UCSF Helen Diller Family Comprehensive Cancer Center

Novel Antibody Drug Conjugates (ADCs) for the Management of Metastatic Breast Cancer: Updates from SABCS 2022

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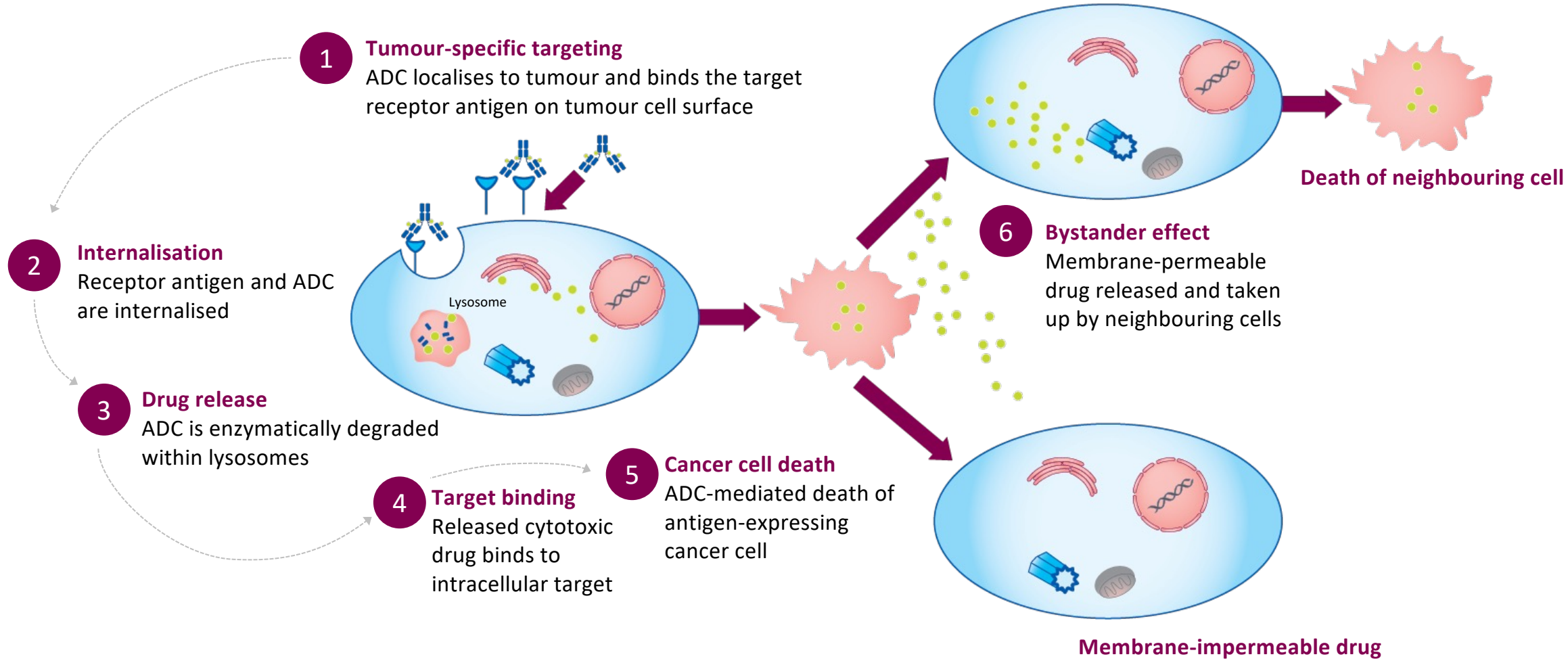
ADC technology enables tumour-specific targeting



ADC=antibody-drug conjugate

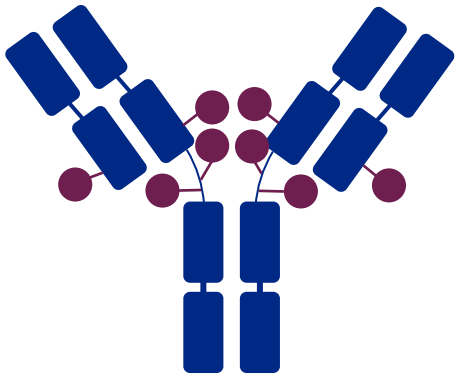
Adapted from: Trail PA, et al. *Pharmacol Ther.* 2018;181:126–142.

Topics!

- **HER2+ disease**
  - Destiny Breast-03: GS2-02
  - Destiny Breast-02: GS2-01
- **T-DXd and HER2low**
  - Review of DB-04
    - Subset analysis (PD11-01) and concordance (HER2-18, HER2-13, and HER2-15)
  - Prognosis: HER2-19 (one of many)
  - Brain mets: PD7-02
  - With immunotherapy in HER2low TNBC: PD11-08
- **Sacituzumab govitecan**
  - Ascent and TROPiCS02 review
  - TROP2 expression and outcome in TROPICS02: GS5-11
- **Datopotomab deruxtecan**
  - Tropion-PanTumor01: HR+ (PD13-08) and TN (P6-10-03)
  - With immunotherapy in TNBC: PD11-09

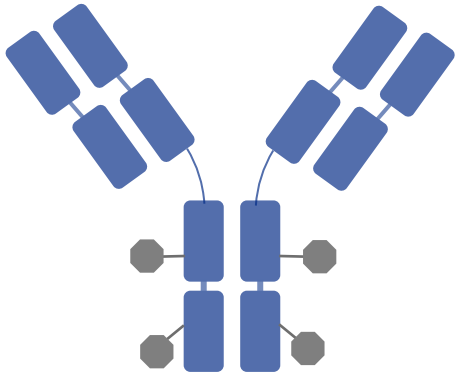
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



Destiny Breast01

Confirmed ORR: 60.9%[a]
(95% CI, 53.4%-68.0%)
Updated ORR: 61.4%
12 CRs (n=169)

CBR x 6 months: 76.1%
(95% CI, 69.3%-82.1%)

Median duration of response: 14.8 months
Updated DOR: 20.8 mo
(95% CI, 15.0 months-NE)

Median time to response: 1.6 months
(95% CI, 1.4-2.6 months)

Modi. NEJM. 2020;382:610

1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42.
4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res.* 2011;17:6437-47.

Destiny Breast-03

Updated Analysis

Demographics

- 50% HR+
- 15% baseline brain mets
- 70% visceral disease

- 61% prior pertuzumab
- Median 2 lines of prior therapy

Anti-cancer therapies in post-trial setting:

- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

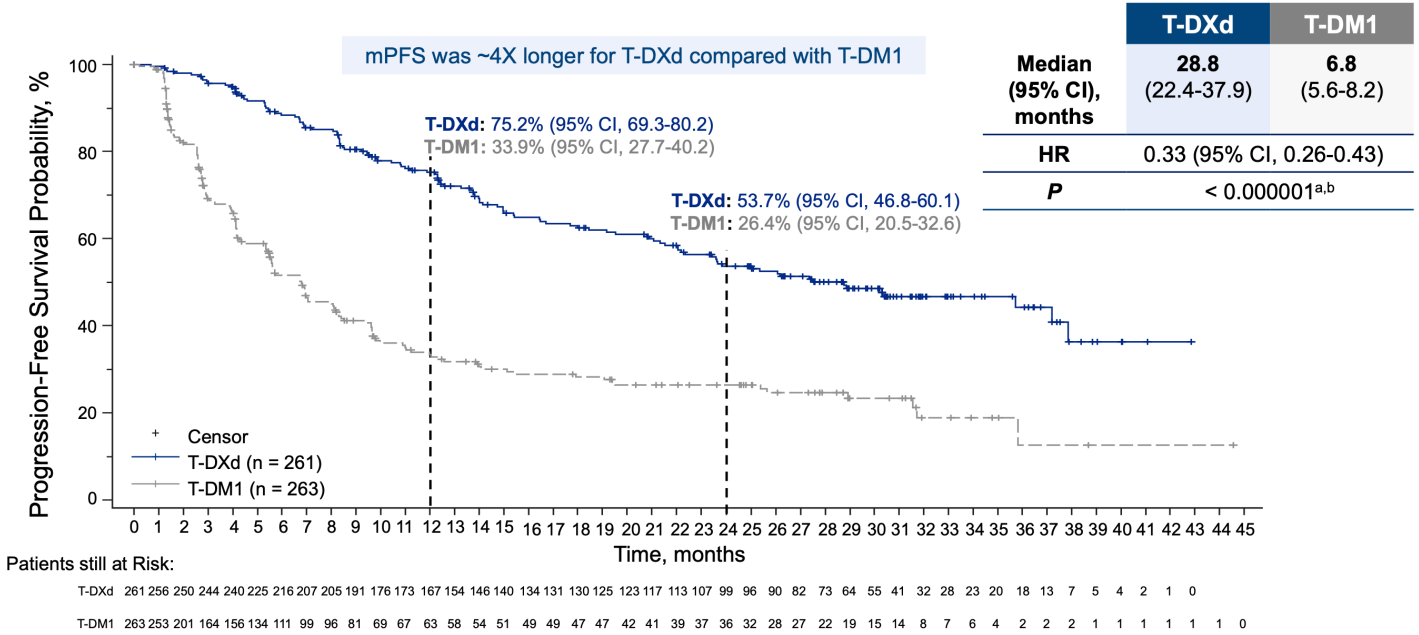
Updated AEs

- ILD: 15.2%, no grade 4 or 5

All grade AE

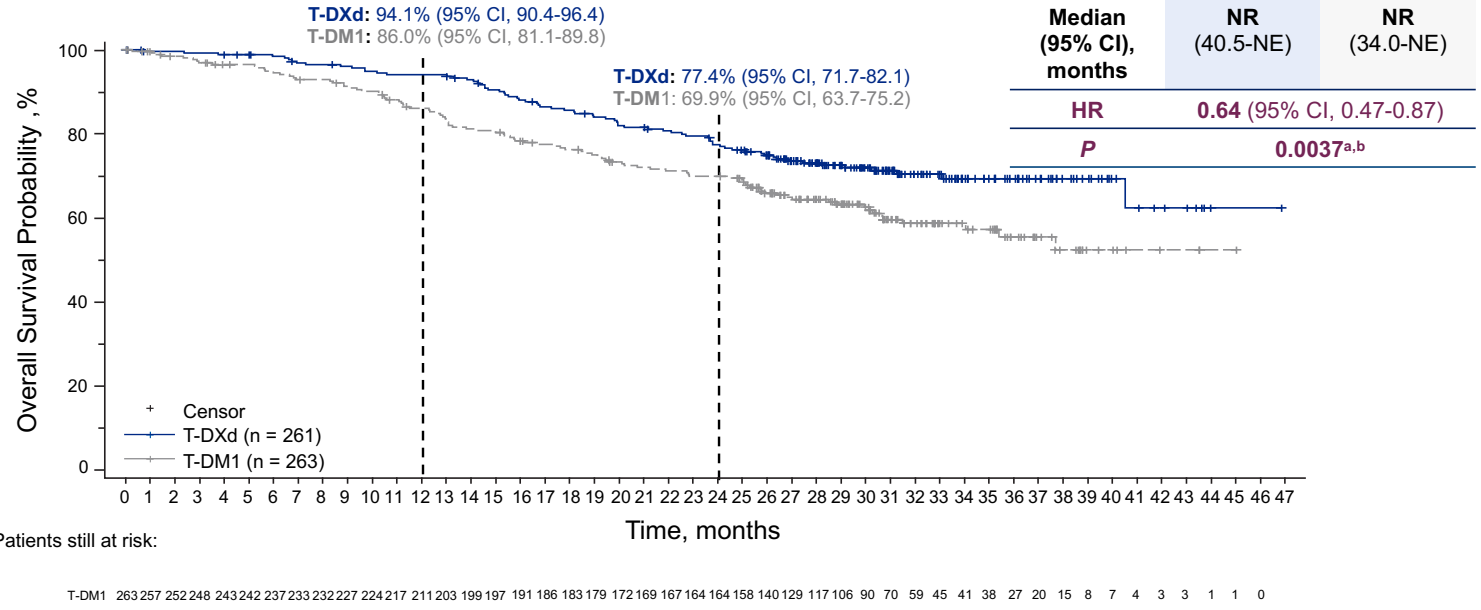
- Nausea: 77%
- Vomiting: 52%
- Alopecia 40%
- Neutropenia ≥grade 3: 16%

Updated Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
Median (95% CI), months	28.8 (22.4-37.9)	6.8 (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Key Secondary Endpoint: Overall Survival



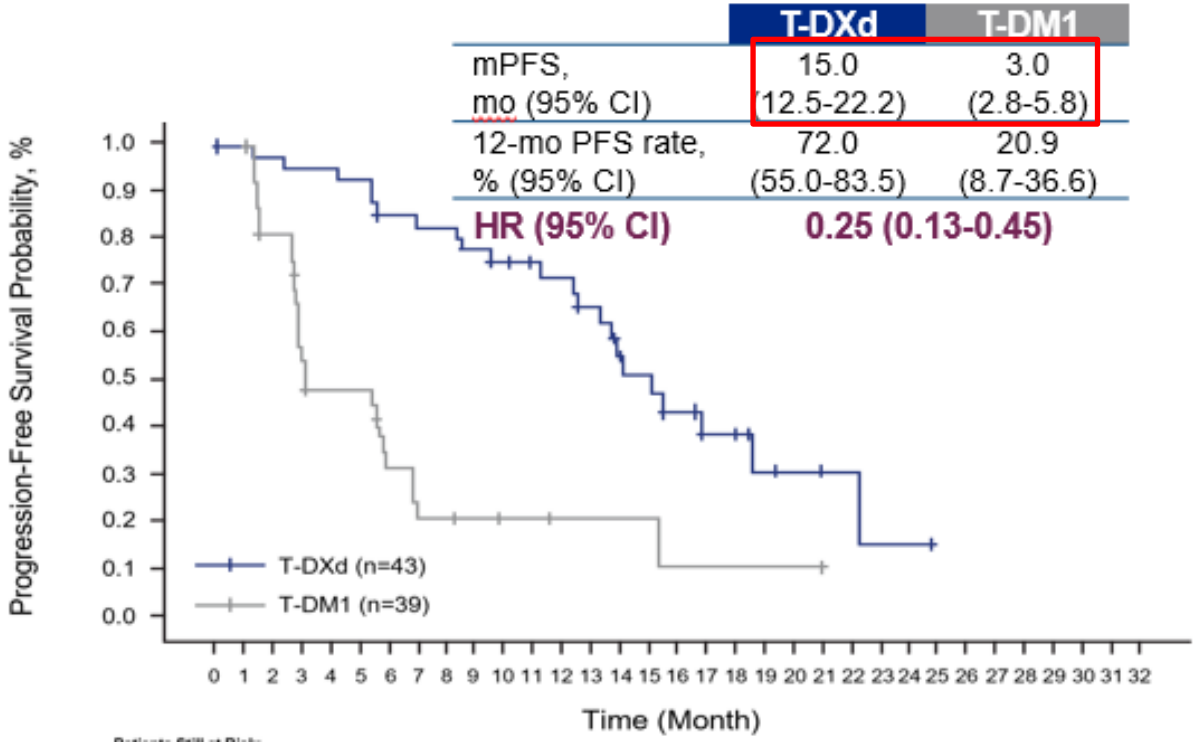
	T-DXd	T-DM1
Median (95% CI), months	NR (40.5-NE)	NR (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	

