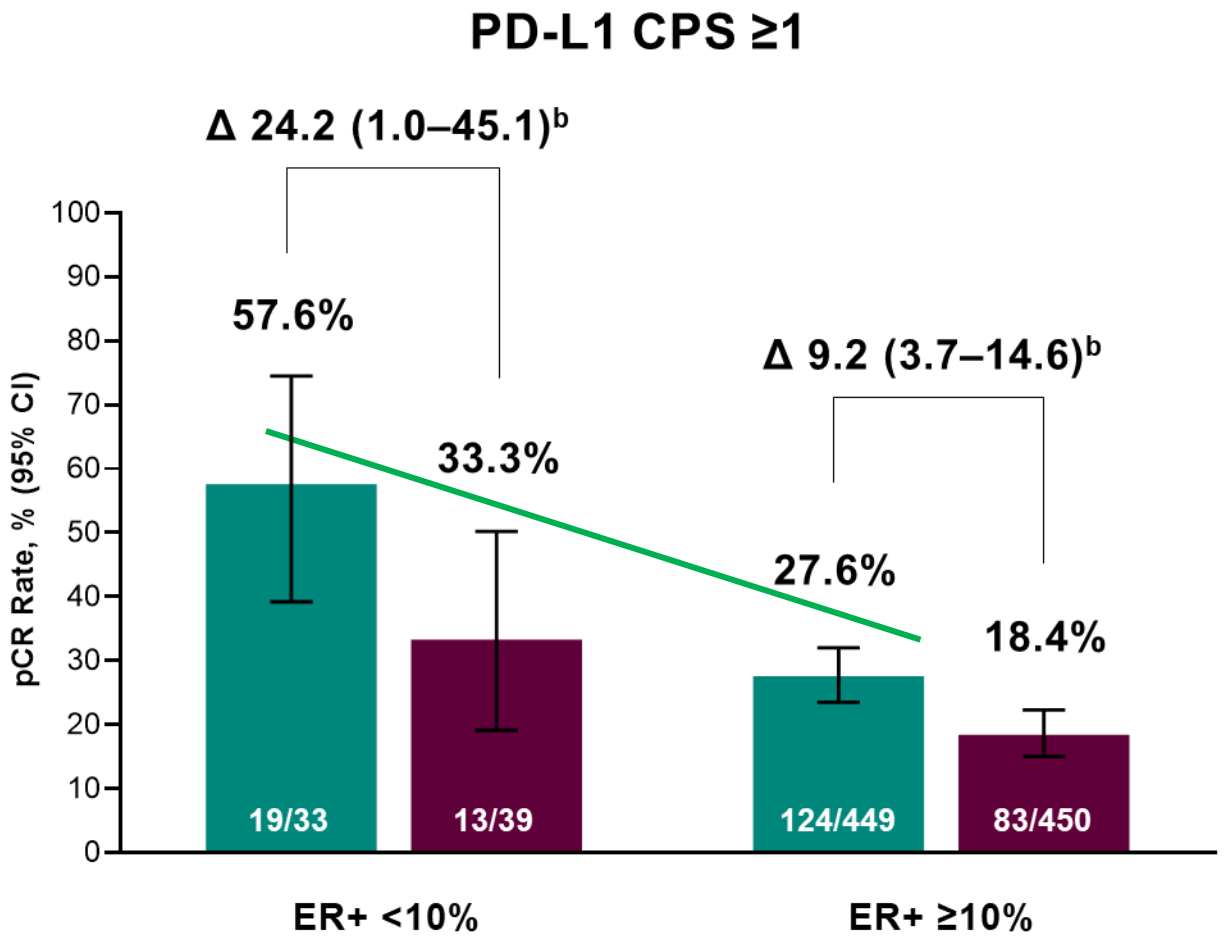
KEYNOTE-756 Results



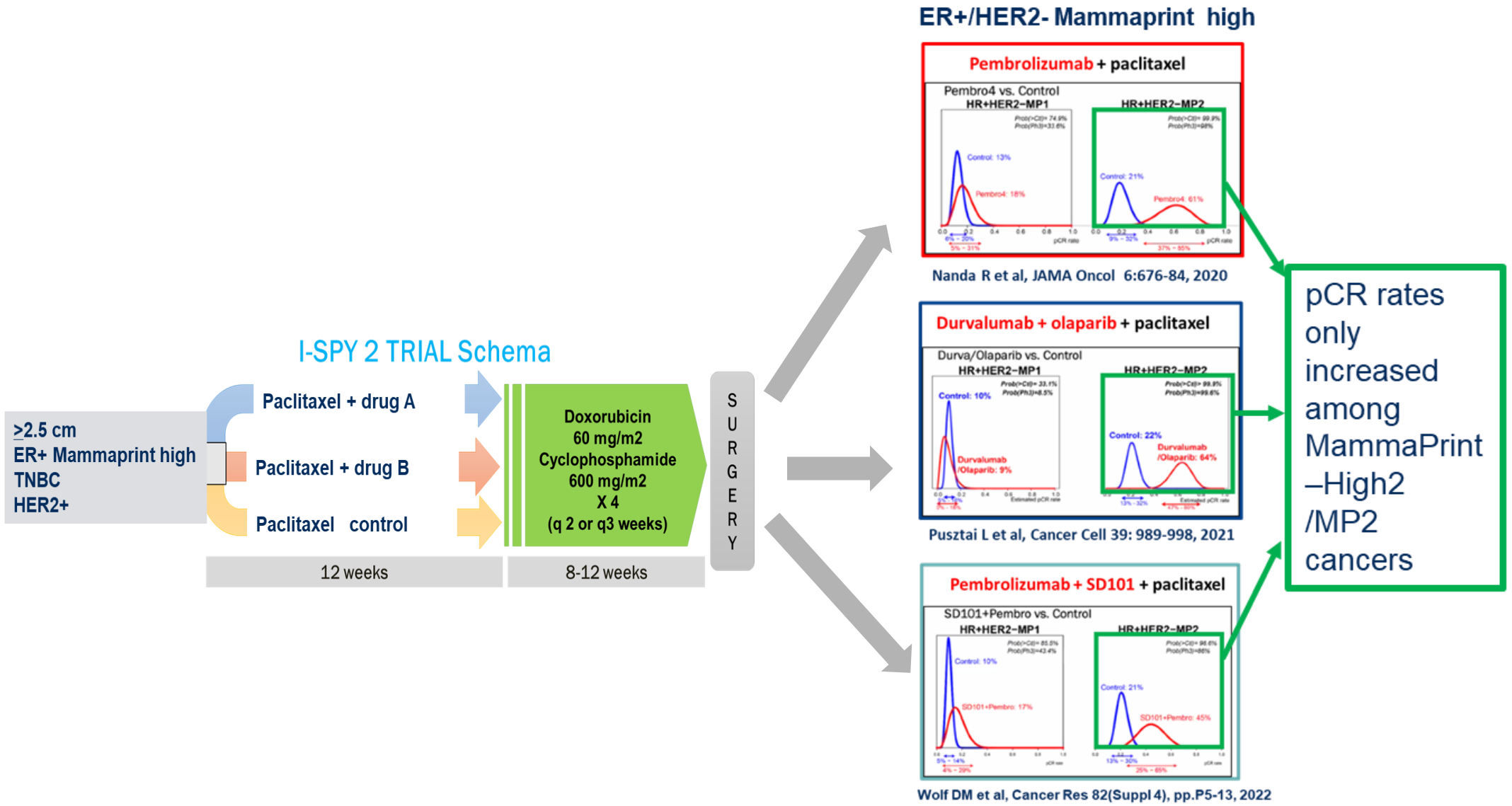


In PDL1 negative cancers no improvement in pCR

pCR rate by ER Status

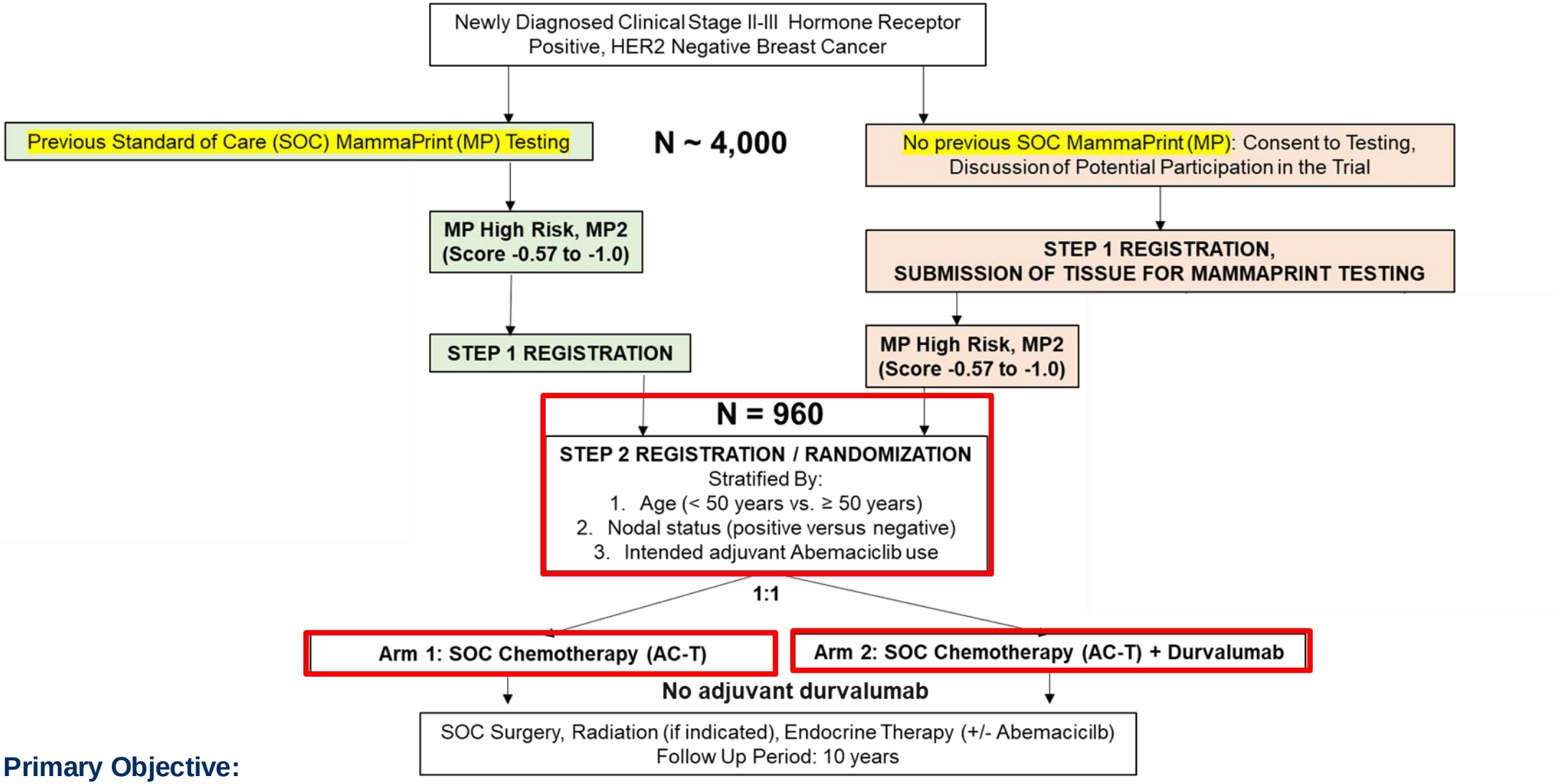


The first signal that neoadjuvant ICI therapy improves pCR rates in a subset of ER+/HER2- cancers came from the I-SPY2 trial along with a biomarker….



An important ongoing clinical trial (NCT 06058377)

SWOG S2206 Neoadjuvant chemotherapy +/- durvalumab for Stage II/III MP2 ER+ breast cancers

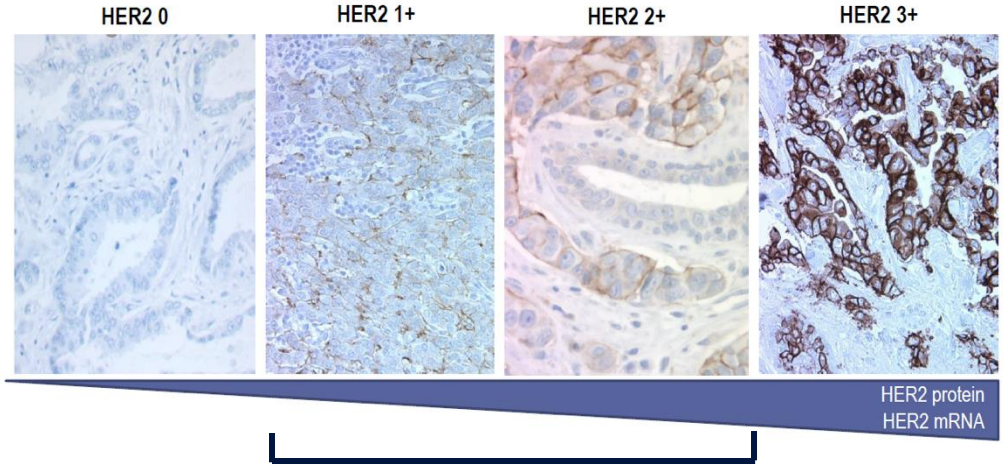


S2206 Primary Objective:

Compare breast cancer event-free survival between AC-T versus AC-T + durvalumab arms

T-DXD has activity in HER2-low breast cancer

HER2: Continuum of expression of in breast cancer

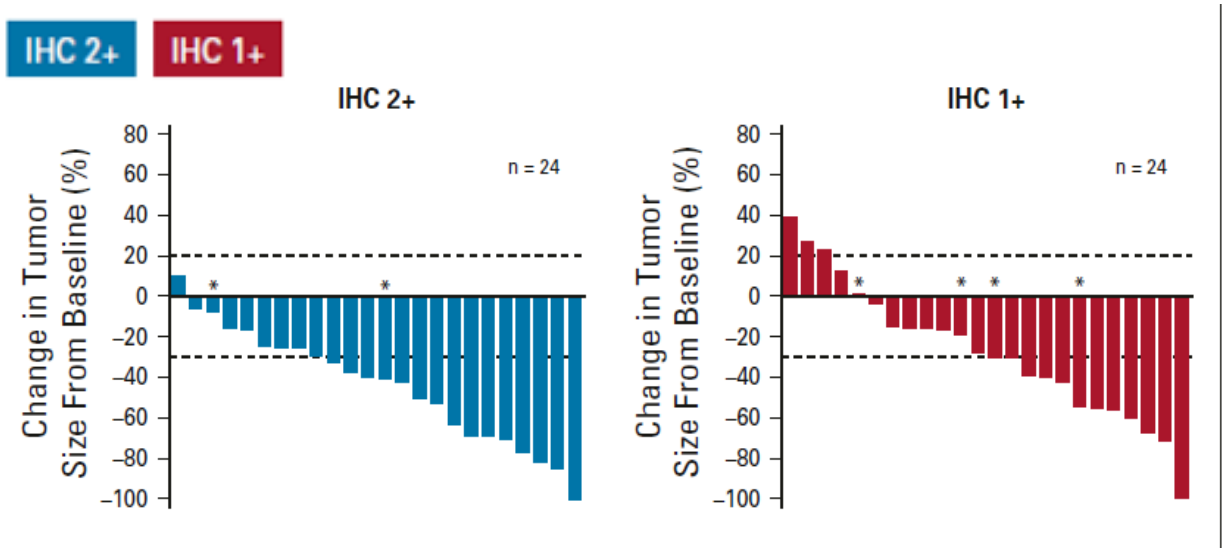


HER2-low

HER2 IHC 2+/ISH- OR IHC 1+/ISH – or untested