Hurvitz S et al. SABCS 2022; Lancet Oncology 2023

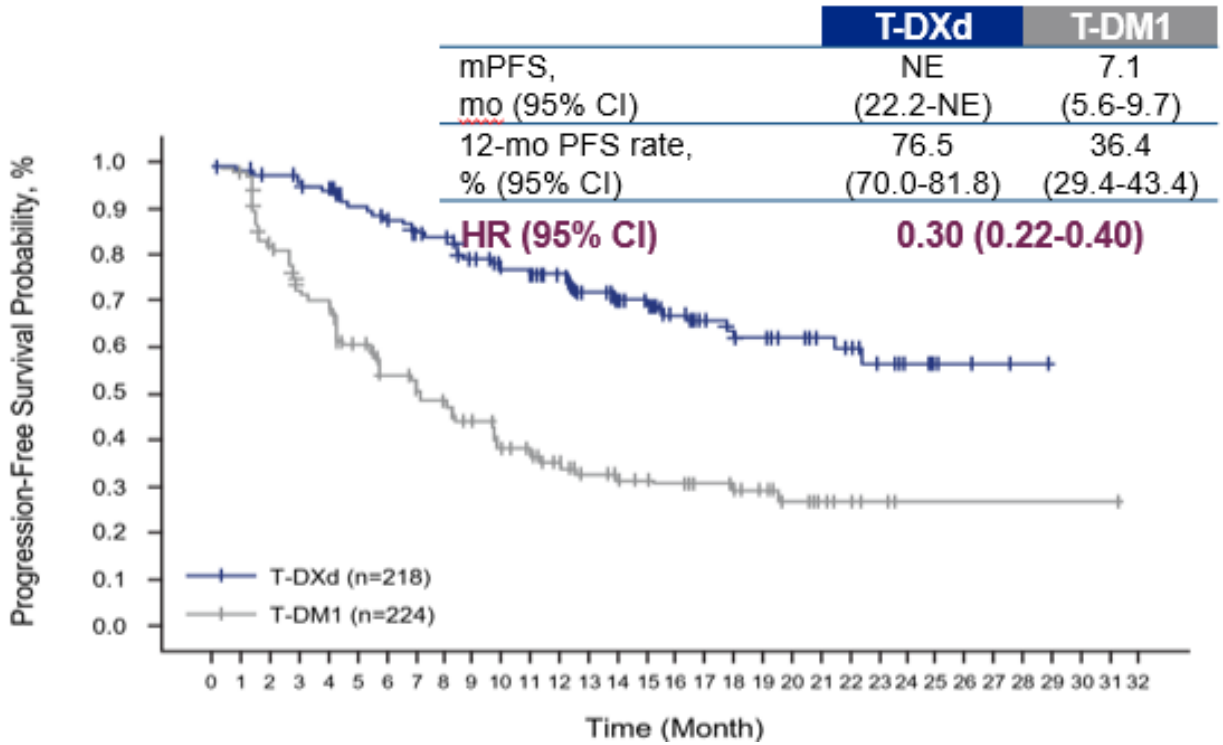
DESTINY Breast03

PFS curves for patients w/ and w/o brain mets

Brain Metastases at Baseline



No Brain Metastases at Baseline



Intracranial response rates in pts with brain mets:
63.9% with T-DXd vs 33.4% with T-DM1

History of BM, n (%)		
Yes | No	62 (23.8) | 199 (76.2)	52 (19.8) | 211 (80.2)
BM at baseline,[b] n (%)		
Yes | No	43 (16.5) | 218 (83.5)	39 (14.8) | 224 (85.2)

Hurvitz S et al. SABCS 2021;
Cortes, NEJM 2022

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

Majority with 2-3 lines of prior therapy

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

PFS

Median (95% CI), months

T-DXd	TPC
17.8 (14.3-20.8)	**6.9** (5.5-8.4)

HR (95% CI): 0.3589 (0.2840-0.4535)
P **< 0.000001**

OS

Median (95% CI), months

T-DXd	TPC
39.2 (32.7-NE)	**26.5** (21.0-NE)

HR (95% CI): 0.6575 (0.5023-0.8605)
P **=0.0021[a]**

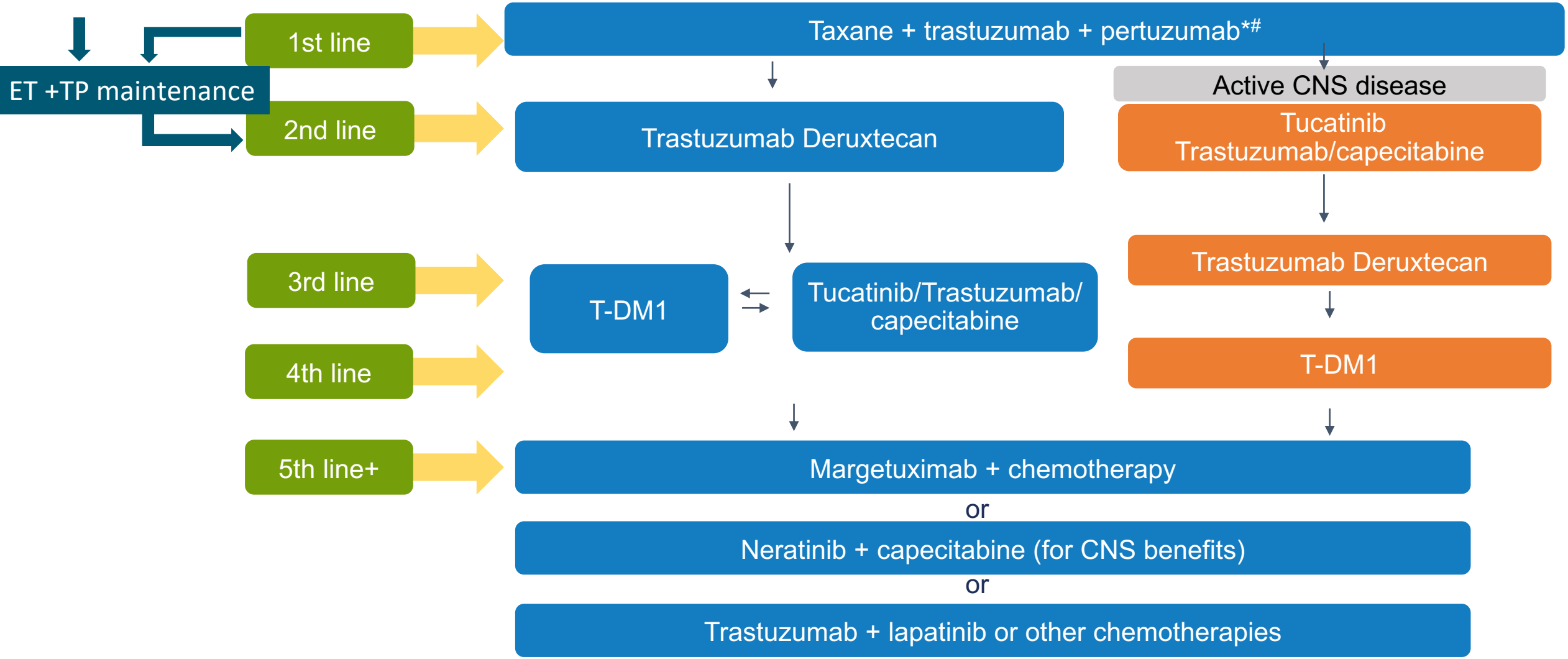
Toxicity
- ILD 10.4% (0.5% gr 5)
- Nausea 72.5%
- Alopecia 37.1%

Krop et al, SABCS 2022

Select Trials in Progress with T-DXd: HER2+

- Early stage
  - Destiny Breast05 (NSABP B-60)
    - T-DM1 vs T-DXd as post neoadjuvant therapy (n=1600)
  - Destiny Breast11
    - Neoadjuvant T-DXd x 8 v T-DXd x 4/THP vs AC/THP (n=624)
- Metastatic
  - Destiny Breast09
    - First-line: THP vs TDXd + placebo vs TDXd + pertuzumab (N=1134)
  - Destiny Breast12
    - 2 cohorts treated with T-DXd, with or without brain mets at baseline (n-500)

2023: Approach to Therapy for Metastatic HER2+ BC:

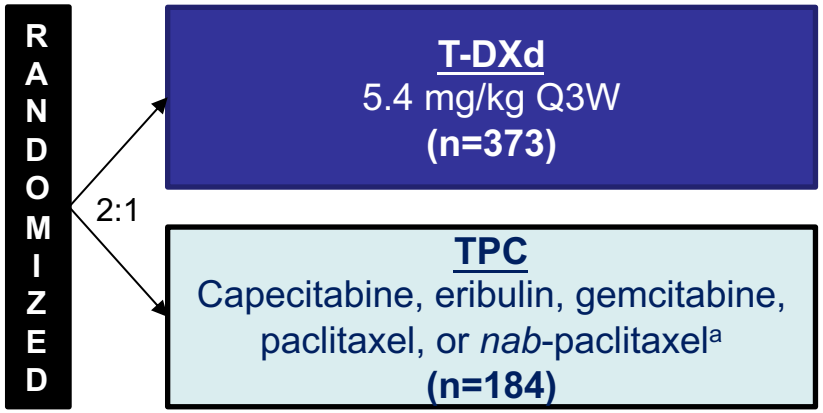


*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Study Design and Patients

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



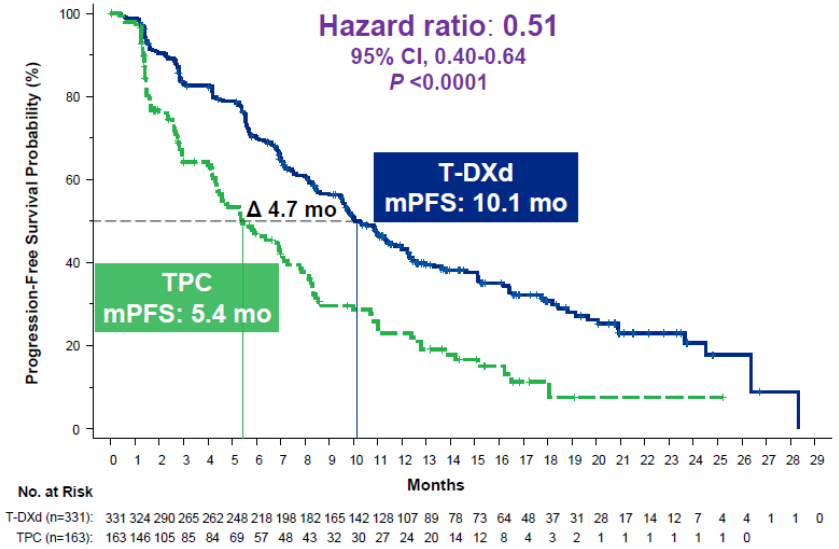
Primary endpoint: PFS by BICR (HR+)
Key secondary endpoints[b]: PFS by BICR (all patients), OS (HR+ and all patients)

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 (0.9)	0	6 (1.6)	0
Prior lines of endocrine therapy (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)

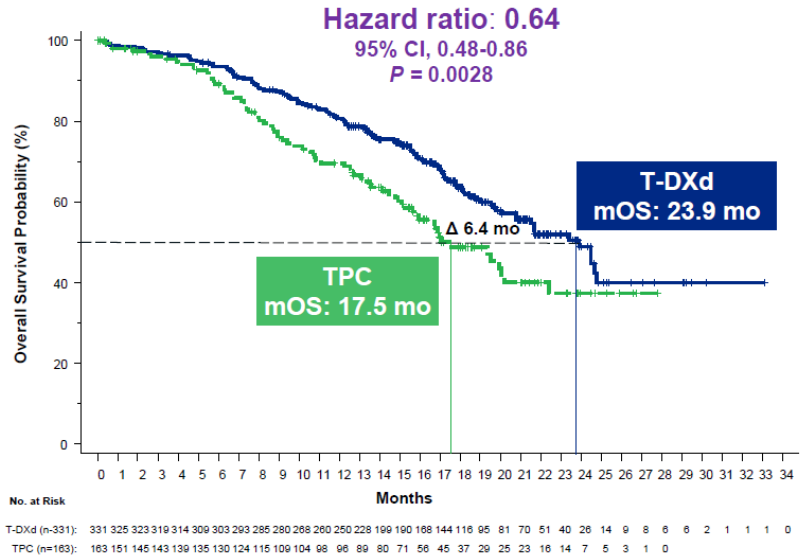
Data cutoff Jan 11, 2022.
[a] TPC was administered according to the label. [b] Other secondary endpoints included ORR (BICR and INV), DOR (BICR), PFS (INV), and safety. Efficacy in the HR- cohort was an exploratory endpoint. [c] HR status was based on data collected using interactive web/voice response system at randomization, which includes mis-stratified patients.
Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. *NEJM* 2022 Jun 5. DOI: 10.1056/NEJMoa2203690

Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Efficacy

PFS in HR+



OS in HR+



Response	HR+		HR-	
	T-DXd (n=333)	TPC (n=166)	T-DXd (n=40)	TPC (n=18)
Confirmed ORR, %	52.6	16.3	50.0	16.7
CR	3.6	0.6	2.5	5.6
PR	49.2	15.7	47.5	11.1
PD	7.8	21.1	12.5	33.3
NE	4.2	12.7	7.5	5.6
CBR, %	71.2	34.3	62.5	27.8
Median DOR, mo	10.7	6.8	8.6	4.9

PFS	HR+		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=373)	TPC (n=184)
Median PFS, months	10.1	5.4	9.9	5.1
HR (95% CI); *P* value	HR 0.51 (0.40-0.64); <0.0001		HR 0.50 (0.40-0.63); <0.0001	

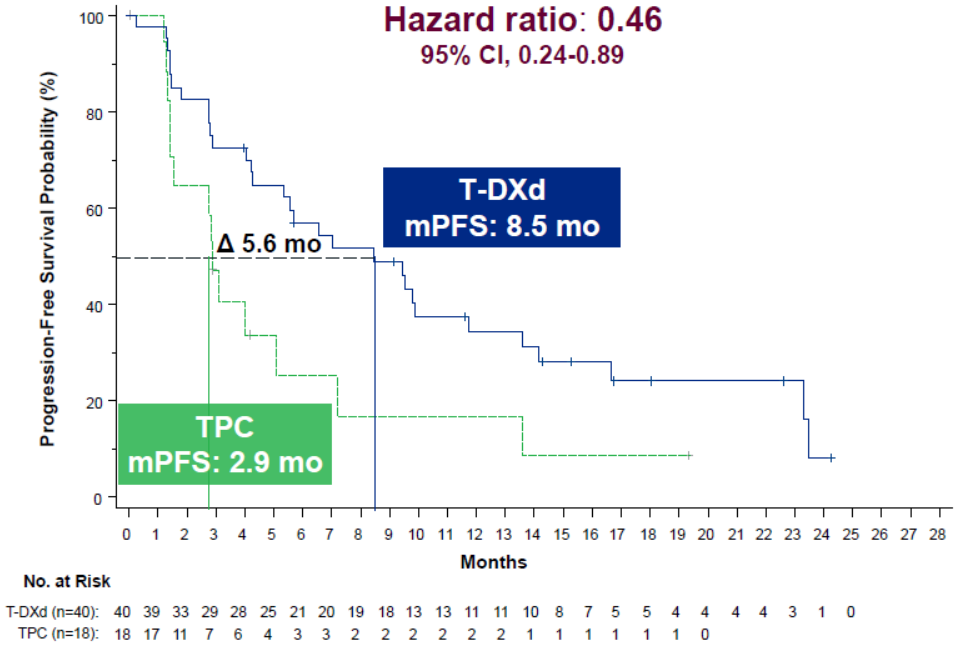
OS	HR+		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=373)	TPC (n=184)
Median OS, months	23.9	17.5	23.4	16.8
HR (95% CI); *P* value	HR 0.64 (0.48-0.86); 0.0028		HR 0.64 (0.49-0.84); 0.0010	

PFS benefit with T-DXd was similar across subgroups according to baseline characteristics and stratification factors (not shown)

Modi S, et al. ASCO 2022. Abstract LBA3, NEJM 2022

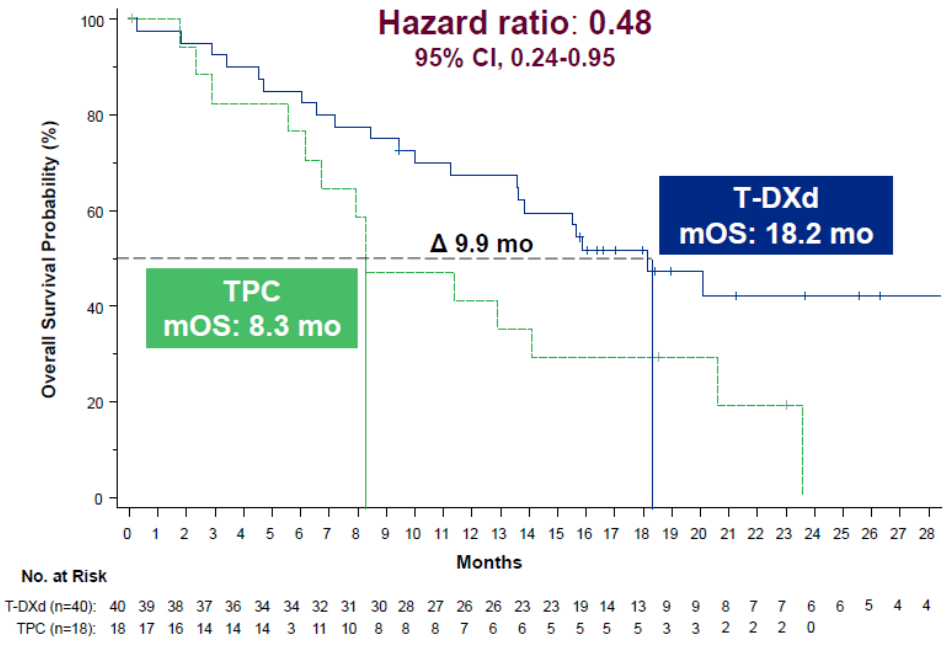
Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Exploratory Analysis in HRneg

PFS in HR-



PFS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median PFS, months	8.5	2.9
HR (95% CI)	0.46 (0.24-0.89)	

OS in HR-

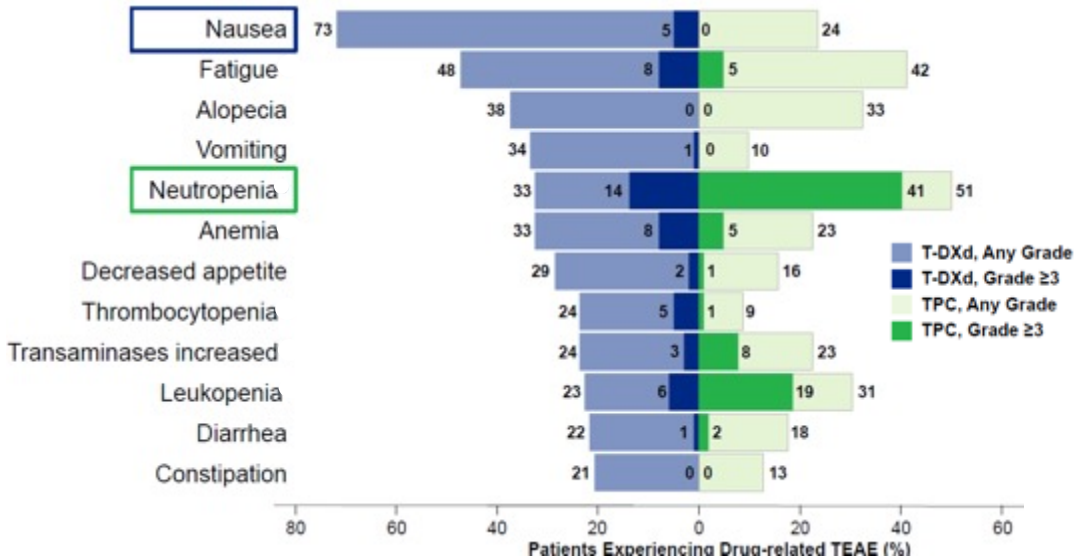


OS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median OS, months	18.2	8.3
HR (95% CI)	0.48 (0.24-0.95)	

Modi S, et al. ASCO 2022. Abstract LBA3, NEJM 2022.

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

Drug-Related TEAEs in ≥20% of Patients



Safety Summary		T-DXd (n=371)	TPC (n=172)
Total patient-years of exposure, years		283.55	63.59
Median treatment duration (range), months		8.2 (0.2-33.3)	3.5 (0.3-17.6)
TEAEs		369 (99)	169 (98)
Grade ≥3		195 (53)	116 (67)
Serious TEAEs, n (%)		103 (28)	43 (25)
TEAEs associated with, n (%)	Dose discontinuations	60 (16)	14 (8)
	Dose interruptions	143 (39)	72 (42)
	Dose reductions	84 (23)	66 (38)
	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 TEAEs associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAEs associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue
  - TPC: 14.0%, neutropenia
- Total on-treatment deaths[a]
  - T-DXd: 3.8%
  - TPC: 4.7%

[a]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.

Modi S, et al. ASCO 2022. Abstract LBA3, NEJM 2022

Subset Analysis from DB-04

Figure 2. PFS Subgroup Analyses From DESTINY-Breast04

Subgroup		No. of Events/ No. of Patients T-DXd	No. of Events/ No. of Patients TPC	Median PFS, mo (95% CI)[a] T-DXd	Median PFS, mo (95% CI)[a] TPC	Hazard Ratio (95% CI)[b]
Prior CDK4/6i use (HR+ cohort)	Yes (n = 348)	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.74)
	No (n = 143)	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
Disease burden[c]	Low (n = 235)	88/150	60/85	11.4 (9.8-16.2)	5.1 (3.1-7.3)	0.41 (0.30-0.58)
	High (n = 322)	155/223	67/99	9.5 (7.5-10.1)	4.8 (2.9-6.9)	0.58 (0.43-0.78)
Rapid progression[d]	Yes (n = 22)	9/14	6/8	8.2 (1.4-NE)	2.2 (0.6-NE)	0.38 (0.12-1.21)
	No (n = 535)	234/359	121/176	9.9 (9.0-11.3)	5.3 (4.2-6.9)	0.51 (0.41-0.64)
HER2 IHC status	IHC 1+ (n = 321)	134/214	75/107	10.0 (8.6-12.3)	4.8 (3.0-7.0)	0.48 (0.36-0.63)
	IHC 2+/ISH– (n = 236)	109/159	52/77	9.9 (8.0-11.5)	5.1 (2.9-7.1)	0.55 (0.39-0.76)
Prior lines of chemotherapy	1 (n = 321)	141/221	68/100	10.1 (8.4-12.2)	6.4 (4.3-7.8)	0.52 (0.39-0.70)
	2 (n = 234)	101/151	59/83	9.7 (8.1-11.4)	4.2 (3.0-5.4)	0.49 (0.35-0.68)
Age	<65 years (n = 426)	191/290	93/136	9.8 (8.4-11.1)	4.6 (2.9-5.9)	0.47 (0.37-0.61)
	≥65 years (n = 131)	52/83	34/48	11.4 (8.3-13.3)	6.2 (4.3-10.8)	0.57 (0.36-0.89)
Baseline CNS metastases	Yes (n = 32)	18/24	6/8	8.1 (4.0-11.3)	4.8 (0.6-11.0)	0.71 (0.28-1.80)
	No (n = 525)	225/349	121/176	10.1 (9.5-11.5)	5.1 (4.2-6.8)	0.49 (0.39-0.62)
Prior anthracycline treatment[e]	Yes (n = 342)	155/239	81/113	9.8 (8.5-11.7)	5.3 (3.0-7.9)	0.53 (0.40-0.70)
	No (n = 205)	88/134	46/71	10.0 (7.2-12.5)	4.6 (3.0-6.8)	0.46 (0.32-0.66)

Figure 4. ORR Subgroup Analyses From DESTINY-Breast04

Subgroup	Patients With Confirmed CR+PR, n/N T-DXd (n = 373)	Patients With Confirmed CR+PR, n/N TPC (n = 184)	Difference of T-DXd vs TPC, % (95% CI)[a]
Prior CDK4/6i use (HR+ cohort)			
Yes	118/233	15/115	37.6 (28.1-47.1)
No	56/96	12/47	32.8 (15.3-50.3)
Disease burden[b]			
Low	81/150	13/85	38.7 (26.7-50.7)
High	114/223	17/99	33.9 (23.3-44.6)
Rapid progression[c]			
Yes[d]	7/14	0/8	50.0 (14.0-86.0)
No	188/359	30/176	35.3 (27.3-43.3)
HER2 IHC status			
IHC 1+	105/214	18/107	32.2 (21.8-42.7)
IHC 2+/ISH–	90/159	12/77	41.0 (28.9-53.2)
Prior lines of chemotherapy			
1	113/221	19/100	32.1 (21.3-43.0)
2	81/151	11/83	40.4 (28.7-52.1)
Age			
<65 years	156/290	20/136	39.1 (30.3-47.9)
≥65 years	39/83	10/48	26.2 (8.8-43.5)
Baseline CNS metastases			
Yes	11/20	2/8	-
No	184/353	28/176	36.2 (28.3-44.1)
Prior anthracycline treatment[e]			
Yes	124/239	21/113	33.3 (23.1-43.5)
No	71/134	9/71	40.3 (27.8-52.8)

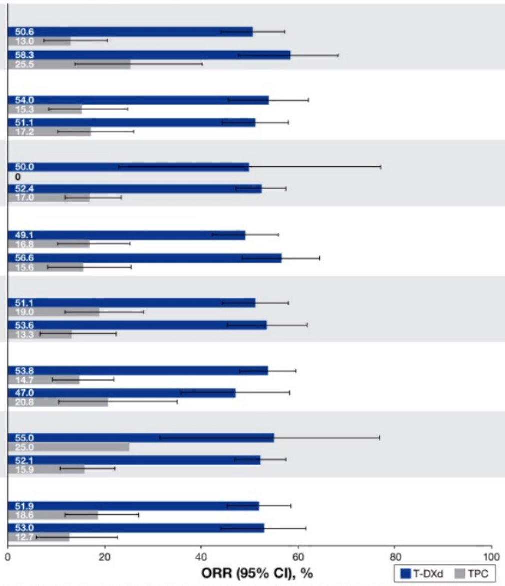
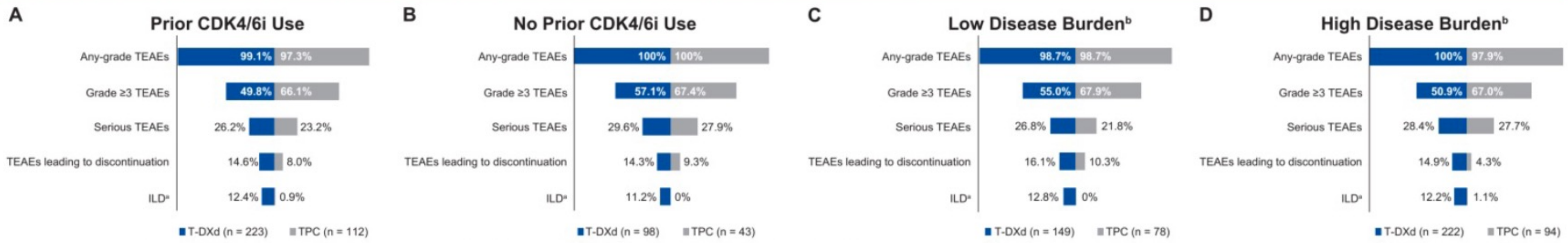


Figure 5. Safety by Prior CDK4/6i Use and Disease Burden in Patients With HER2-Low Breast Cancer



[a]Adjudicated ILD events per the ILD Adjudication Committee. [b]Disease burden was defined by the number of metastatic disease sites at baseline (low = 0-2; high = 3+). At baseline, 69.8% of patients had liver metastases.

Modi et al, SABCS 2022; PD 11-01

Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Safety (cont'd) and Summary

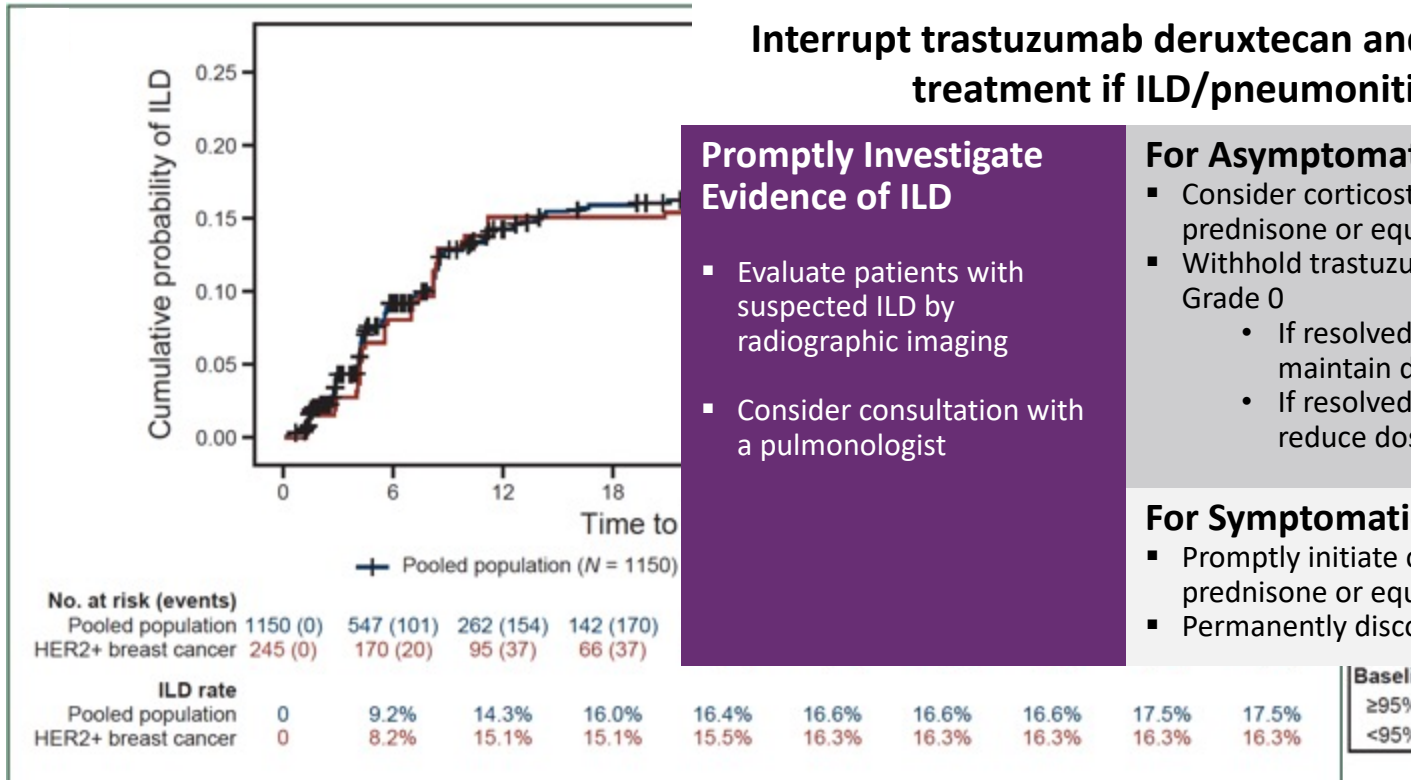
AEs of Special Interest, n (%)			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Adjudicated as drug-related ILD/pneumonitis[a]		**T-DXd (n=371)**	**13 (3.5)**	**24 (6.5)**	**5 (1.3)**	**0**	**3 (0.8)**	**45 (12.1)**
		TPC (n=172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction[b]	Ejection fraction 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

- T-DXd treatment resulted in statistically significant and clinically meaningful improvements in PFS and OS vs TPC in patients with HER2-low MBC
- Benefit was observed across all stratification subgroups, including according to HER2-low (IHC 1+ or IHC 2+/ISH-) and prior CDK4/6i
- The safety profile of T-DXd was consistent with previous studies
- These results support HER2-low MBC, historically considered HER2-, as a new targetable patient population

[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in T-DXd arm. 1 patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

Modi S, et al. ASCO 2022. Abstract LBA3; NEJM 2022.