Of ~6100 breast cancer cases by IHC
~ 75% of cases of HR+ BC were considered HER2-low
~ 49% of cases of TNBC were considered HER2-low

T-DXd: Best percent change in tumor size in HER2-low MBC



Confirmed ORR: 37%
Confirmed DCR: 87%
Median DoR: 10.4 months
Median PFS: 11.1 months

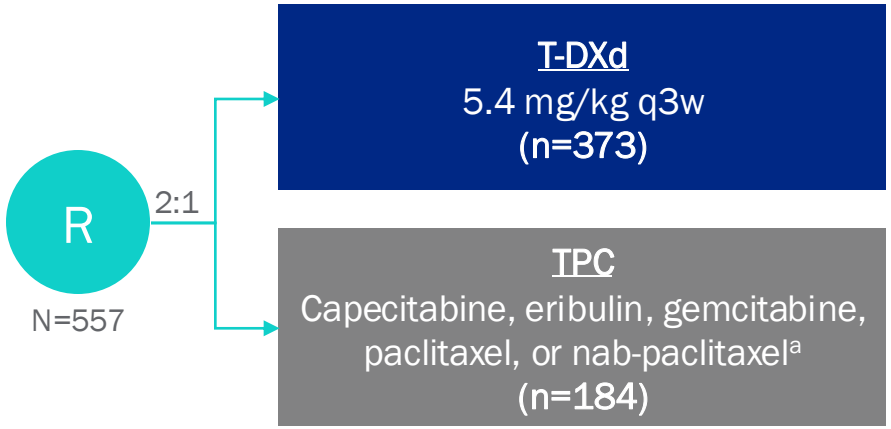
- T-DXD demonstrated significant anti-tumor activity in HER2 IHC 2+ and 1+ tumors

Penault-Llorca F. ESMO E-learning module
Modi S et al. JCO 2020

Results From the Phase 3 DESTINY-Breast04 Trial of T-DXd in HER2-Low MBC: Study Design[1] and Patients[2]

Key Eligibility Criteria

- HER2-low (IHC 1+ or IHC 2+/ISH–) unresectable and/or MBC
- ≥1 prior line of chemotherapy in the metastatic setting
- ≥1 line of ET if HR+ MBC



Primary endpoint: PFS by BICR (HR+)
Key secondary endpoints[b]: PFS by BICR (all patients), OS (HR+ and all patients)