Pooled Analysis of ILD/Pneumonitis in 9 Trastuzumab deruxtecan Monotherapy Studies



Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

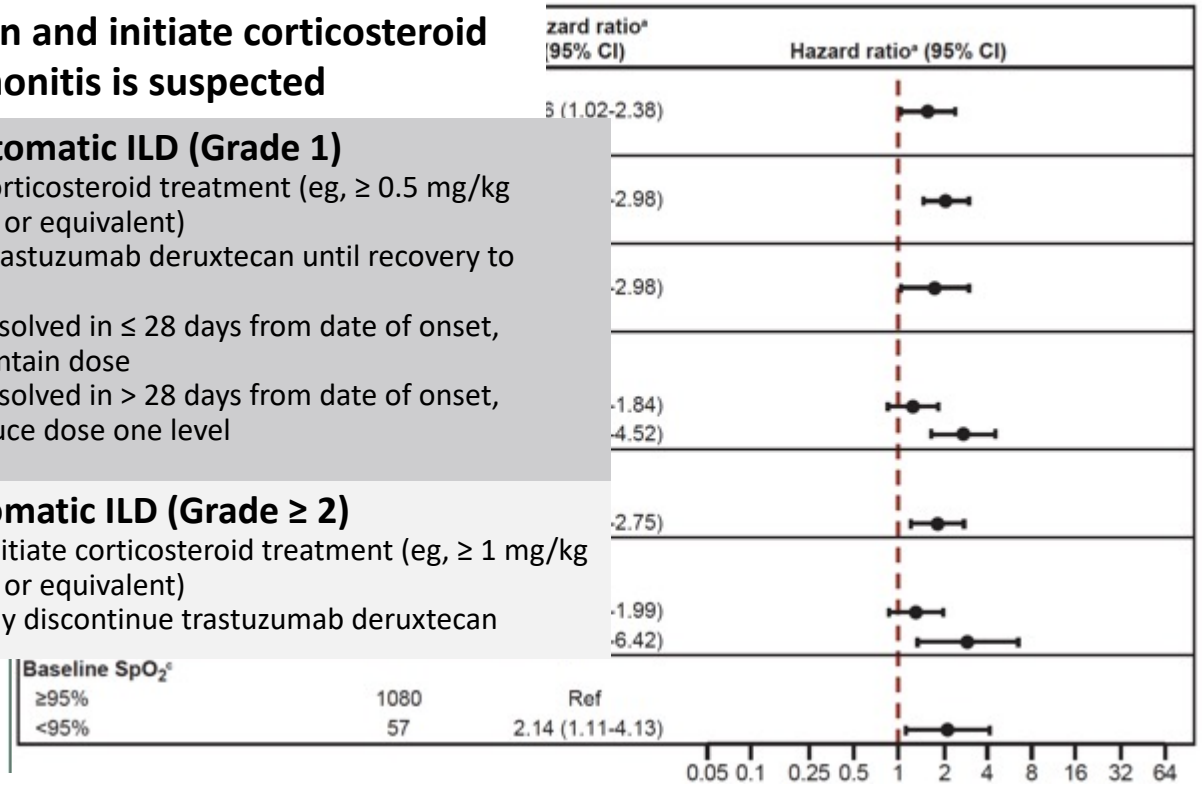
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan



- 1150 pts (44.3% breast cancer) with a median treatment duration 5.8 mo (0.7-56.3)
- Overall incidence: 15.4% (grade 5: 2.2%); grade 1-2: 77.4%
- 87% had their first event within 12 months of their first dose

Powell et al, ESMO Open 2022

DESTINY-BREAST04: Concordance Between Historical and Central HER2 IHC Results for HER2 Low

HER2 Status by Central Testing, n	HER2 Status by Historical Result, n				Total
	IHC 0	IHC 1+	IHC 2+/ISH−	IHC 2+/ISH+	
IHC 0	18	157	51	2	228
IHC 1+	18	**344**	**126**	3	491
IHC 2+/ISH−	5	**122**	**231**	0	358
IHC 2+/ISH+	0	9	11	1	21
IHC 3+	1	2	7	0	10
Total	42	634	426	6	1108

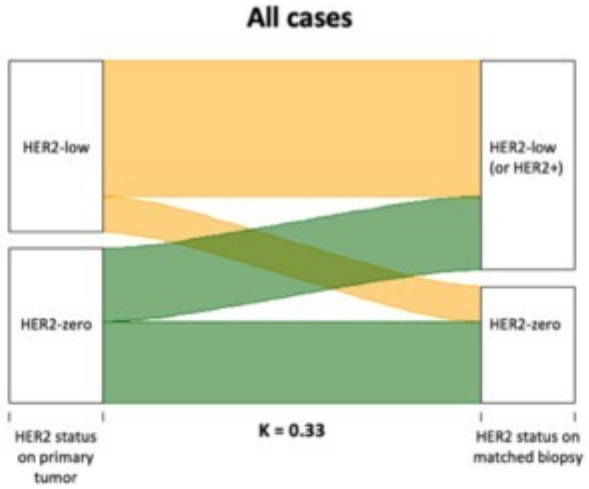
- **78% (823/1060) of samples designated as HER2-low by prior historical (local) result were confirmed as HER2-low by central testing using the PATHWAY HER2 4B5 assay** (and INFORM HER2 Dual ISH DNA Probe Cocktail when applicable)
- **Among the 22% (237/1060) of discordant samples**, **208/237 (88%) were centrally scored as IHC 0, and 29/237 (12%) were scored as IHC 2+/ISH+ or IHC 3+**
- Scoring agreement of HER2 tumor samples varied by region and collection date
- **Median PFS was identical regardless of whether samples used for HER2 testing were primary (35%) or metastases (35%), and regardless of time from tissue collection until study entry (31% 2014-2018)**

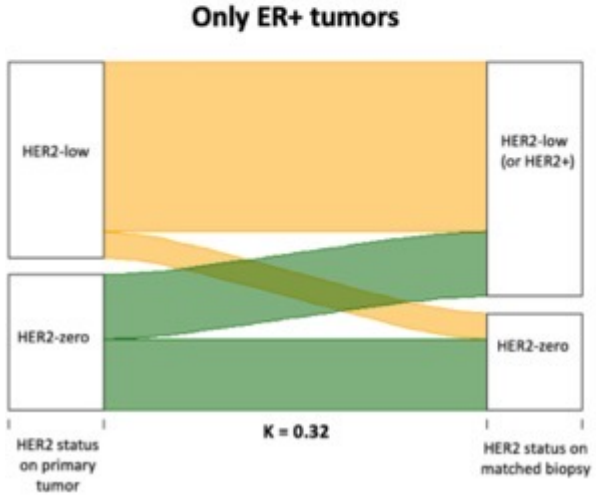
[a]Table includes some samples submitted for central testing that were not HER2-low by historical assessment. Subjects confirmed to have prior HER2 positive results or those without a history of HER2-low tumors were excluded from additional screening procedures. In few instances, prior history of local HER2-low status was confirmed based on a sample different than the one submitted for central testing.

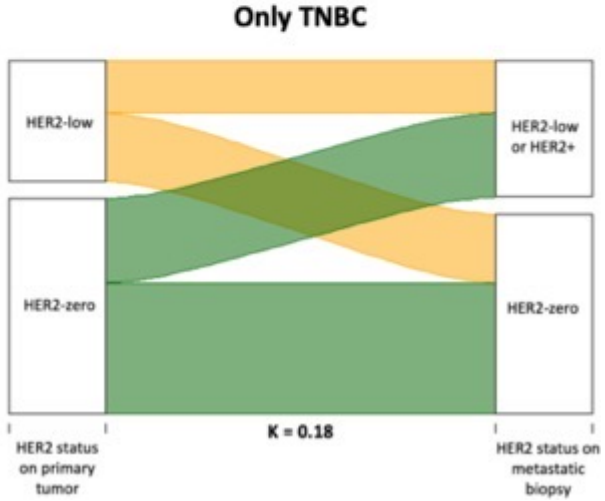
Prat A et al. SABCS 2022; Poster HER2-18.

HER2-Low Expression Is Dynamic
Expression May Change from Early- to Late-Stage Disease

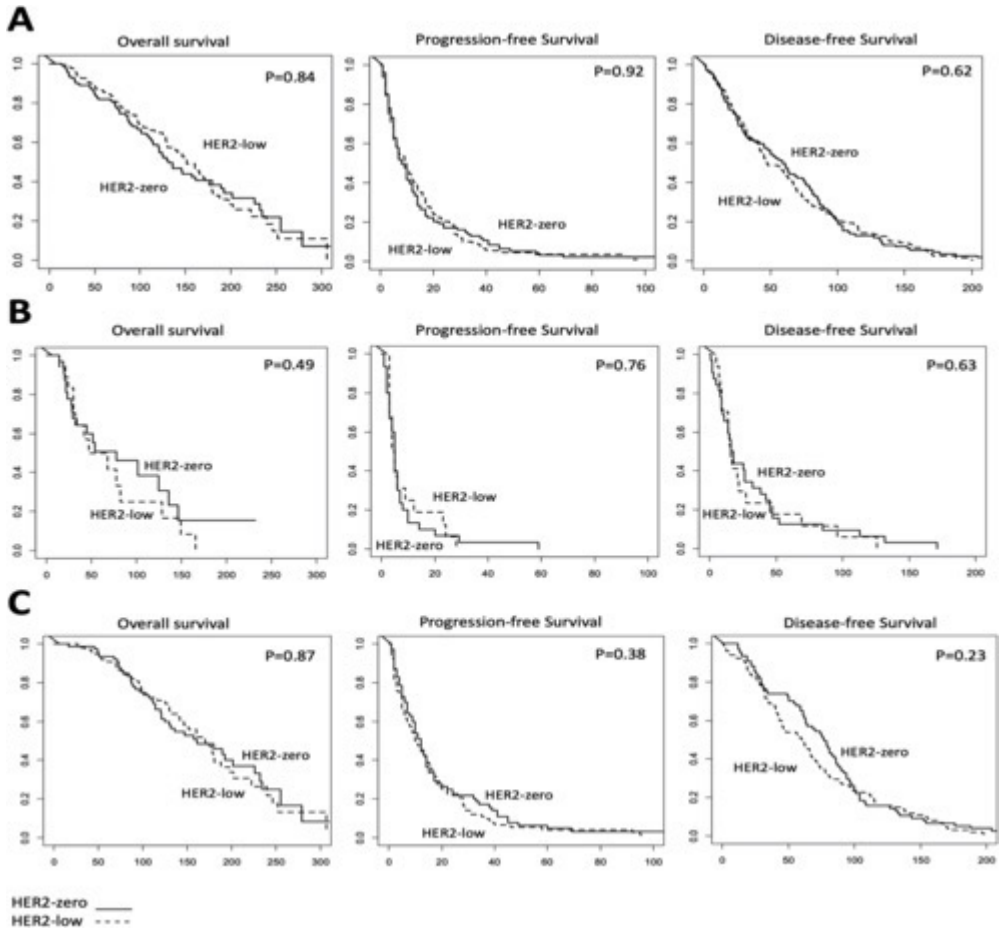
N-232







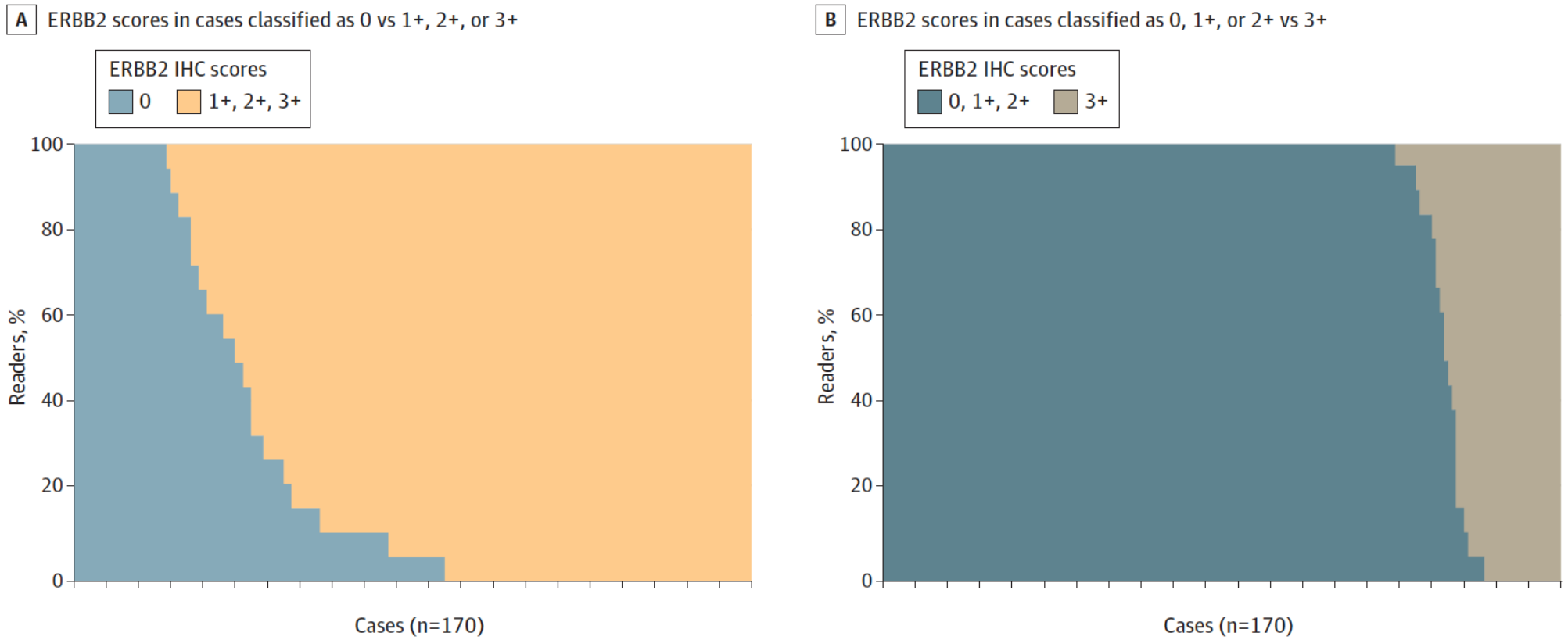
No difference in survival in HER2 low vs 0 primary tumors



Tarantino P, et al. *Eur J Cancer*. 2022;63:35-43.

How Concordant is Testing?

Figure. Distribution of ERBB2 Immunohistochemistry (IHC) Scores in 170 Cases Read by 18 Pathologists/Readers of Whole Tissue Sections in the Yale Cohort



- 18 pathologists read scanned slides from a selected set of breast cancer biopsies (170) using a 4-point scale
  - 26% concordance between 0 vs 1+
  - 58% concordance between 2+ vs 3+.

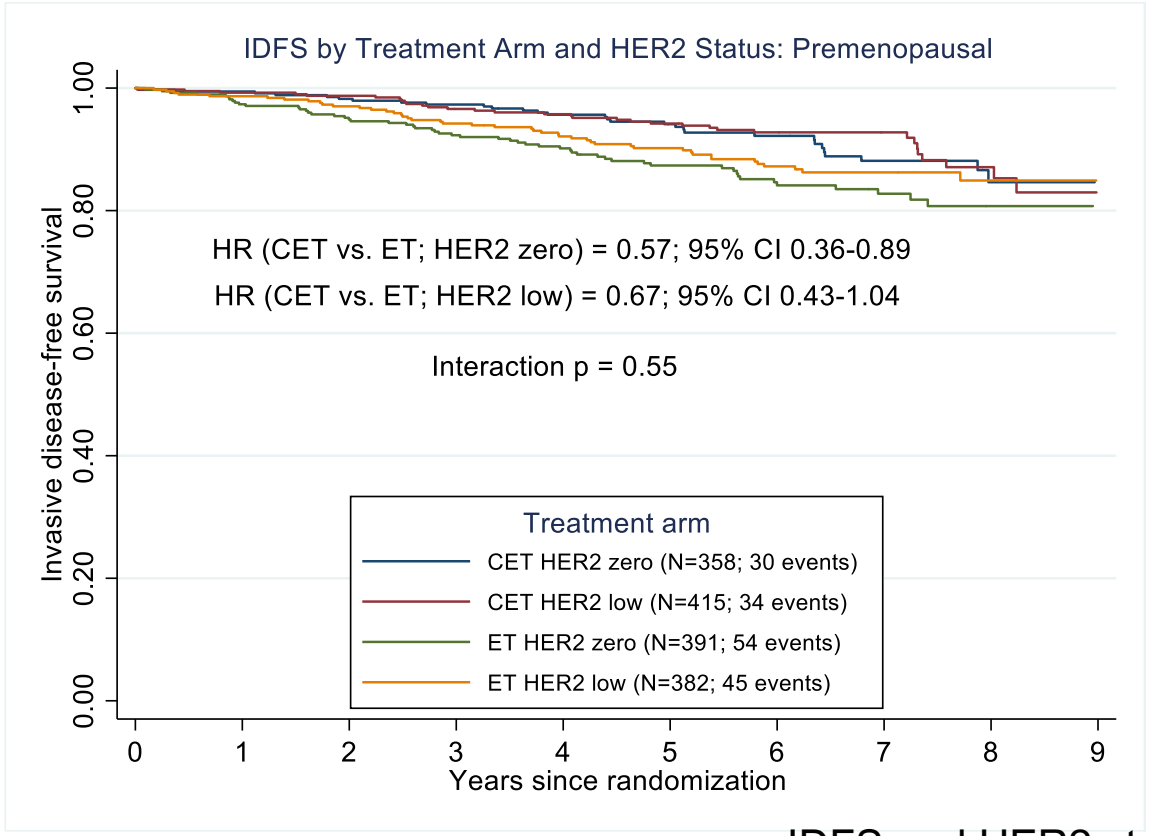
Fernandez et al, JAMA Oncol 2022

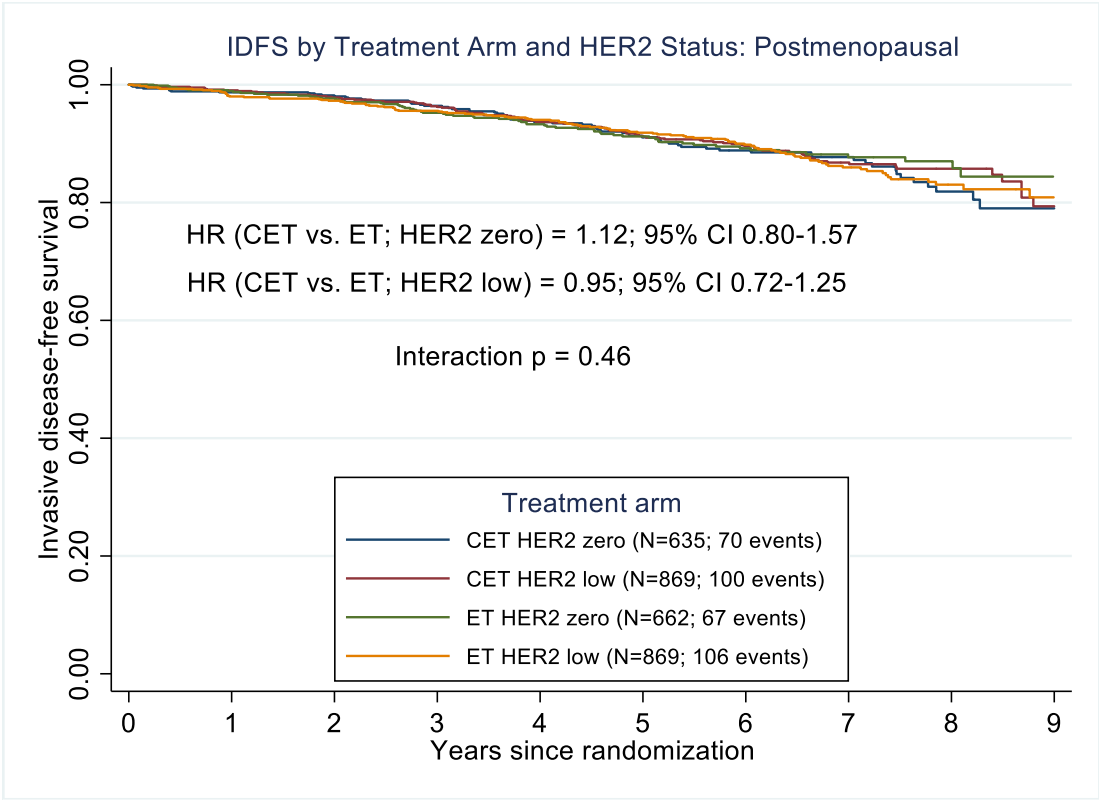
SABCS HER2-low Abstracts: Pathology/Scoring

- **Viale et al (HER2-15)**
  - Overall % agreement between rescored and historical HER2 scores was 81.2%; agreement was numerically greater for HER2-low than HER2 IHC 0 (n=781)

- **Ruschoff et al (HER2-13)**
  - Overall score concordance for HER2-low was >80% overall rater agreement benchmark for both 4B5 and Hercept Test and higher than previously reported (Fernandez et al. JAMA Oncol 2022)
  - These data demonstrate pathologists' ability to achieve an acceptable level of accuracy for identifying HER2-low patients (n=80 pathologists)

No Difference in Outcome for HER2 0 vs HER2 Low in RxPONDER





IDFS and HER2 status, by menopausal status

- Left: Among pre-menopausal women adjusting for RS, CET led to a numerical improvement in IDFS among both HER2 low (HR=0.67; 95% CI 0.43-1.04) and HER2 zero subgroups (HR=0.57; 95% CI 0.36-0.89) (interaction p=0.55)
- Right: Among post-menopausal women, there was no difference in IDFS between CET vs ET among HER2 low (HR=0.98; 95% CI 0.75-1.29) and HER2 zero (HR=1.12; 95% CI 0.80-1.56) subgroups (interaction p=0.57)

Spring L et al, SABCS 2022; HER2-19

Testing Trastuzumab Deruxtecan in HER2 'Ultralow' DESTINY-Breast06

Key differences with DB-04:

- Includes IHC0 (ultralow)
- Larger (n=850)
- Restricted to HR+ disease
- Chemo-naïve patients

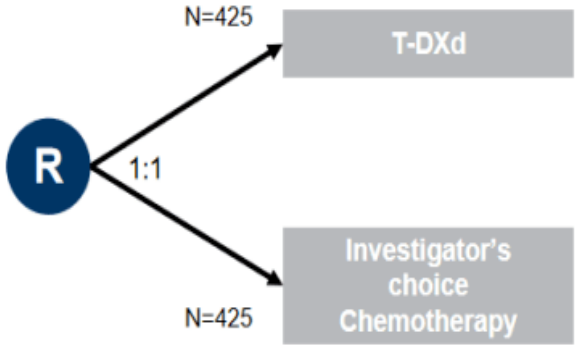
POPULATION

- Advanced/metastatic breast cancer after progression on 2 prior ETs
- HR+
- HER2 IHC 0+ or 1+ or 2+ (determined based on central IHC assessment of archival tissue collected at time of diagnosis of first metastatic disease or later)

Stratification factors:

- Prior CDK4/6 inhibitor
- HER2 IHC 2+ v. 1+ v. 0+
- Prior taxane in non-metastatic setting

TREATMENT



- Chemotherapy options: capecitabine, paclitaxel, nAb-paclitaxel
- Treatment continues until progressive disease or toxicity
- HER2 IHC 0+ defined by any IHC staining up to 10% of tumor cells
- Futility analysis in HER2 IHC 0+ cohort will be done

ENDPOINTS

Primary:

- PFS (BICR) in HER2 IHC 1+/2+ population

Key Secondary:

- OS in HER2 IHC 1+/2+ population
- PFS in ITT population
- OS in ITT population

Secondary:

- PFS (investigator assessed) in HER2 IHC 1+/2+
- ORR and DOR of HER2 IHC 1+/2+ and ITT populations
- Safety and tolerability
- Symptoms, functioning and HRQoL

Exploratory:

- PRO
- Pharmacodynamic biomarkers

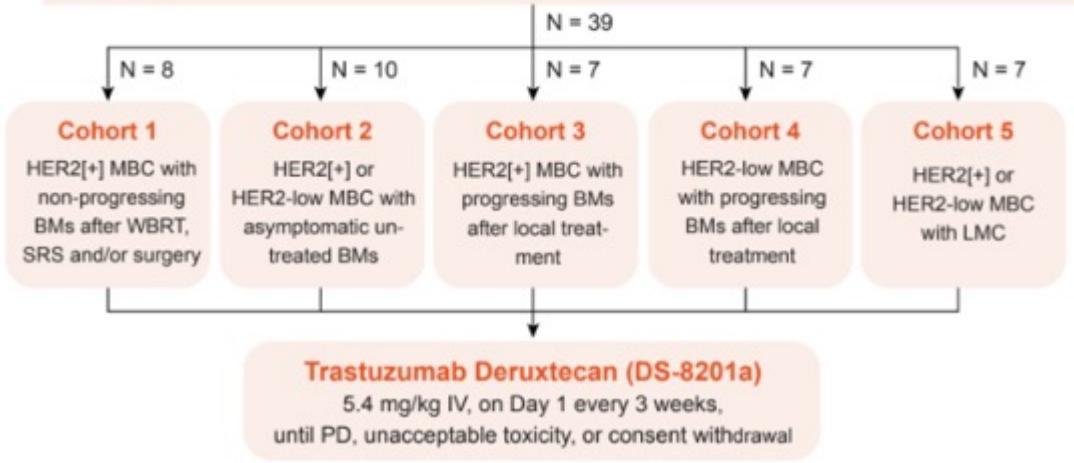
DEBBRAH: T-DXd for HER2-low Brain Mets

STUDY DESIGN

Figure 1. Study Design of DEBBRAH (NCT04420598)

Key elegibility criteria

- Female or male pts aged ≥18 years
- HER2[+] or HER2-low ABC pts with stable, progressing, or untreated BMs and/or LMC
- ECOG PS 0 or 1 (0–2 for cohort 5)
- Pts with HER2[+] ABC: prior taxane-based regimen and ≥1 prior line of HER2-targeted therapy in the metastatic setting
- Pts with HER2-low ABC and:
  - HR[-]: ≥1 prior regimen of CT in the metastatic setting
  - HR[+]: 1 prior line of ET and ≥1 prior regimen of CT in the metastatic setting
- Cohorts 2, 3, 4: Measurable brain disease on T1-weighted, gadolinium-enhanced MRI
- Cohort 5: LMC with positive CSF cytology results



Abbreviations: ABC, advanced breast cancer; BMs, brain metastases; CSF, Cerebrospinal fluid; CT, chemotherapy; ECOG PS, Eastern

Table 2. Best Intracranial Response (RANO-BM) in HER2-Low Patients

Tumor response, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
Overall Response, n (%)			
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	4 (66.7%)	2 (33.3%)	6 (50.0%)
SD ≥ 24w	1 (16.7%)	1 (16.7%)	2 (16.7%)
SD < 24w	1 (16.7%)	3 (50.0%)	4 (33.3%)
PD	0 (0.0%)	0 (0.0%)	0 (0.0%)
ORR-IC, n (%)	4 (66.7%)	2 (33.3%)	6 (50.0%)
CBR-IC, n (%)	5 (83.3%)	3 (50.0%)	8 (66.7%)
DoR-IC, Median (Min; Max)	3.6 (2.0; 7.1)	7.8 (7.3; 8.3)	5.8 (2.0; 8.3)

- **Abbreviations:** CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. ORR: CR + PR; CBR: CR + PR + SD ≥ 24w; w, weeks.
- n (%), number of patients (percentage based on N); N, Number of patients in the FAS population

Table 3. Overall Response in HER2-Low Patients

Tumor response, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
ORR, n (%)	3 (50.0%)	2 (33.3%)	5 (41.7%)
CBR, n (%)	3 (50.0%)	3 (50.0%)	6 (50.0%)
DoR, Median (Min; Max)	4.5 (3.5; 7.1)	5.8 (5.5; 6.1)	5.5 (3.5; 7.1)
PFS	5.67 months (95% CI:4.7-NA) (Events: 9/12)		