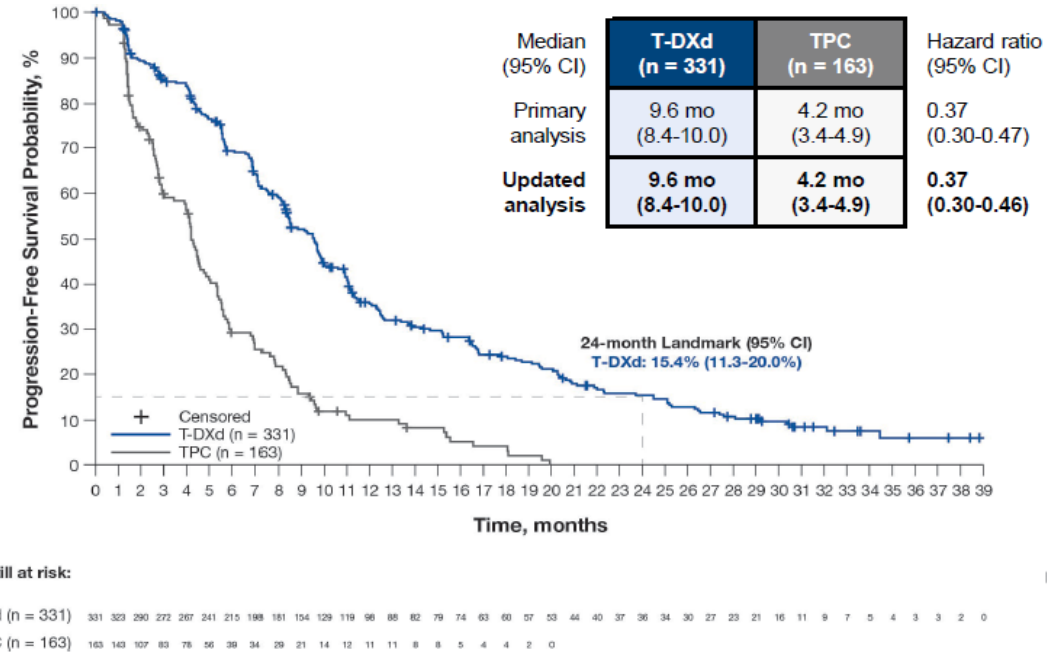
Patient Characteristics			HR+		All Patients	
			T-DXd (n=331)	TPC (n=163)	T-DXd (n=373)	TPC (n=184)
Median age (range), years			57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
HER2 status (IHC), n (%)		1+	193 (58)	95 (58)	215 (58)	106 (58)
		2+/ISH–	138 (42)	68 (42)	158 (42)	78 (42)
HR positive,[c] n (%)			328 (99)	162 (99)	333 (89)	166 (90)
ECOG PS, n (%)		0	187 (56)	95 (58)	200 (54)	105 (57)
		1	144 (44)	68 (42)	173 (46)	79 (43)
Metastases at baseline, n (%)	Brain		18 (5)	7 (4)	24 (6)	8 (4)
	Liver		247 (75)	116 (71)	266 (71)	123 (67)
	Lung		98 (30)	58 (36)	120 (32)	63 (34)
Prior lines of Chemo (MBC setting)		Median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
		≥3, n (%)	3 (1)	0	6 (2)	0
Prior lines of ET (MBC setting)		Median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
		≥3, n (%)	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)		Targeted	259 (78)	132 (81)	279 (75)	140 (76)
		CDK4/6i	233 (70)	115 (71)	239 (64)	119 (65)

Data cutoff: March 1, 2023.
[a] TPC was administered according to the label. [b] Other secondary endpoints included ORR (BICR and INV), DOR (BICR), PFS (INV), and safety. Efficacy in the HR– cohort was an exploratory endpoint. [c] HR status was based on data collected using interactive web/voice response system at randomization, which includes mis-stratified patients.

1. Modi S, et al. ESMO 2023. Abstract 3760. **2.** Modi S, et al. ASCO 2022. Abstract LBA3.

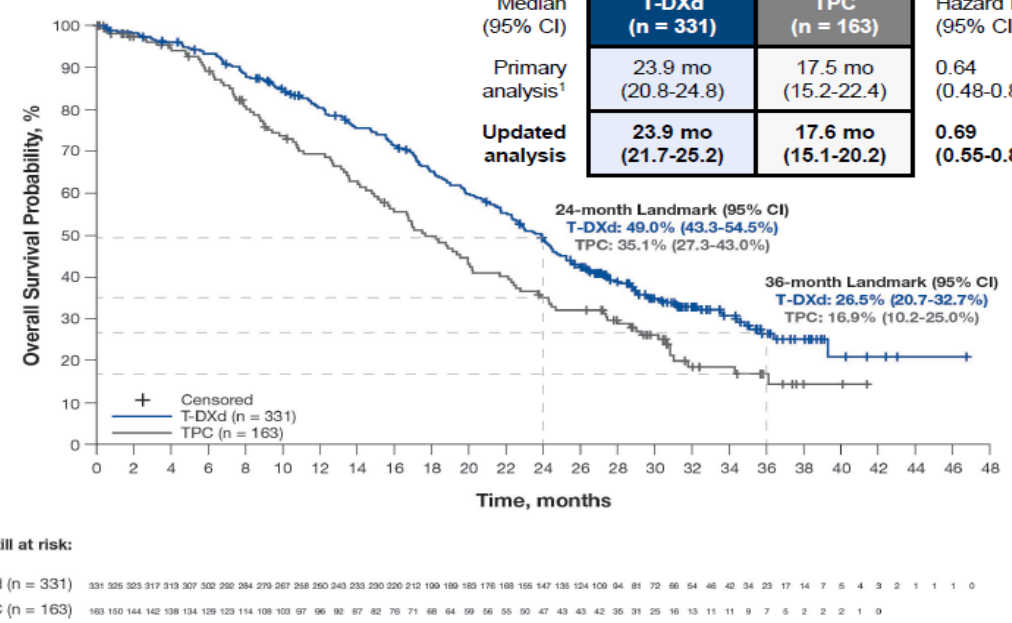
Results From the Phase 3 DESTINY-Breast04 Trial of T-DXd in HER2-Low MBC: Efficacy in Patients With HR+ Disease

PFS in HR+ (by INV)[a]



Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

OS in HR+



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)**

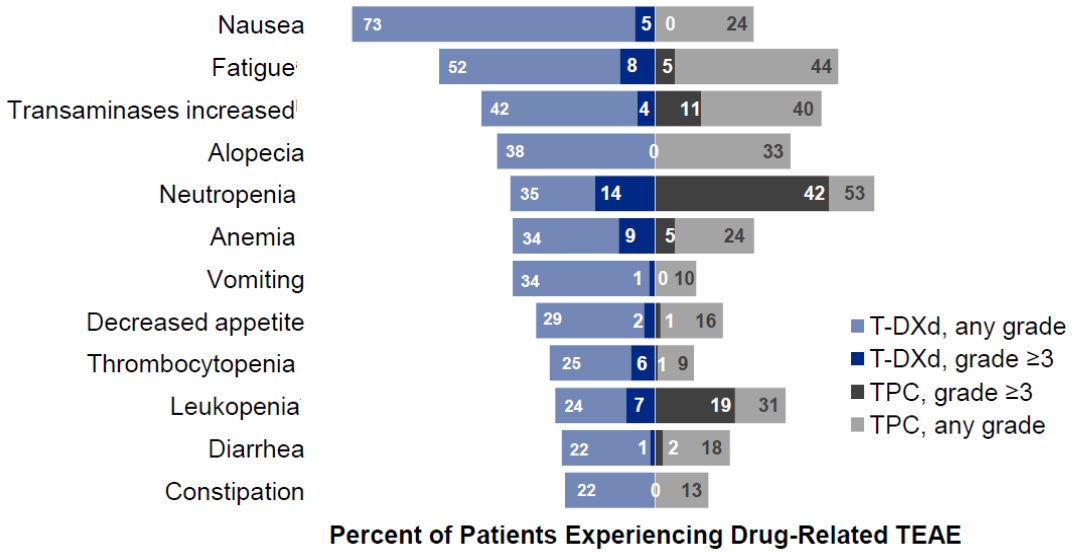
	PFS in HR+ Patients (by INV)		OS in HR+ Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=331)	TPC (n=163)
Median, months	9.6 (8.4-10.0)	4.2 (3.4-4.9)	23.9 (21.7-25.2)	17.6 (15.1-20.2)
HR (95% CI)	0.37 (0.30-0.46)		0.69 (0.55-0.87)	

[a] Analysis of 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 (HR=0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (HR=0.50). The updated analysis is based on PFS by investigator.

Modi S, et al. ESMO 2023. Abstract 3760.

Results From the Phase 3 DESTINY-Breast04 Trial of T-DXd in HER2-Low MBC: Safety

Drug-Related TEAEs in ≥20% of Patients



Safety Summary		T-DXd (n=371)	TPC (n=172)
Median treatment duration (range), months		8.2 (0.2-39.1)	3.5 (0.3-19.7)
TEAEs Grade ≥3		369 (99.5) 202 (54.4)	169 (98.3) 116 (67.4)
Serious TEAEs, n (%)		108 (29.1)	44 (25.6)
TEAEs associated with, n (%)	Dose discontinuations	62 (16.7)	14 (8.1)
	Dose interruptions	155 (41.8)	73 (42.4)
	Dose reductions	89 (24.0)	65 (37.8)
	Deaths	15 (4.0)	5 (2.9)
Total on-treatment deaths		14 (3.8)	8 (4.7)

AEs of Special Interest, n (%)		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Adjudicated as drug-related ILD/pneumonitis	T-DXd (n=371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
	TPC (n=172)	1 (0.6)	0	0	0	0	1 (0.6)

- Most common TEAEs associated with treatment discontinuation
  - T-DXd: 10.2%, ILD/pneumonitis
  - TPC: 2.3%, peripheral sensory neuropathy

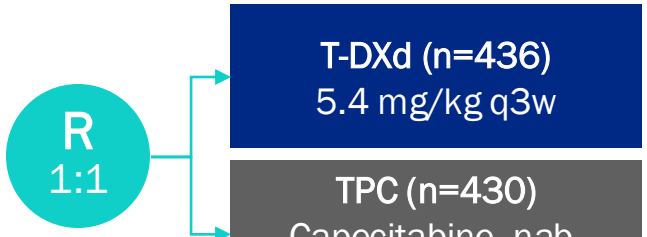
[a] At the primary analysis (data cutoff date: January 11, 2022), grade 3 adjudicated drug-related ILD was reported in 5 patients (1.3%). At the current data cutoff, grade 3 adjudicated drug-related ILD was reported in 4 patients (1.1%) as 1 grade 3 ILD case worsened to grade 5 ILD. Consequently, there was an increase in the rate of grade 5 ILD (from 0.8% to 1.1%) without impact on the overall rate of adjudicated drug-related ILD. No ILD cases were pending adjudication at the updated data cutoff.

Modi S, et al. ESMO 2023. Abstract 3760.