Perez-Garcia JM et al, SABCS 2022; PD7-02

Proposed Mechanism of ADC + IO Synergy

1: ADCs bind to the cancer cell

2: The ADC is internalized into the cancer cell, causing immunogenic cell death

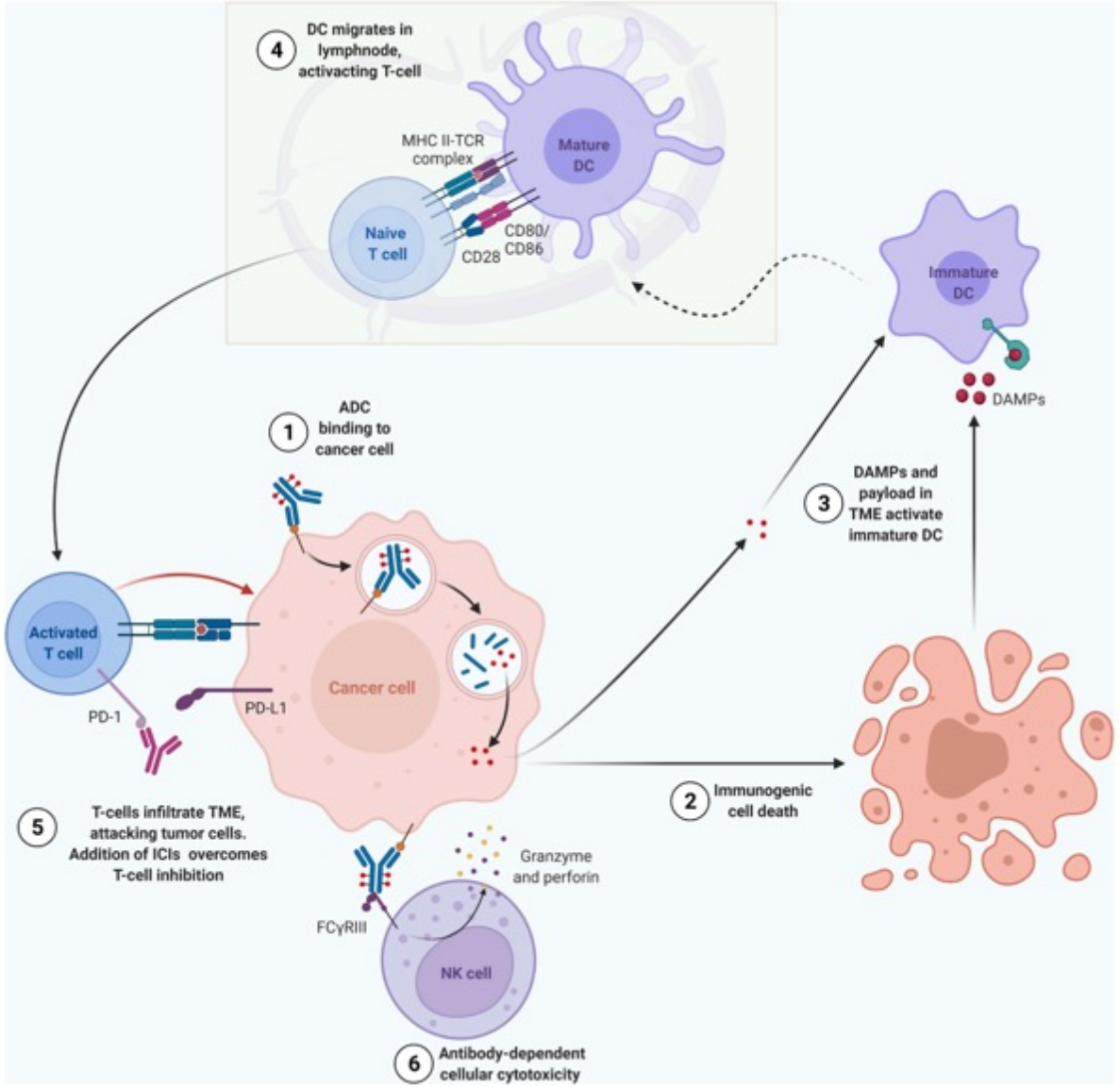
3: Damage-associated molecular patterns (DAMPs) are released in the tumor microenvironment (TME), stimulating the maturation of dendritic cells

4: Dendritic cells (DCs) migrate into the lymph nodes, activating T cells

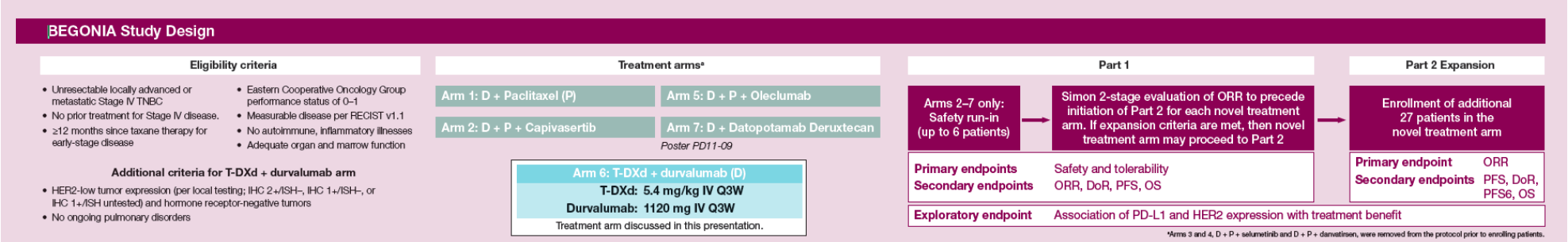
5: Activated T cells infiltrate the TME, attacking tumor cells. The addition of immune checkpoint inhibitors (ICIs) overcomes T cell inhibition

6: ADCs activate the immune system through antibody-dependent cellular cytotoxicity

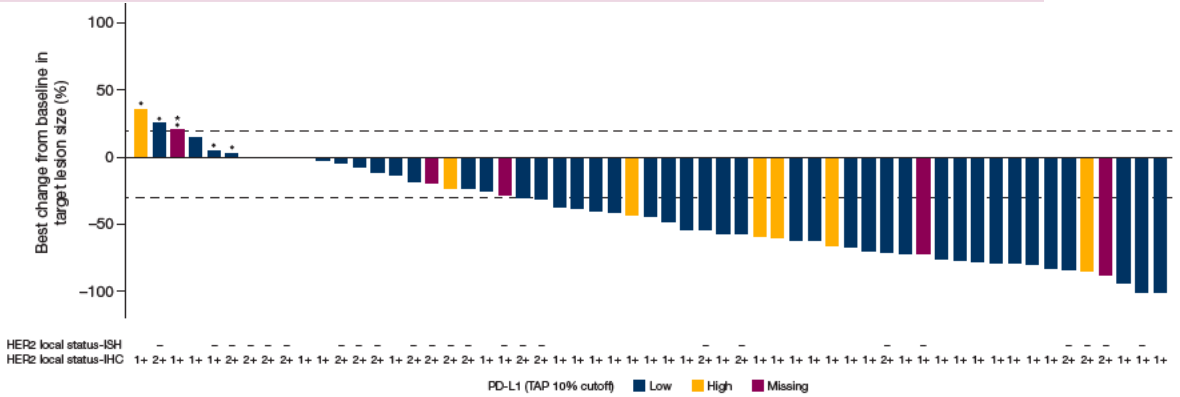
Nicolo et. al. *Cancer Treatment Reviews* 2022



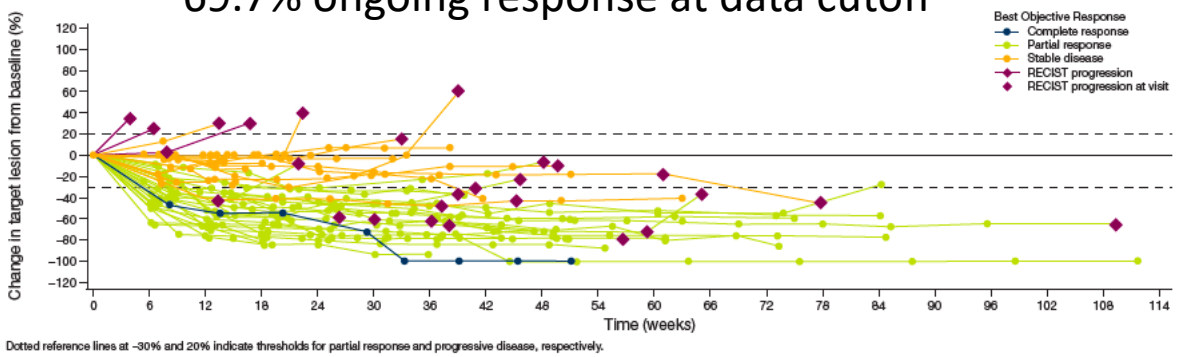
T-DXd + Durvalumab: The Begonia Trial



- First-line basket trial for HER2-low mTNBC
  - Arm 6 (n=58)
    - PD-L1 testing using SP263
    - ORR 56.9% (n=33)
    - PFS 12.6 mo (8.3-NC)
  - Safety
    - 8 cases of adjudicated ILD, 2 more pending review
      - Grade 1 (3), grade 2 (2), grade 3 (1), grade 5 (1, Covid related)
      - 17% stopped rx due to AEs

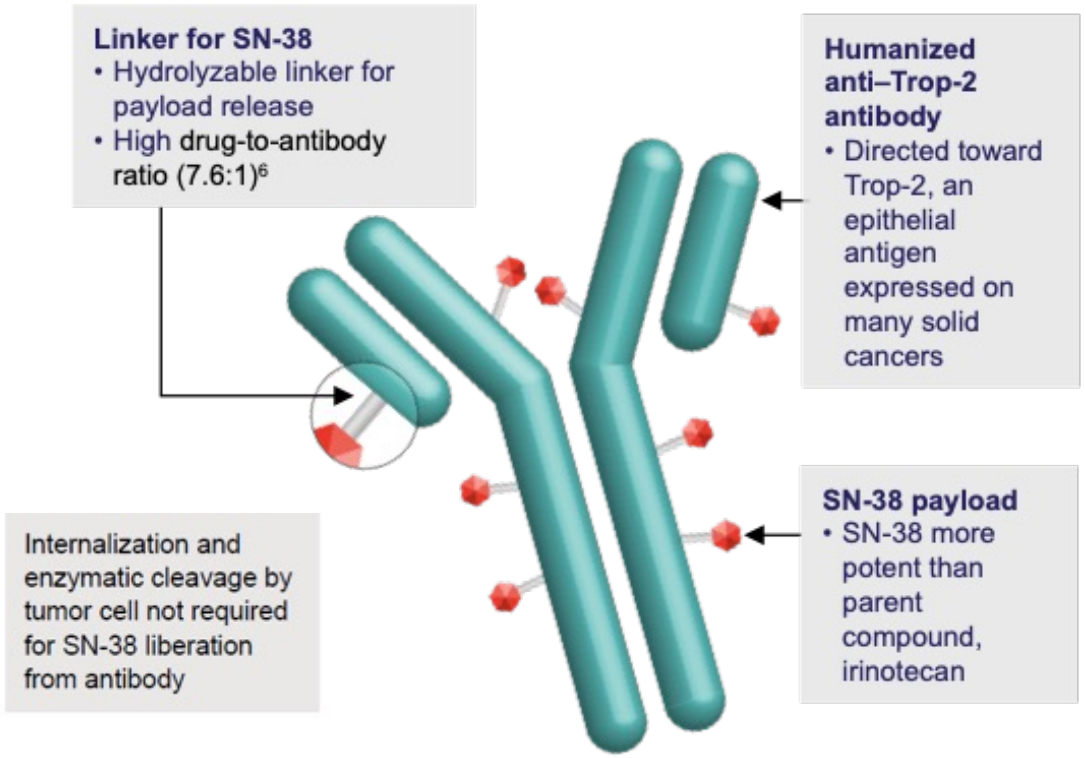


69.7% ongoing response at data cutoff



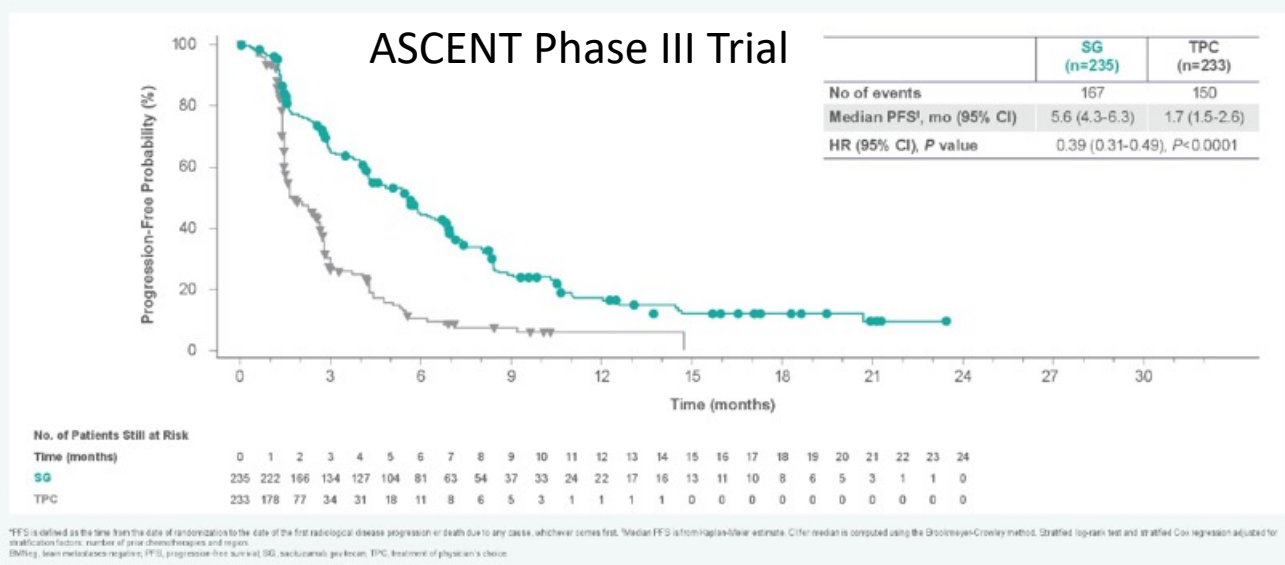
Schmid et al, SABCS 2022; PD11-08

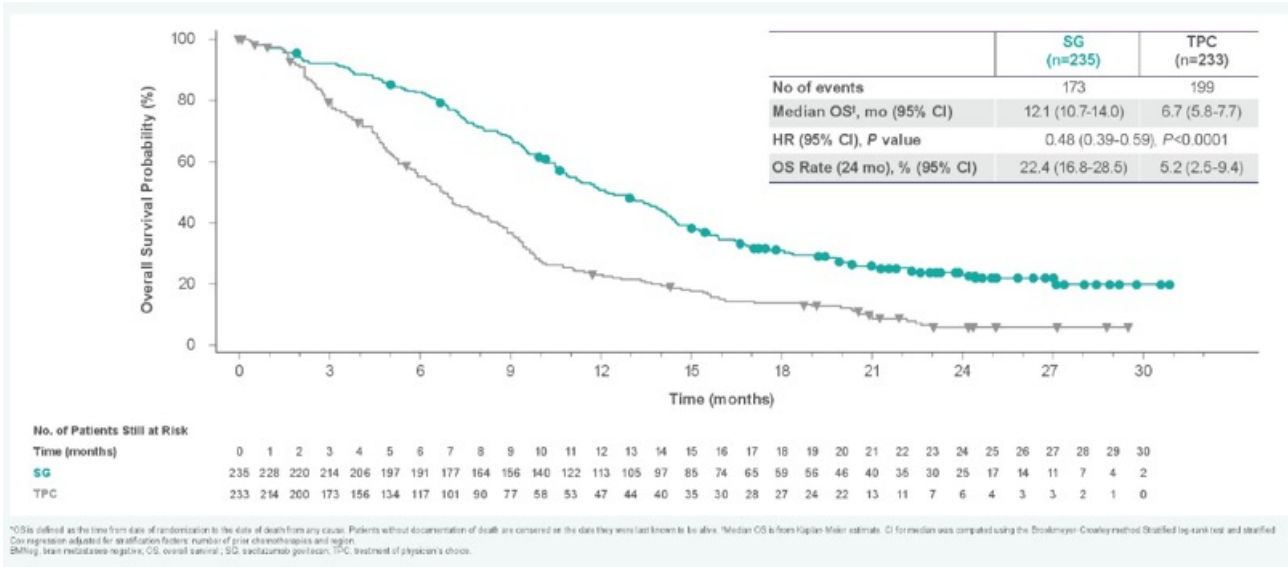
Sacituzumab Govitecan (SG): First-in-Class Trop-2–Directed ADC



- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- Full approval for the treatment of mTNBC and accelerated approval for advanced urothelial cancer

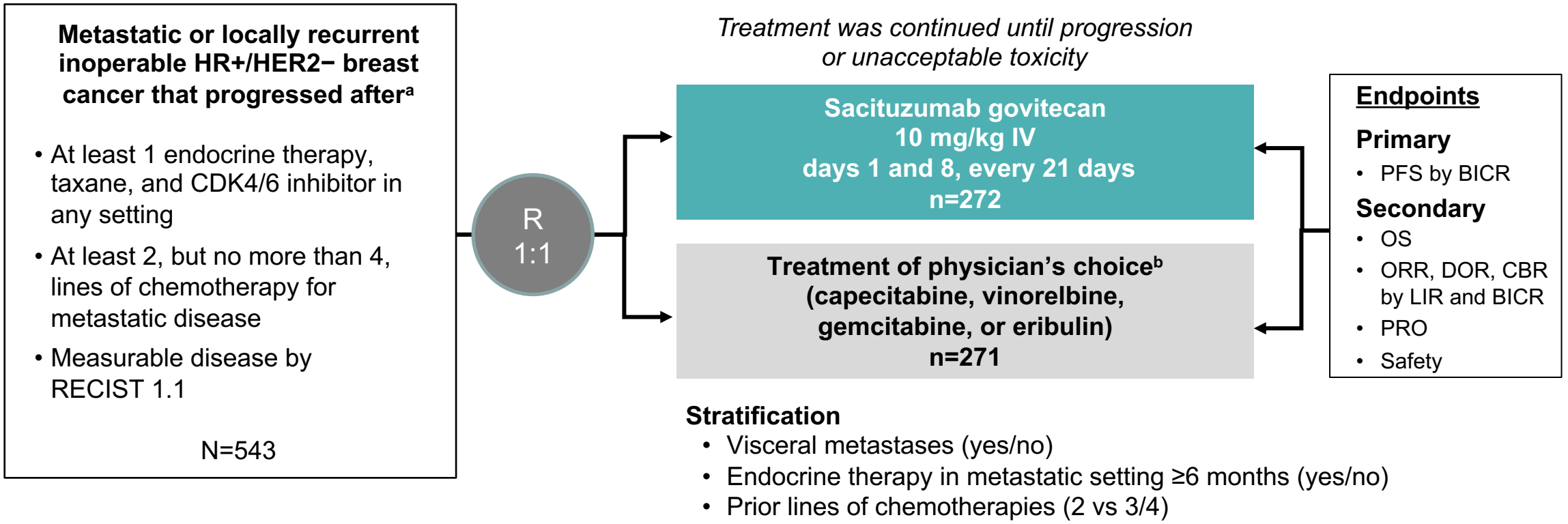
ASCENT Phase III Trial





Bardia et al. *NEJM*. 2021.