Primary Results From the Phase 3 DESTINY-Breast06 Trial of T-DXd in HER2-Low and –Ultralow MBC With Prior ET: Study Design and Patients

Key Eligibility Criteria

- HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) or HR+/HER2-ultralow (IHC 0 with membrane staining) MBC[a]
- Chemotherapy-naive in the MBC setting
- ≥2 lines of ET ± targeted therapy for MBC **OR**
- 1 line for MBC **AND**
  - Progression ≤6 mo of starting 1L ET + CDK4/6i **OR** recurrence ≤24 mo of starting adjuvant ET



ITT (N=866)
HER2-low (n=713)
HER2-ultralow (n=153)[b]

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 nonmetastatic setting (yes vs no)

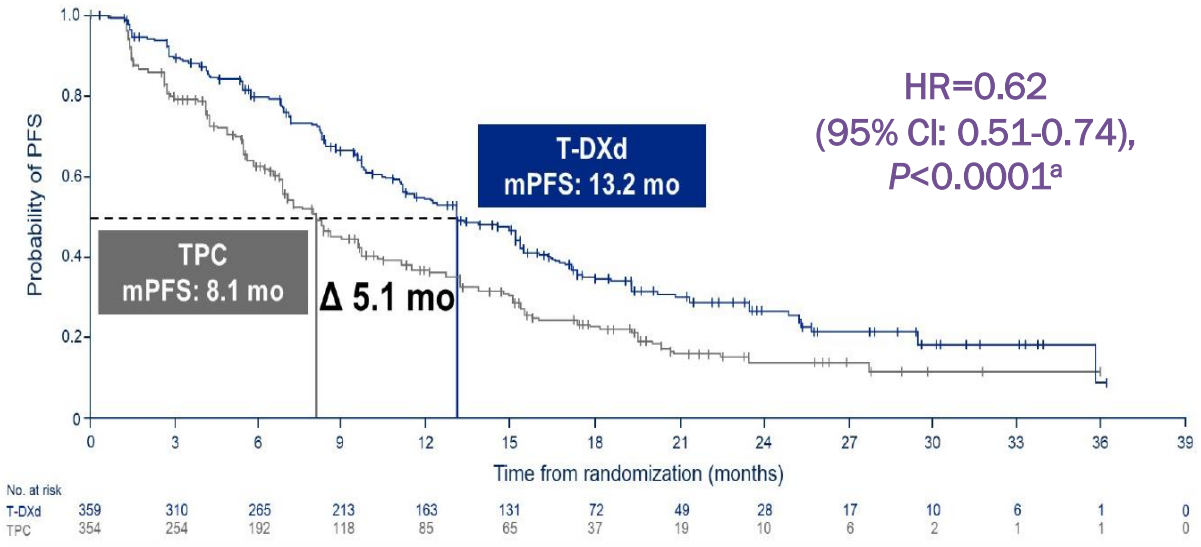
Primary endpoint: PFS (BICR) in HER2-low
Key secondary endpoints: PFS (BICR) in ITT, (HER2-low + –ultralow), OS in HER2-low, OS in ITT (HER2-low + –ultralow)

Patient Characteristics		HER2-low[c]		ITT	
		T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)
Median age (range), years		58 (28-87)	57 (32-83)	58 (28-87)	57 (32-83)
ECOG PS, n (%)[d]	1	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)
	2	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)
HER2 status, n (%)[e]					
HER2-ultralow[f]		–	–	76 (17.4)	76 (17.7)
IHC 1+ (HER2-low)		238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)
IHC 2+/ISH– (HER2-low)		117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)
Primary endocrine resistance, n (%)[g]		105 (29.2)	116 (32.8)	128 (29.4)	140 (32.6)
ET in MBC setting	Median lines (range)	2 (1-4)	2 (1-5)	2 (1-4)	2 (1-5)
	ET monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)
	ET + CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)
	ET + other therapy[h]	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)

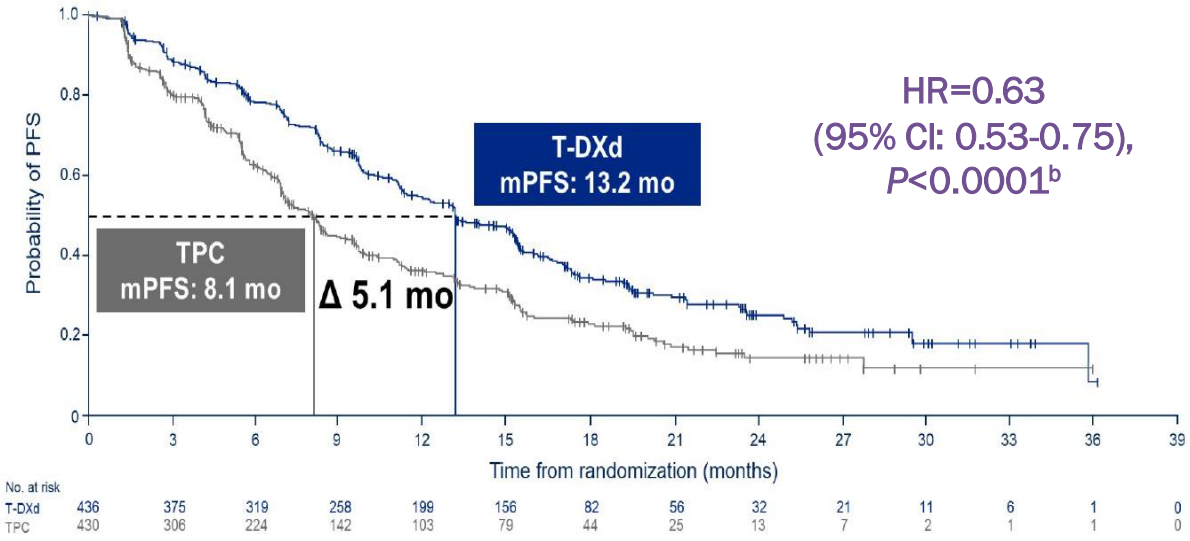
[a] HER2 status was determined based on most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+). [b] HER2-ultralow status as determined per interactive response technology data (efficacy analyses in the HER2-ultralow subgroup were based on n=152 per central laboratory testing data). [c] HER2-low status defined at randomization per interactive response technology data. [d] n=14 patients had missing ECOG PS status at baseline. [e] n=2 patients in the ITT (1 per treatment group) were found to have HER2 IHC 0 with absent membrane staining per central lab testing. [f] Defined as IHC 0 with membrane staining. [g] Defined as relapse while on the first 2 years of adjuvant ET, or progression within the first 6 mo of 1L ET for MBC. [h] mTORi (23.8%), PI3Ki (4.2%), or PARPi (0.9%) in the ITT population.
Curigliano G, et al. ASCO 2024. Abstract LBA1000.

Primary Results From the Phase 3 DESTINY-Breast06 Trial of T-DXd in HER2-Low and –Ultralow MBC With Prior ET: PFS in Patients With HER2-Low Disease and the ITT Population

PFS (BICR) in HER2-Low



PFS (BICR) in ITT (HER2-Low + HER2-Ultralow)

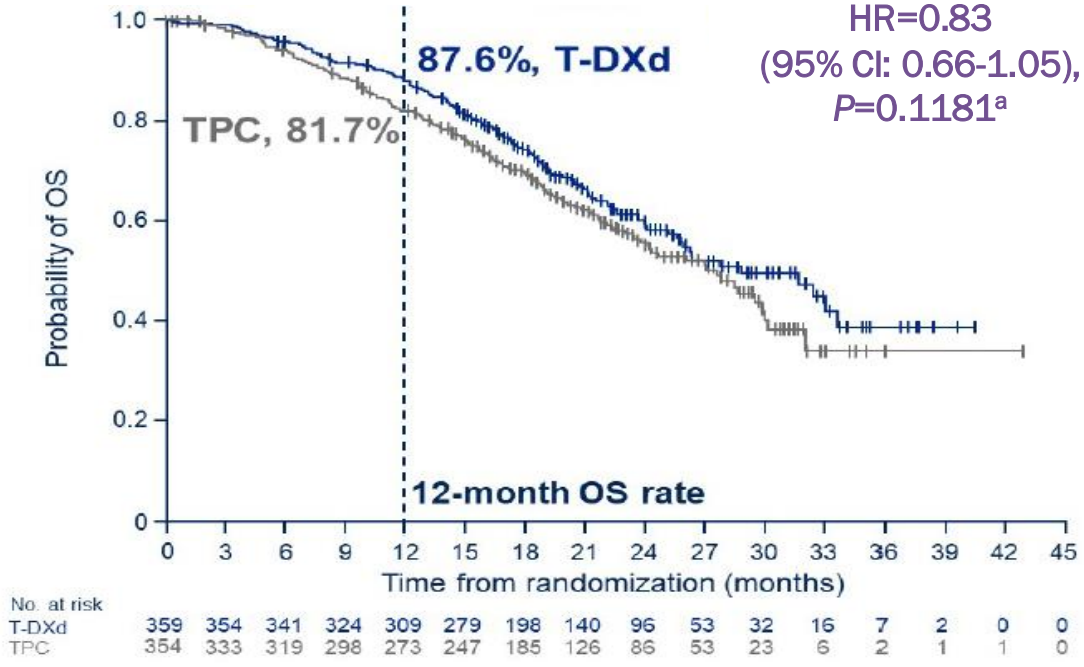


- PFS benefit for T-DXd vs TPC was generally consistent across predefined subgroups in the HER2-low population, including patients aged ≥65 years, those with prior CDK4/6i or taxane use, and those with primary endocrine resistance

[a] *P*-value of <0.05 required for statistical significance. [b] P-value of <0.015 required for statistical significance.
Curigliano G, et al. ASCO 2024. Abstract LBA1000.

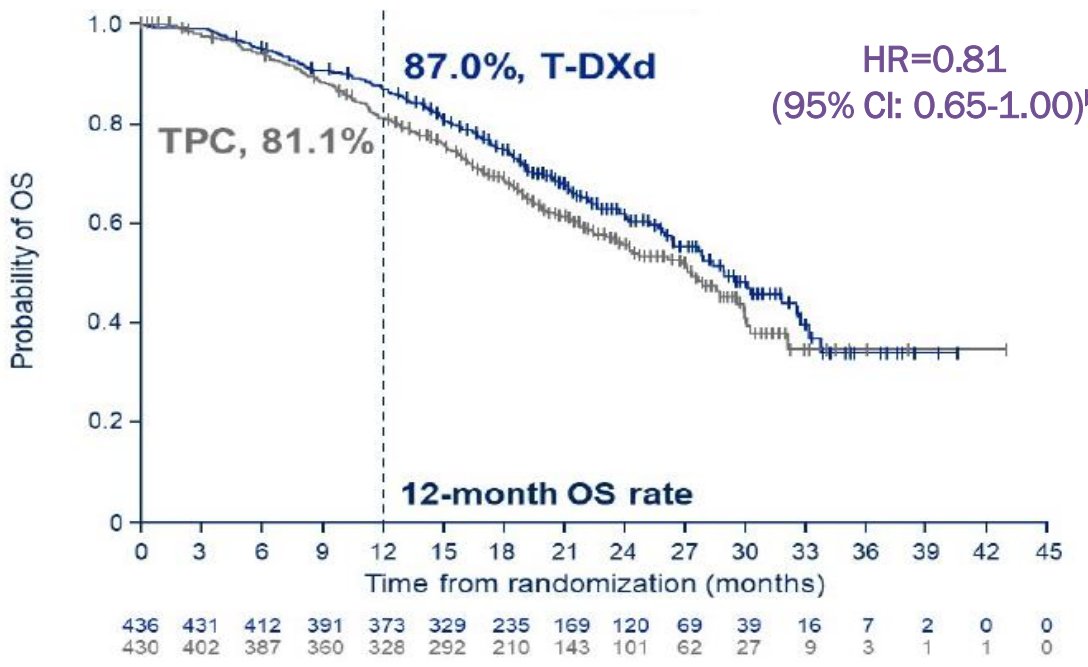
Primary Results From the Phase 3 DESTINY-Breast06 Trial of T-DXd in HER2-Low and –Ultralow MBC With Prior ET: OS in Patients With HER2-Low Disease and the ITT Population

OS in HER2-Low



20.1% of patients in the TPC group received T-DXd after treatment discontinuation (HER2-low)

OS in ITT (HER2-Low + HER2-Ultralow)



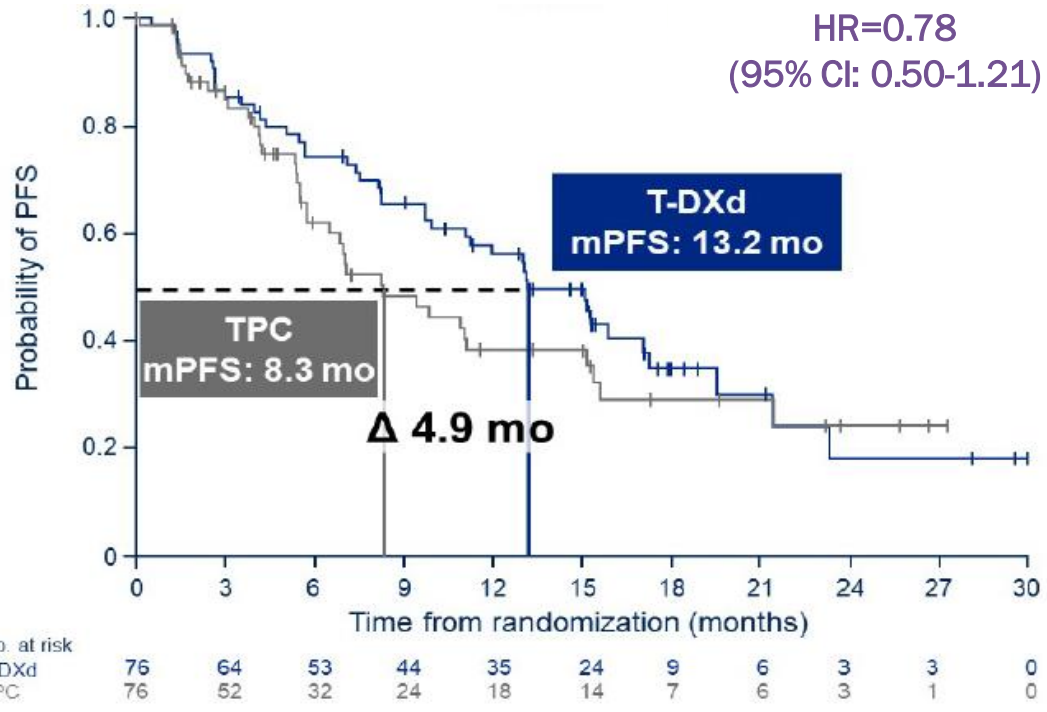
17.9% of patients in the TPC group received T-DXd after treatment discontinuation (ITT)

[a] *P*-value of <0.0046 required for statistical significance. [b] No test of significance was performed in line with the multiple testing procedure.

Curigliano G, et al. ASCO 2024. Abstract LBA1000.

Primary Results From the Phase 3 DESTINY-Breast06 Trial of T-DXd in HER2-Low and –Ultralow MBC With Prior ET: PFS in Patients With HER2-Ultralow Disease and ORR

PFS (BICR) in HER2-Ultralow (Prespecified Exploratory Analysis)



ORR

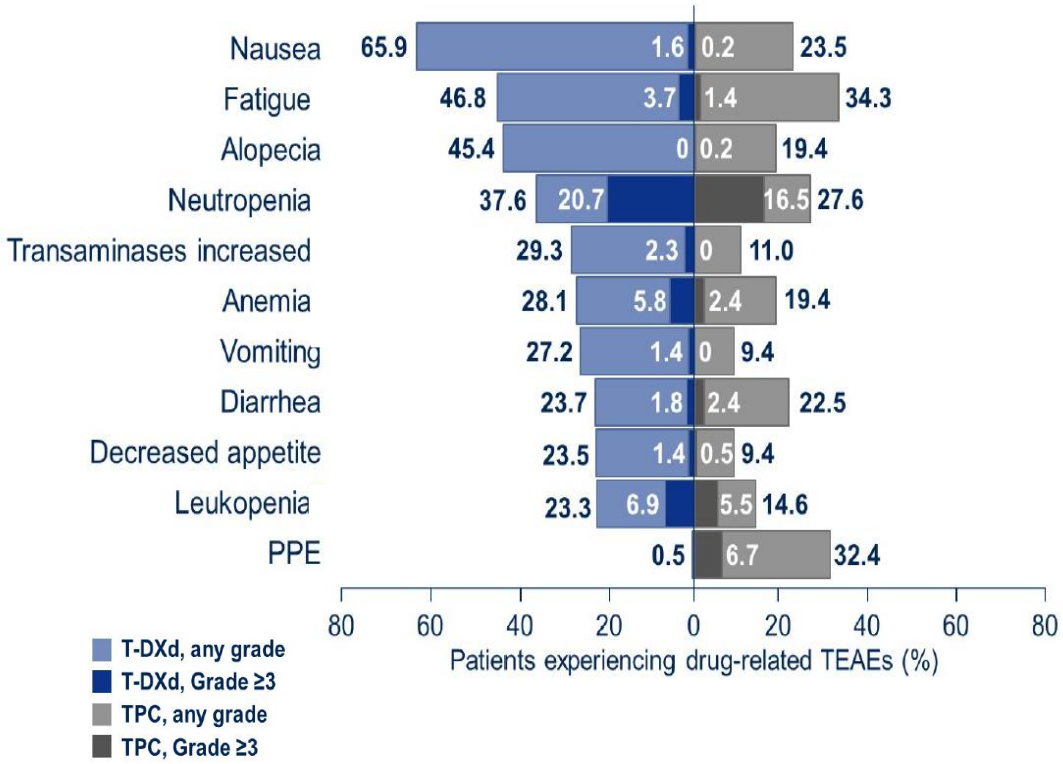
Responses		HER2-Low[a] T-DXd (n=359)	HER2-Low[a] TPC (n=354)	ITT T-DXd (n=436)	ITT TPC (n=430)	HER2-Ultralow[a] T-DXd (n=76)	HER2-Ultralow[a] TPC (n=76)
Confirmed ORR, n (%)		203 (56.5)	114 (32.2)	250 (57.3)	134 (31.2)	47 (61.8)	20 (26.3)
Best overall response	CR	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
	PR	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
	SD	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)[b]		275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Median DOR, mo		14.1	8.6	14.3	8.6	14.3	14.1

- Interim OS analysis was at ~35% maturity and showed a trend in favor of T-DXd for the HER2-ultralow population (HR=0.75, 95% CI: 0.43-1.29)

[a] HER2-low status defined at randomization per interactive response technology data and HER2-ultralow status defined by central laboratory testing data. [b] Defined as CR + PR + SD at week 24 by BICR.
Curigliano G, et al. ASCO 2024. Abstract LBA1000.