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

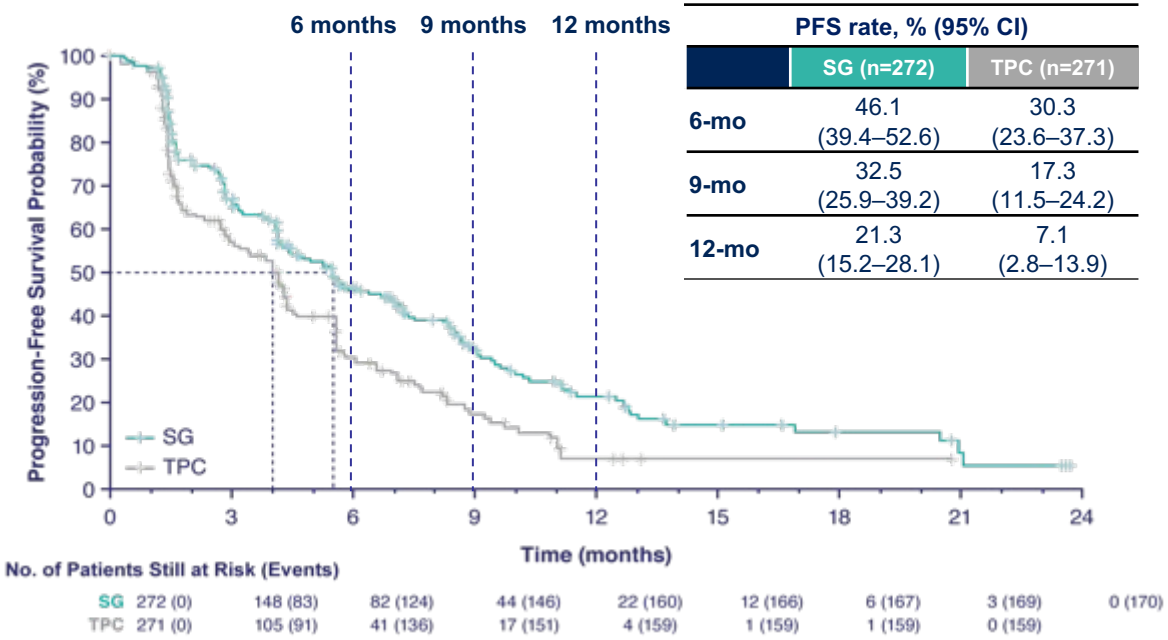


[a]Disease histology based on ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; 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.

PFS & OS in the ITT Population

PFS[1]

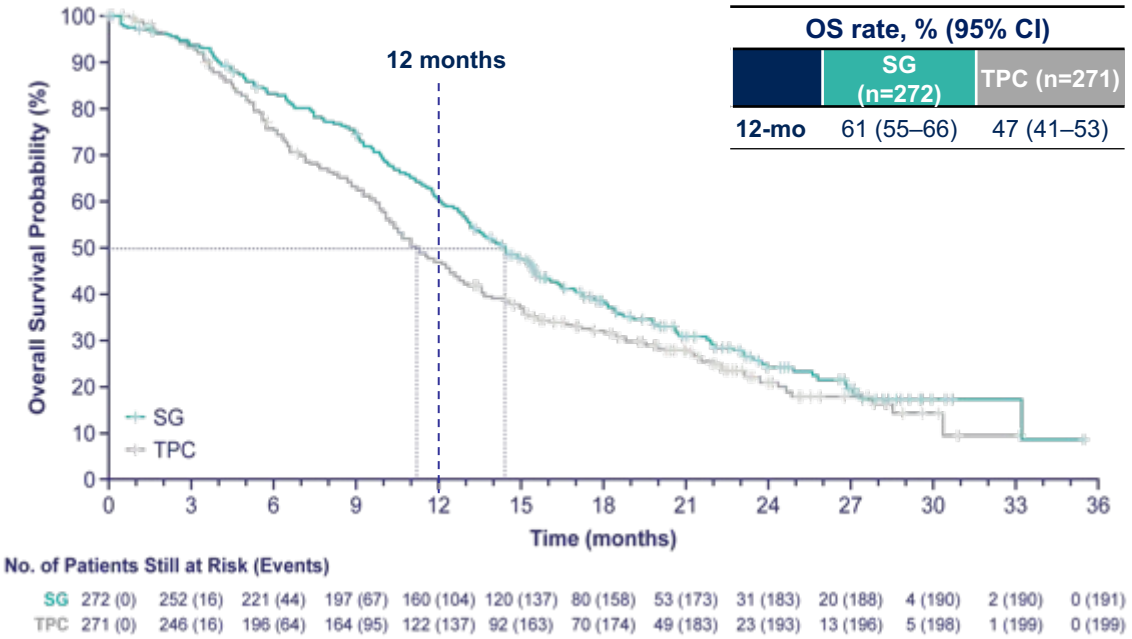
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

OS[2]

	SG (n=272)	TPC (n=271)
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	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Median follow-up was 10.2 months.

BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

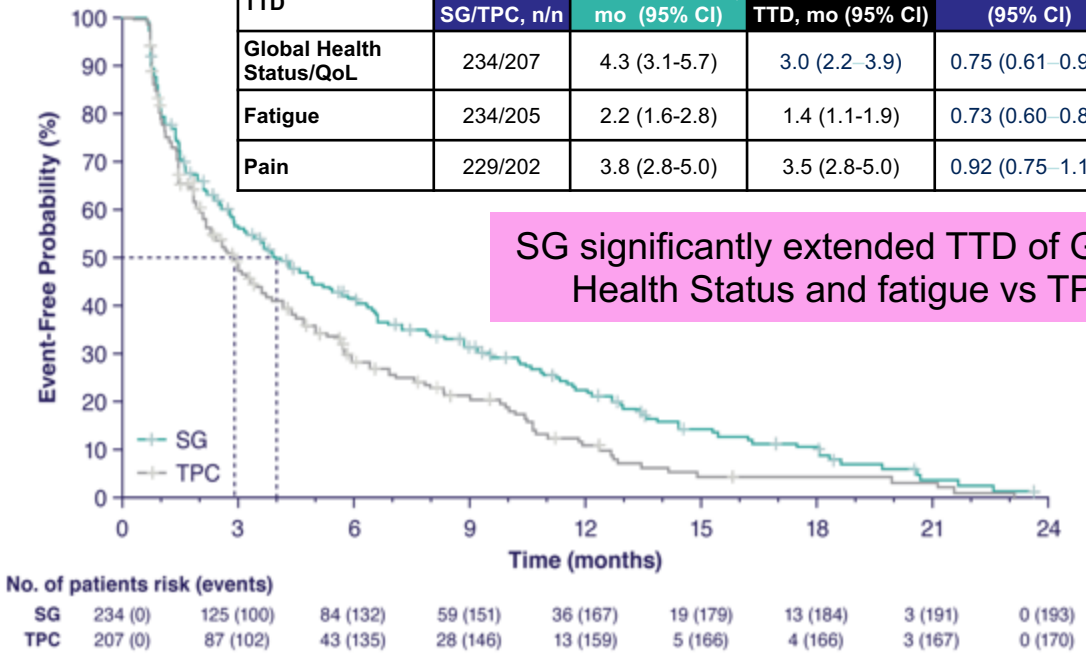
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol. 2022*. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76.

Updated Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: Efficacy and Safety

BICR Analysis		SG (n=272)	TPC (n=271)
ORR, n (%)		57 (21)	38 (14)
Odds ratio (95% CI); *p* value		1.63 (1.03–2.56), *P*=0.035	
Best overall response, n (%)	CR	2 (1)	0
	PR	55 (20)	38 (14)
	SD	142 (52)	106 (39)
	SD ≥6 months	35 (13)	21 (8)
	PD	58 (21)	76 (28)
	NE	15 (6)	51 (19)
CBR[a], n (%)		92 (34)	59 (22)
Odds ratio (95% CI); *p* value		1.80 (1.23–2.63), *P*=0.003	
Median DOR, months (95% CI)		7.4 (6.5-8.6)	5.6 (3.8-7.9)

SG significantly improved ORR compared with TPC, with a prolonged DOR

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	4.3 (3.1-5.7)	3.0 (2.2–3.9)	0.75 (0.61–0.92)	0.006
Fatigue	234/205	2.2 (1.6-2.8)	1.4 (1.1-1.9)	0.73 (0.60–0.89)	0.002
Pain	229/202	3.8 (2.8-5.0)	3.5 (2.8-5.0)	0.92 (0.75–1.13)	0.415



SG significantly extended TTD of Global Health Status and fatigue vs TPC

- The most common TE serious AEs (≥2% incidence) were
  - SG: diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), and neutropenic colitis (2%)
  - TPC: febrile neutropenia (4%), pneumonia (2%), nausea (2%), and dyspnea (2%)
- The safety profile was consistent with previous studies of SG

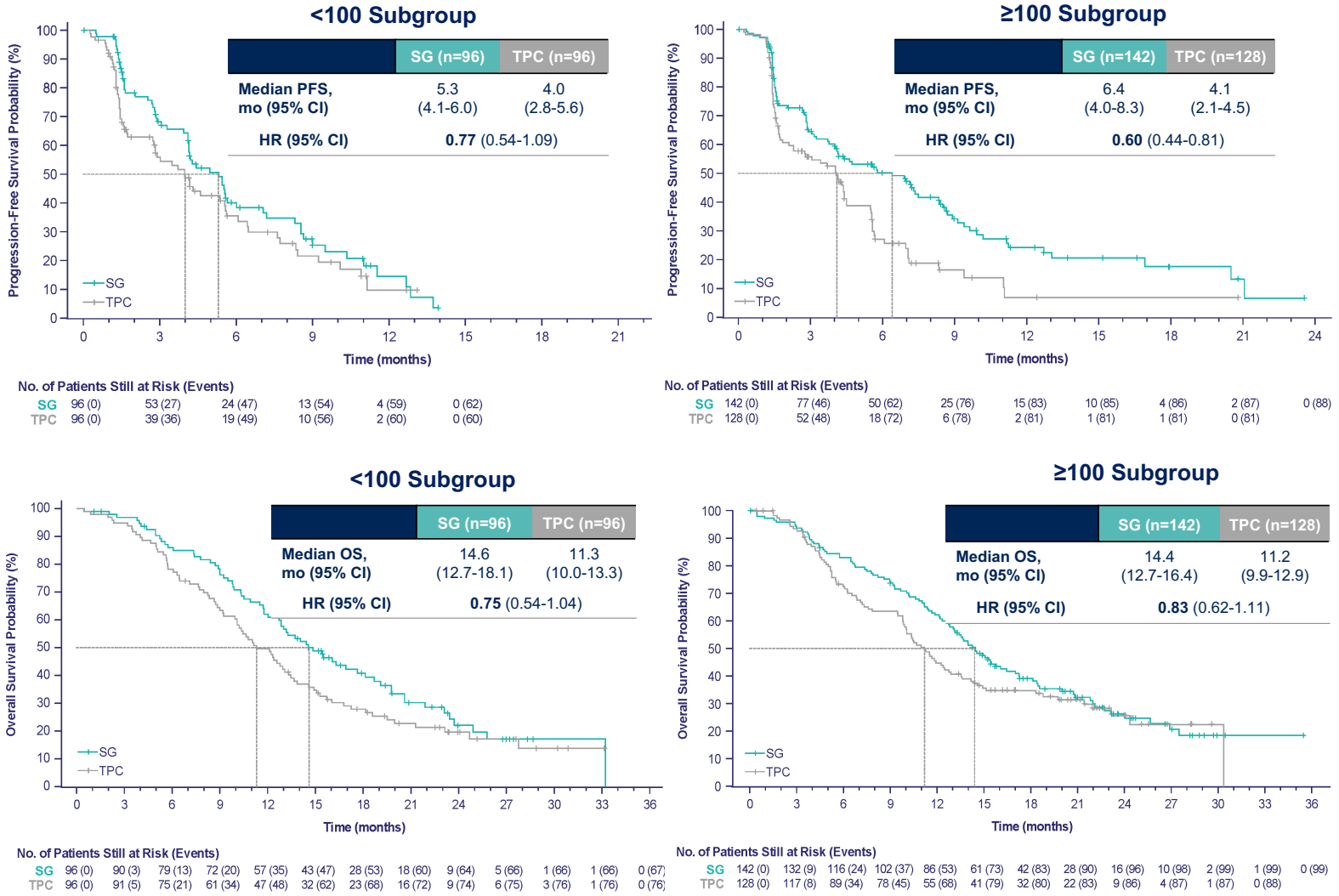
[a]CBR : % with a confirmed best OR of CR, PR and SD ≥6 months. [b]Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment-related (septic shock due to neutropenic colitis). The other 5 were: COVID-19 pneumonia, pulmonary embolism, pulmonary sepsis, nervous system disorder and arrhythmia. Upon detailed review of the TEAEs leading to death, there were no patterns identified.