Primary Results From the Phase 3 DESTINY-Breast06 Trial of T-DXd in HER2-Low and –Ultralow MBC With Prior ET: Safety

Drug-Related TEAEs in ≥20% of Patients in Either Treatment Group



Safety Summary		T-DXd (n=434)	TPC (n=417)
Total exposure, patient-years		438.5	263.5
Treatment-related TEAEs		417 (96.1)	373 (89.4)
Grade ≥3		176 (40.6)	131 (31.4)
Serious TEAEs, n (%)		88 (20.3)	67(16.1)
TEAEs associated with, n (%)	Dose discontinuations	62 (14.3)	39 (9.4)
	Dose interruptions	210 (48.4)	160 (38.4)
	Dose reductions	107 (24.7)	161 (38.6)
	Deaths	11 (2.5)	6 (1.4)
Treatment-related deaths (investigator assessed)[a]		5 (1.2)	0

AESI Adjudicated as Drug-Related ILD/Pneumonitis[b]						
n (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n=434)	49 (11.3)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)
TPC (n=417)	1 (0.2)	0	1 (0.2)	0	0	0

- In the T-DXd vs TPC arms, 35 (8.1%) vs 12 (2.9%) patients experienced any grade ejection fraction decreased, and 0 vs 3 (0.7%) patients experienced any grade cardiac failure

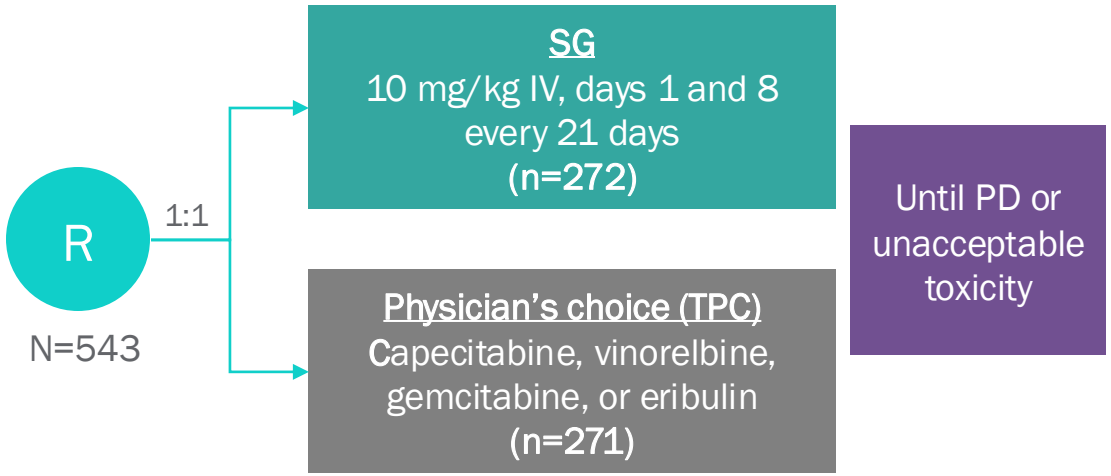
[a] Reasons were ILD (n=2), sepsis (n =1), neutropenic sepsis (n=1), and general physical health deterioration (n=1). [b] Grouped term. Median time to first onset of ILD/pneumonitis for patients with T-DXd was 141 days (range, 37-835). No pending cases of drug-related ILD/pneumonitis to be adjudicated. One ILD-related death per investigator assessment was upheld by the adjudication committee. An additional 2 deaths were adjudicated as ILD related by the adjudication committee.

Curigliano G, et al. ASCO 2024. Abstract LBA1000.

Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2– MBC: Study Design and Patients

Key Eligibility Criteria

- HR+/HER2– MBC (or locally recurrent inoperable) with PD after:
  - ≥1 ET, taxane, and CDK4/6i in any setting
  - ≥2 to ≤4 lines of chemotherapy for metastatic disease
  - Measurable disease by RECIST v1:1



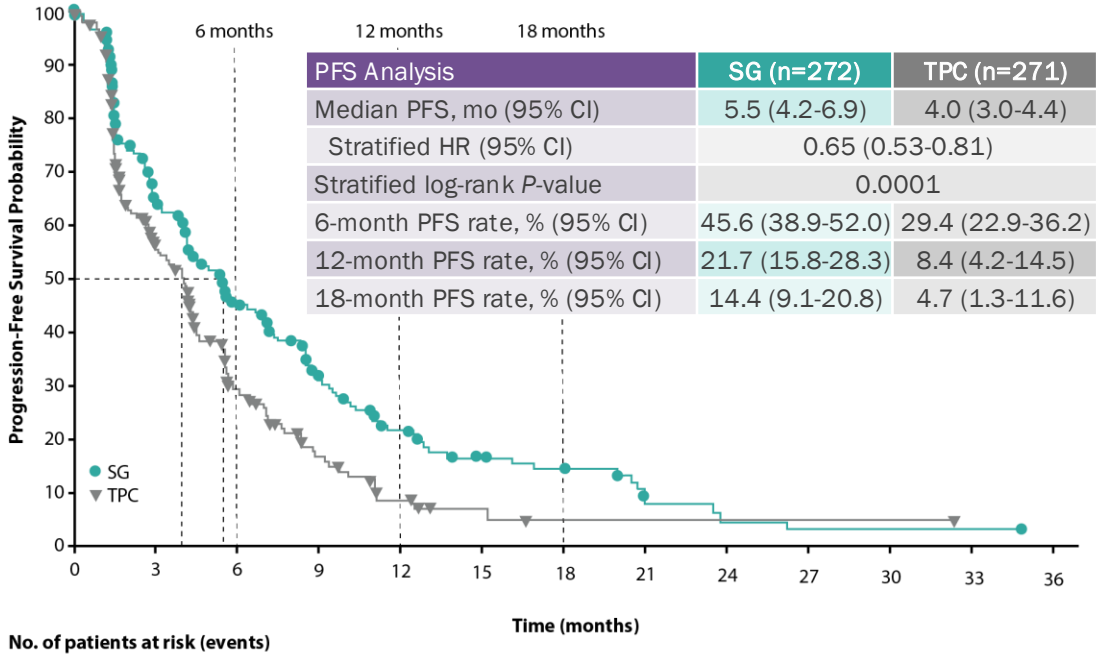
Primary endpoint: PFS by BICR
Secondary endpoints: OS, ORR, DOR, CBR by local investigator review and BICR, PRO, safety

Patient Characteristics		SG (n=272)	TPC (n=271)
Median age (range), years		57 (29-86)	55 (27-78)
ECOG PS, n (%)	0	116 (43)	126 (46)
	1	156 (57)	145 (54)
Visceral metastases at baseline, n (%)		259 (95)	258 (95)
Liver metastases, n (%)		229 (84)	237 (87)
Median time from initial MBC diagnosis to randomization (range), months		48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)		173 (64)	184 (68)
Prior ET use in the metastatic setting ≥6 months, n (%)		235 (86)	234 (86)
Prior CDK4/6i, 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 (range), n		3 (0-8)	3 (1-5)

Rugo H, et al. ASCO 2022. Abstract LBA1001.

Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2– MBC: Updated PFS and OS

BICR-Assessed PFS in the ITT Population

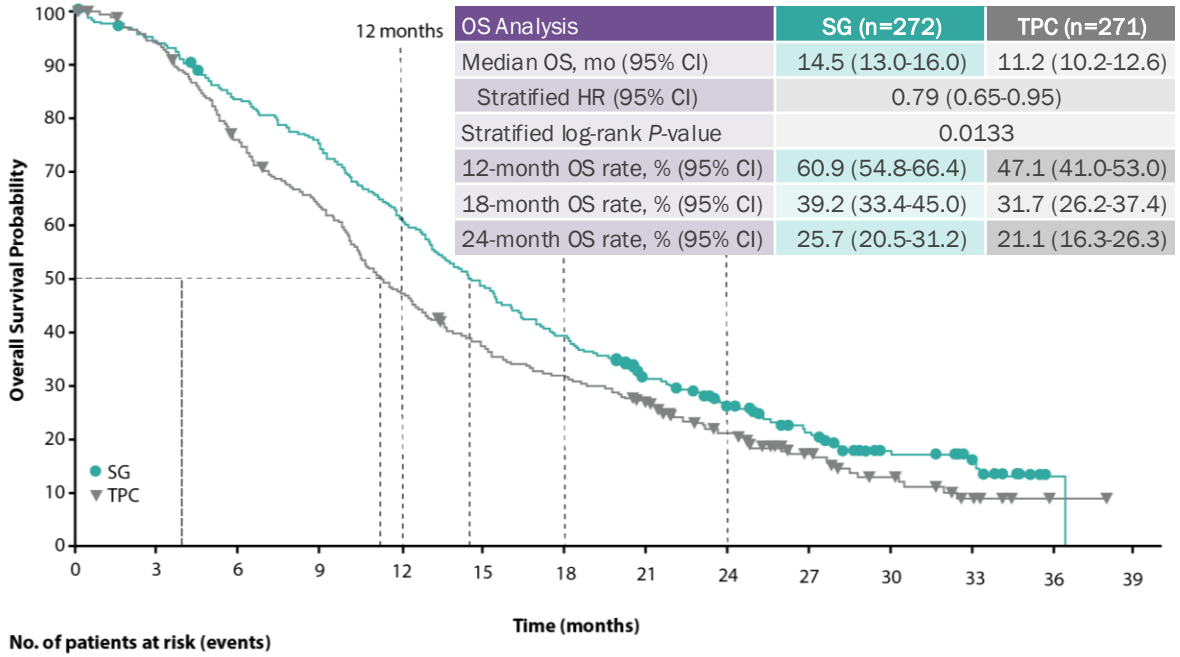


PFS Analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
Stratified log-rank *P*-value	0.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

No. of patients at risk (events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

OS in the ITT Population



OS Analysis	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)	
Stratified log-rank *P*-value	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)

No. of patients at risk (events)

SG	272 (0)	253 (17)	223 (45)	200 (68)	163 (105)	130 (138)	105 (163)	71 (184)	52 (196)	33 (204)	19 (209)	13 (211)	1 (213)	0 (214)
TPC	271 (0)	251 (16)	199 (66)	167 (97)	124 (140)	96 (166)	82 (180)	66 (193)	46 (206)	27 (214)	15 (220)	7 (224)	1 (224)	0 (224)

- SG improved efficacy outcomes vs TPC irrespective of Trop-2 expression level and in both HER2-low and HER2 IHC0 HR+/HER2– MBC, consistent with the ITT population

Tolaney S, et al. ASCO 2023. Abstract 1003.

Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2– MBC: Updated Safety

TEAEs (All Grade >20%), n (%)		SG (n=268)		TPC (n=249)	
		All grade	Grade ≥3	All grade	Grade ≥3
Hematologic	Neutropenia	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia	98 (37)	20 (7)	69 (28)	8 (3)
GI	Diarrhea	166 (62)	27 (10)	57 (23)	3 (1)
	Nausea	157 (59)	3 (1)	87 (35)	7 (3)
	Constipation	93 (35)	1 (<1)	61 (24)	0
	Vomiting	64 (24)	3 (1)	39 (16)	4 (2)
	Abdominal pain	53 (20)	10 (4)	34 (14)	2 (1)
Other	Alopecia	128 (48)	0	46 (18)	0
	Fatigue	105 (39)	16 (6)	82 (33)	9 (4)
	Asthenia	62 (23)	6 (2)	50 (20)	5 (2)
	Decreased appetite	57 (21)	4 (1)	52 (21)	2 (1)

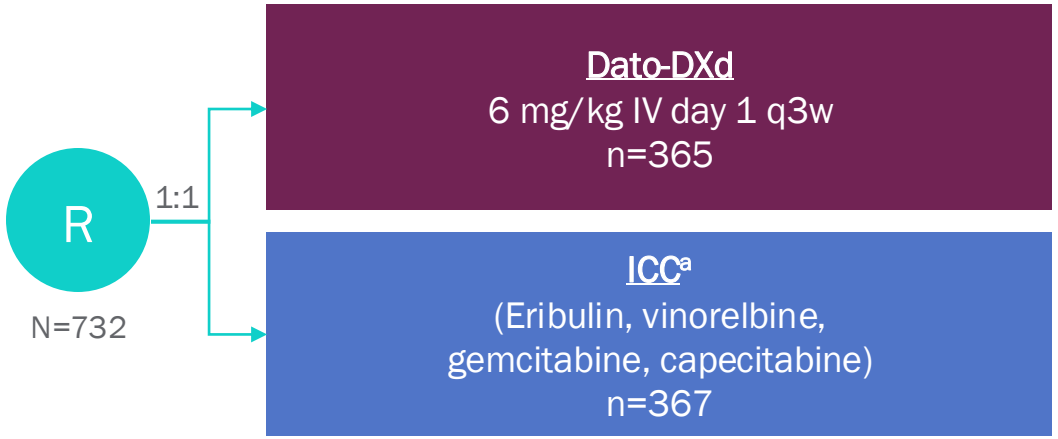
- Treatment discontinuations due to AEs occurred in **17 patients (6%)** receiving SG and **11 patients (4%)** receiving TPC
- No new safety signals were identified with extended follow-up

Tolaney S, et al. ASCO 2023. Abstract 1003.

Results From the Phase 3 TROPION-Breast01 Trial of Dato-DXd in HR+/HER2– MBC: Study Design and Patients[1,2]

Key Eligibility Criteria

- HR+/HER2– MBC (HER2 IHC 0/1+/2+; ISH–)
- Progressed on and not suitable for ET
- 1-2 prior lines of Chemo in inoperable/metastatic setting
- ECOG PS 0-1



Dual primary endpoints: PFS by BICR per RECIST v1.1, OS
Secondary endpoints: ORR, PFS by investigator, time to first subsequent therapy, safety, PROs

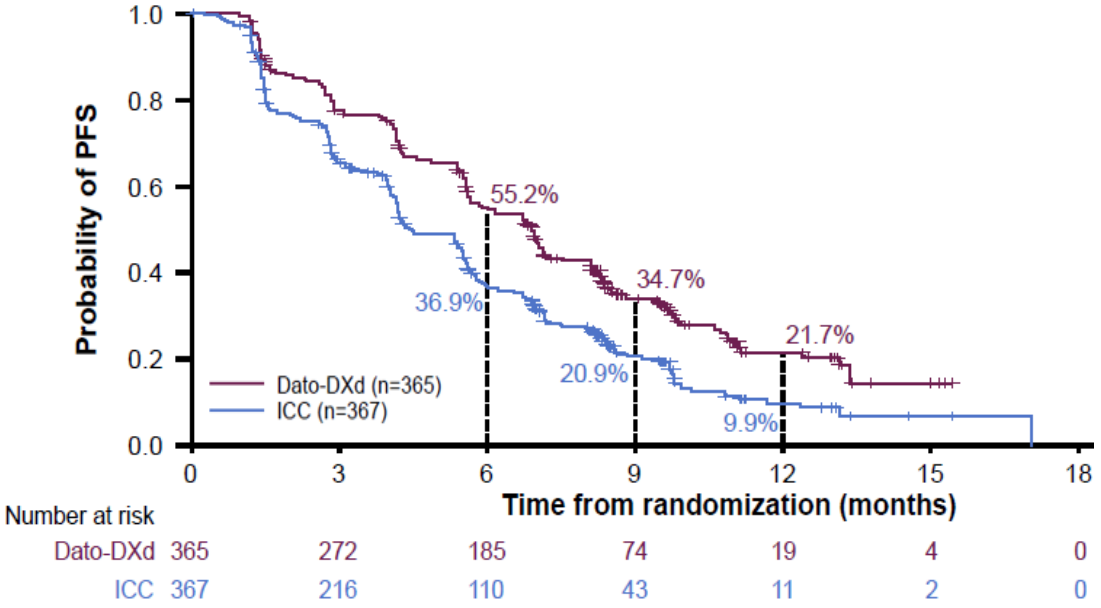
Patient Characteristics, n (%)		Dato-DXd (n=365)[b]	ICC (n=367)[c]
Median age (range), years		56 (29-86)	54 (28-86)
Race	Black or African American	4 (1)	7 (2)
	Asian	146 (40)	152 (41)
	White	180 (49)	170 (46)
	Other	35 (10)	38 (10)
Ethnicity	Hispanic or Latino	40 (11)	43 (12)
	Not Hispanic or Latino	322 (88)	318 (87)
Prior lines of Chemo	1	229 (63)	225 (61)
	2	135 (37)	141 (38)
Prior CDK4/6i		288 (82)	286 (78)
Prior taxane and/or anthracycline		330 (90)	339 (92)

[a] Investigator's choice of chemotherapy was administered as follows: eribulin, 1.4 mg/kg IV on D1, 8, q3w; vinorelbine, 25 mg/m^2 IV on D1, 8, q3w; gemcitabine 1000 mg/m^2 IV on D1, 8, q3w; capecitabine 1000 or 1250 mg/m^2 (dose per standard institutional practice) orally twice daily D1-14, q3w. [b] 360 patients received treatment with Dato-DXd. [c] 351 patients received treatment with ICC: eribulin (n=220); vinorelbine (n=38); capecitabine (n=76); gemcitabine (n=33).

1. Bardia A, et al. ESMO 2023. Abstract LBA11. **2.** Bardia A, et al. SABCS 2023. Abstract GS02-01.

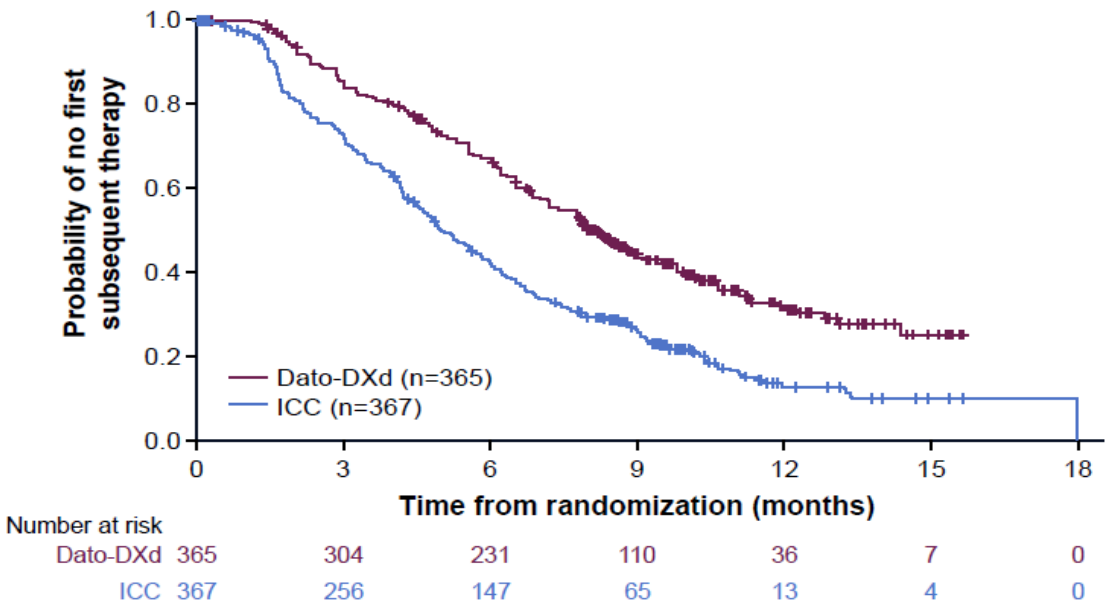
Results From the Phase 3 TROPION-Breast01 Trial of Dato-DXd in HR+/HER2– MBC: PFS and Time to First Subsequent Therapy

PFS by Investigator Assessment[1]



PFS by Investigator	Dato-DXd (n=365)	ICC (n=367)
Median PFS, mo (95% CI)	6.9 (5.9-7.1)	4.5 (4.2-5.5)
HR (95% CI)	0.64 (0.53-0.76)	

Time to First Subsequent Therapy[1]



PFS by Investigator	Dato-DXd (n=365)	ICC (n=367)
Median TFST, mo (95% CI)	8.2 (7.4-8.9)	5.0 (4.6-5.7)
HR (95% CI)	0.53 (0.45-0.64)	

- Median PFS by BICR (primary endpoint): 6.9 vs 4.9 mo; HR=0.63 (95% CI: 0.52-0.76); *P*<0.0001[1]
- OS data are immature with 39% of events; a trend favoring Dato-DXd was observed (HR=0.84, 95% CI: 0.62-1.14)[2]

1. Bardia A, et al. SABCS 2023. Abstract GS02-01. **2.** Bardia A, et al. ESMO 2023. Abstract LBA11.

Results From the Phase 3 TROPION-Breast01 Trial of Dato-DXd in HR+/HER2– MBC: Safety

TRAEs, n (%)	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	105 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

TRAEs (in ≥15%), n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia	39 (11)	4 (1)	149 (42)	108 (31)
Dry eye	78 (22)	2 (1)	27 (8)	0
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Alopecia	131 (36)	0	72 (21)	0

- Median treatment duration: 6.7 mo (Dato-DXd), 4.1 mo (ICC)
- Most TRAEs were grade 1/2 and manageable
- Oral mucositis/stomatitis led to discontinuation in 1 patient in the Dato-DXd group
- Most ocular events were dry eye; 1 patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD rate was low, mainly grade 1/2: 9 (3%) all grades with 2 (1%) grade ≥3 events

Bardia A, et al. ESMO 2023. Abstract LBA11.

Retrospective Study of Sequential ADC Use in Patients With HER2-Low MBC: Study Design and Patients[1,2]

Key Eligibility Criteria

- HER2-low MBC
- Received both T-DXd and SG in either order, per SOC or on clinical trial with ADC monotherapy

Retrospective Multi-Institutional Cohort Study[a]

HR+ n=56	SG→T-DXd (n=24)
	T-DXd→SG (n=32)
HR– n=28	SG→T-DXd (n=25)
	T-DXd→SG (n=3)

Study Objective

- Determine real-world efficacy (rwPFS, rwOS, time to treatment failure) of sequential ADC use in patients with HER2-low MBC

Patient Characteristics		HR+ (n=56)	HR– (n=28)
Median age at time of ADC1 (range), years		60.4 (23.0-81.7)	54.0 (37.7-79.1)
Histology, n (%)	Ductal	41 (73.2)	23 (82.1)
	Lobular	7 (12.5)	2 (7.1)
	Mixed ductal/lobular	5 (8.9)	1 (3.6)
	Other/unknown	3 (5.4)	2 (7.1)
Metastatic sites prior to ADC1, n (%)	Bone	41 (73.2)	20 (71.4)
	Liver	34 (60.7)	11 (39.3)
	Lung	20 (35.7)	14 (50.0)
	CNS	8 (14.3)	6 (21.4)
Median time from MBC diagnosis to ADC1 (range), months		44.0 (0.7-199.3)	10.2 (0.5-59.6)
Median # of LOT prior to ADC1 (range)	ET	2 (0-6)	0 (0-1)
	Chemotherapy	2 (0-7)	1 (0-4)
	Total	4 (0-10)	2 (0-5)
Prior CDK4/6i, n (%)		45 (80.4)	N/A
Prior immunotherapy, n (%)		13 (23.2)	18 (64.3)

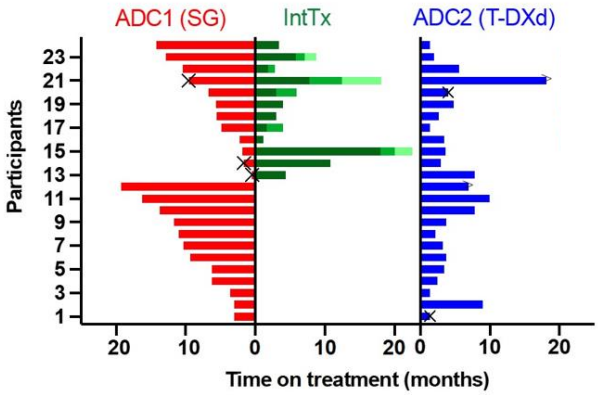
[a] This was a retrospective multi-institutional cohort study at 5 academic centers where patients were identified with HER2-low MBC who had received both T-DXd and SG sequentially, in either order, per SOC or on a clinical trial with ADC monotherapy. rwPFS and rwOS calculations were performed using the Kaplan-Meier estimator.

1. Huppert L, et al. SABCS 2023. Abstract PS08-04. **2.** Huppert L, et al. ASCO 2024. Abstract 1083.

Retrospective Study of Sequential ADC Use in Patients With HER2-Low MBC: Efficacy

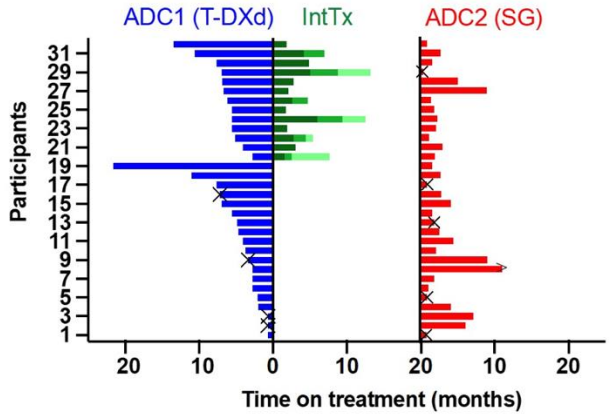
HR+/HER2-Low (n=56)[a]

SG→T-DXd (n=24)



n=24	ADC1 (SG)	ADC2 (T-DXd)
mrwPFS, mo	6.5	3.6
mrwOS, mo	20.1	7.7

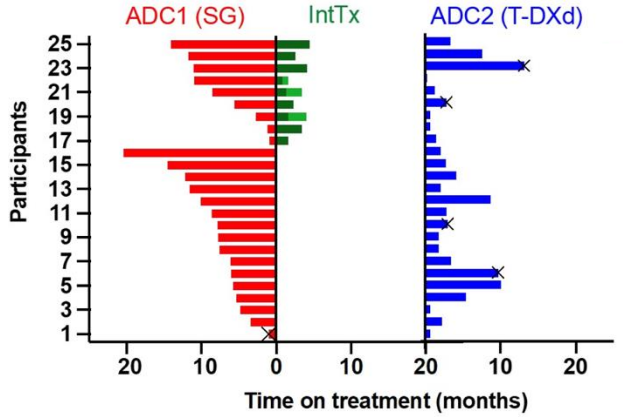
T-DXd→SG (n=32)



n=32	ADC1 (T-DXd)	ADC2 (SG)
mrwPFS, mo	5.3	2.1
mrwOS, mo	15.1	5.6

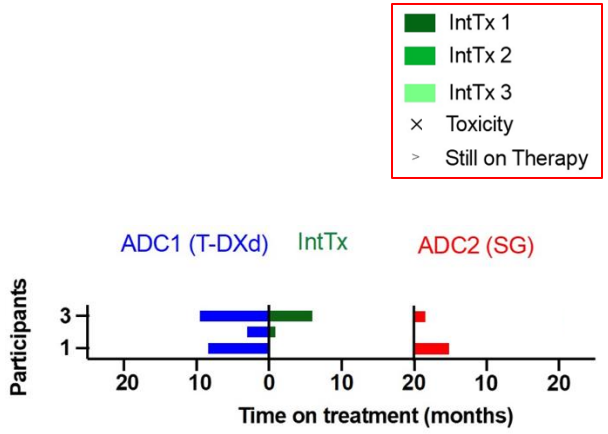
HR–/HER2-Low (n=28)[b]

SG→T-DXd (n=25)



n=25	ADC1 (SG)	ADC2 (T-DXd)
mrwPFS, mo	7.7	2.8
mrwOS, mo	16.2	6.5

T-DXd→SG (n=3)



n=3	ADC1 (T-DXd)	ADC2 (SG)
mrwPFS, mo	NE	NE
mrwOS, mo	NE	NE

- rwPFS was longer for ADC1 than ADC2 regardless of HR status and ADC sequence order; however, a subset of patients appeared to have more durable responses to ADC2
- There was no statistically significant difference in rwPFS of ADC2 in patients who received an intervening therapy between ADCs vs those who did not

IntTx, intervening chemotherapies; IntTx 1/2/3, first/second/third intervening chemotherapy.
[a] Median LOT for MBC prior to SG (range): 3.0 (0-9); median LOT for MBC prior to T-DXd (range): 4.5 (2-10).
[b] Median LOT for MBC prior to SG (range): 2.0 (0-5); median LOT for MBC prior to T-DXd (range): 3.0 (1-5).
Huppert L, et al. ASCO 2024. Abstract 1083.

HR+ HER2- Chemotherapy and Immunotherapy Updates

- Anthracycline benefit may be greatest in HR+ HER2- EBCs with high 21-gene RS or High2 70-gene signature
- Three randomized trials (KN-756, CM-7FL, I-SPY2) demonstrated improved pCR rate with neoadjuvant ICI added to wT/AC in a subset of HR+ HER2- stage II-III breast cancers
- In KN-756 pCR improvement was greater in the PD-L1+ cancers
- Based on their biological features, pts with MP-H2 HR+ HER2- cancers are most likely to benefit from chemotherapy plus ICI therapy
  - The ongoing SWOG S2206 trial is testing durvalumab in this patient population

HR+ HER2- Chemotherapy and Immunotherapy Updates

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- In KN-756 pCR improvement was greater in the PD-L1+ cancers
- Based on their biological features, pts with MP-H2 HR+ HER2- cancers are most likely to benefit from chemotherapy plus ICI therapy
  - The ongoing SWOG S2206 trial is testing durvalumab in this patient population

- T-DXd is more effective than single agent chemotherapy in HER2 low (and ultralow) 1L (PFS) and 2L (PFS and OS) HR+ HER2- MBC. Surveillance for ILD is needed
- Sacituzumab improves PFS and OS in 2L/3L HR+ HER2- MBC vs chemotherapy
- Datopotamab improves PFS in 2L/3L HR+ HER2- MBC vs chemotherapy
- Sequencing ADCs with topo1 inhibitor payloads is of limited benefit – ADCs with novel payloads and targets under development