Rugo H, et al. ASCO 2022. Abstract LBA1001. Rugo et al, JCO 2022; Rugo et al, ESMO 2022

Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients With HR+/HER2– Metastatic Breast Cancer

- Trop 2 expression found in 95% of tumor samples
- H score ≥100 in 58%
- 7.7 mo median time from tissue collection to randomization
- No impact of Trop-2 expression on response or safety

No Impact of TROP2 expression on efficacy



Rugo et al, SABCS 2022; GS5-11

ASCENT-03 (NCT05382299): PD-L1 negative
N=540

First-line therapy
- PD-L1 neg TNBC
- TNBC Rxd with IO in early stage

→ Sacituzumab govitecan

→ TPC: paclitaxel, nab-paclitaxel, gem/carbo

ASCENT-04 (NCT05382286): PD-L1 positive
N=570

1L mTNBC PD-L1+
- Previously untreated, inoperable, locally advanced, OR metastatic TNBC
- PD-L1+ (CPS ≥10, IHC 22C3 assay)
- PD-L1 and TNBC status centrally confirmed
- Prior anti-PD-(L)1 allowed in the curative setting
- ≥6 months since treatment in curative setting

1:1

N=570
(≤25% *de novo*)

→ SG + pembrolizumab
(SG: 10 mg/kg IV on days 1 and 8 of 21-day cycles; Pembro: 200 mg IV on day 1 of 21-day cycles)

→ TPC chemotherapy + pembrolizumab
(Pembro dosed as above. TPC: gem 1000 mg/m² with carbo AUC 2 IV on days 1 and 8 of 21-day cycles OR paclitaxel 90 mg/m² IV on days 1, 8, and 15 of 28-day cycles OR nab-paclitaxel: 100 mg/m² IV on days 1, 8, and 15 of 28-day cycles)

SACI-IO TNBC and HR+: Sacituzumab govitecan +/– pembrolizumab in 1L PD-L1– mTNBC and HR+

Garrido-Castro/Tolaney

mTNBC
- No prior chemo
  No prior PD-1/L1
- PD-L1 <1% by SP-142
  ER ≤5%
  PR ≤5%
  HER2-
- Stable brain mets
- Exclude prior: PD-1/L1, SG, Irinotecan

mHR+/HER2-
- ≥ 1 Hormonal
- 0-1 Prior Chemo
- Exclude prior: PD-1/L1, SG, Irinotecan

N=110

1:1

N=110

→ Sacituzumab govitecan
10 mg/kg IV d1, 8 q21 days
+
pembrolizumab
200 mg/kg d1 q21 days

→ Sacituzumab govitecan
10 mg/kg d1,8 q21 days

80% power to detect PFS improvement from 5.5 months (Arm B) to 8.5 months (Arm A)

Endpoints
Primary
- PFS

Secondary
- OS, ORR
- Duration and time to objective response, time to progression, CBR
- Safety and tolerability

Ascent-07:
First-line Chemotherapy in HR+

Key eligibility criteria:
- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)

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

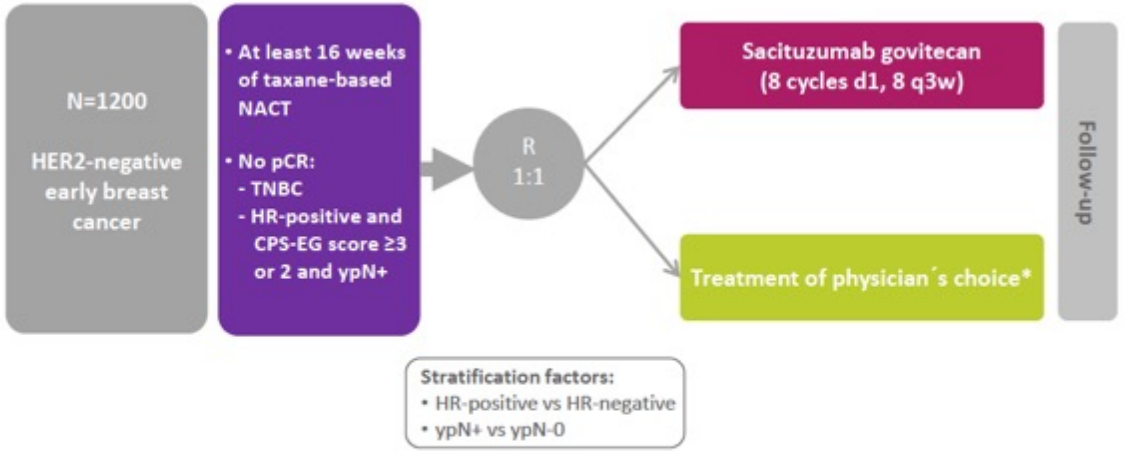
Primary Endpoint
- PFS by BICR

Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints
- PFS by investigator
- ORR by investigator
- DOR
- Safety

GBG: SASCIA Post-Neoadjuvant Trial

NCT04595565

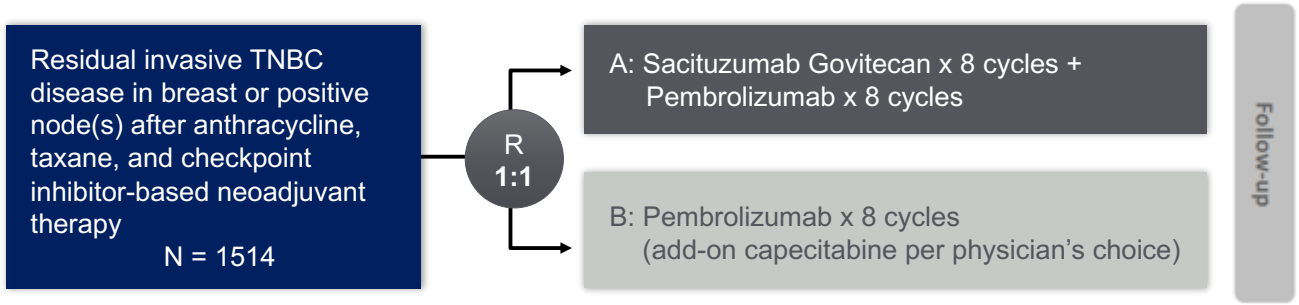


Challenge combining ER+ and TNBC pts

*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation.
Background therapy: in patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

Phase III Trial: Optimice-RD/ASCENT-05

Residual disease in TNBC



PI: Sara Tolaney
Alliance Foundation Trial

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative

Preferred Regimens		Other Recommended Regimens[i]	Useful in Certain Circumstances[i]
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • Sacituzumab govitecan-hziy (for TNBC [category 1] or HR+/HER2-)[d]	• For HER2 IHC 1+ or 2+/ISH negative: ▸ Fam-trastuzumab deruxtecan-nxki[e,f] (category 1) • For germline *BRCA1/2* mutations[g] see additional targeted therapy options (BINV-R)[h] • Platinum (for TNBC and germline *BRCA1/2* mutation)[g] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[h]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

HER2-Positive Disease, see BINV-Q (2 of 8)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.

[b] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.

[c] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.

[d] For adult patients with metastatic TNBC who received at least two prior therapies, with For patients with HR positive, HER2 negative cancers after prior treatment including endocrine therapy, a CDK4/6 inhibitor and at least two lines of chemotherapy (including a taxane) for advanced breast cancer.

[e] For patients with tumors that are HER2 IHC 1+ or 2+ and ISH negative, who have received at least 1 prior line of chemotherapy for metastatic disease and, if tumor is HR+, are refractory to endocrine therapy.

[f] Fam-trastuzumab deruxtecan-nxki is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).

[g] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.

[h] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).

[i] Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

T-DXd FDA Approval

- On August 5, 2022, the FDA approved fam-trastuzumab deruxtecan-nxki for HER2-low mBC with prior chemotherapy in the metastatic setting or disease recurrence w/in six months of completing adjuvant chemotherapy

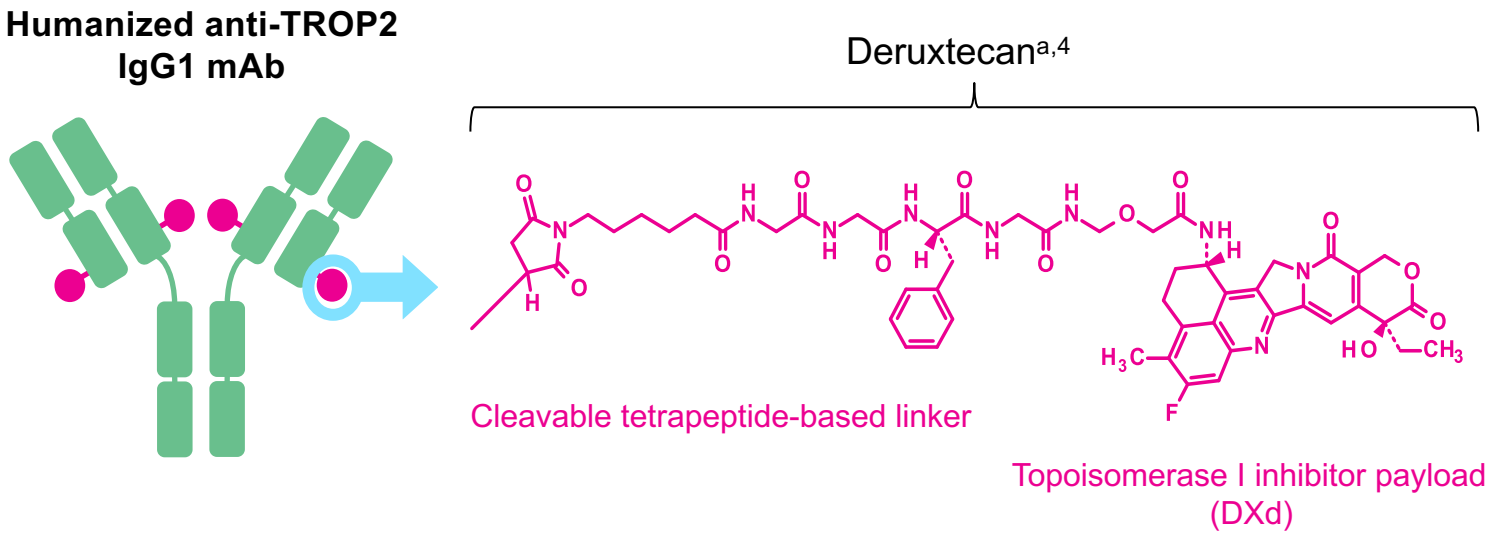
Sacituzumab FDA Approval!

- On February 3, 2023, the FDA approved sacituzumab govitecan-hziy for locally advanced or metastatic HR positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) MBC who have received endocrine-based therapy and ≥2 systemic therapies for metastatic disease

Datopotamab Deruxtecan (Dato-DXd)

Dato-DXd is an ADC with 3 components[1,2]:

- A humanized anti-TROP2 IgG1[3] monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker

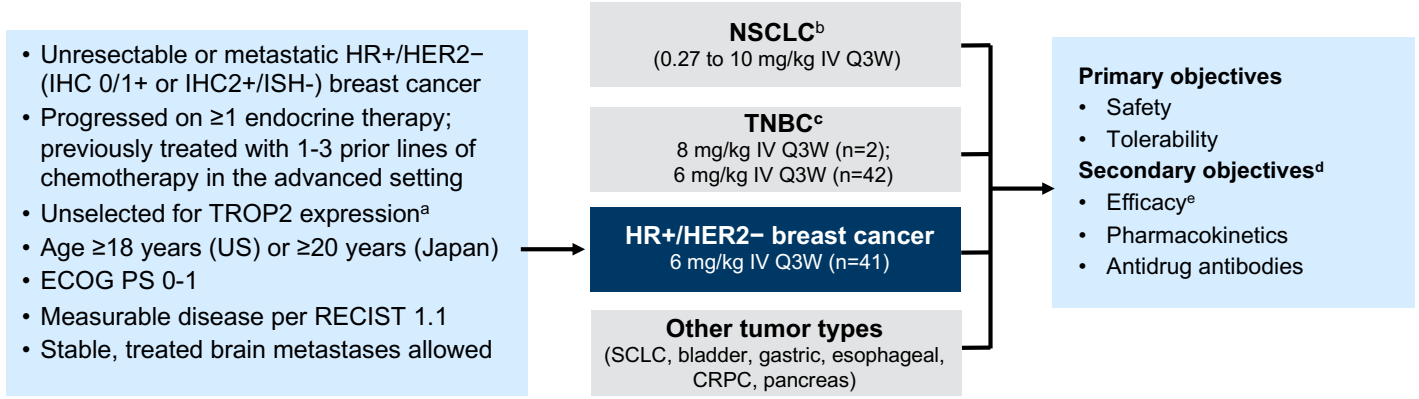


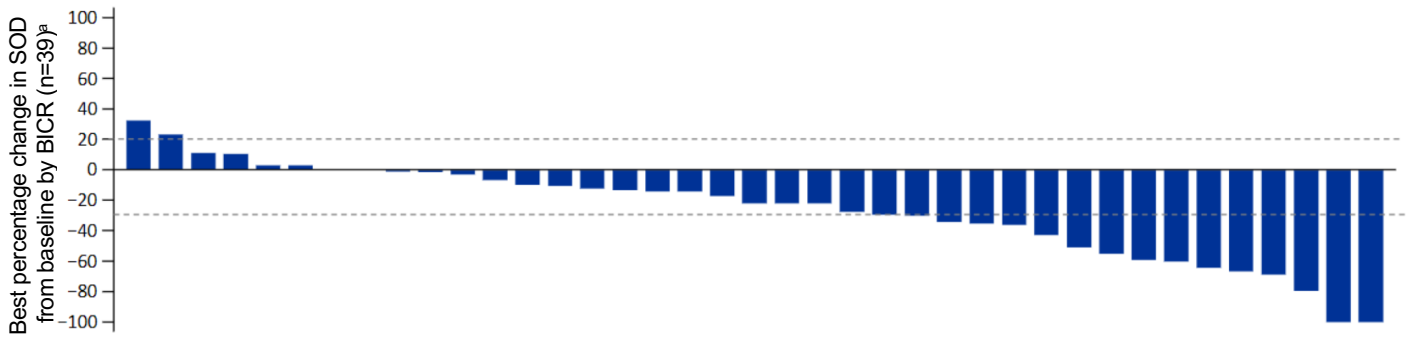
Payload mechanism of action: topoisomerase I inhibitor [b,1]
High potency of payload [b,2]
Optimized drug to antibody ratio ≈4 [b,c,1]
Payload with short systemic half-life [b,c,2]
Stable linker-payload [b,2]
Tumor-selective cleavable linker [b,2]
Bystander antitumor effect [b,2,5]

[a] Image is for illustrative purposes only; actual drug positions may vary. [b] The clinical relevance of these features is under investigation. [c] Based on animal data.

1. Okajima D, et al. AACR-NCI-EORTC 2019; [abstract C026]; 2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173-185; 3. Daiichi Sankyo Co. Ltd. DS-1062. Daiichi Sankyo.com. Accessed October 6, 2020. https://www.daiichisankyo.com/media_investors/investor_relations/ir_calendar/files/005438/DS-1062%20Seminar%20Slides_EN.pdf; 4. Krop I, et al. SABCS 2019; [abstract GS1-03]; 5. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

Phase 1 TROPION-PanTumor01: Datopotomab deruxtecan in HR+/HER2neg MBC





- N=41
  - Median of 2 prior chemo for MBC (Range: 1-6)
  - 95% prior CDKi
- Efficacy:
  - ORR (all PR): 27%;
  - CBR: 44%
  - Med PFS 8.3 mo
  - 59% alive for >1 year
- Safety (all Gr/≥Gr 3):
  - Stomatitis: 83/10%
  - Nausea: 56/0%
  - Alopecia: 37%
  - Pneumonitis: Gr 2 and 3 (2 pts)

Meric-Bernstam et al, SABCS 2022

TROPION-PanTumor01 Study: Dato-DXd Efficacy in TNBC

- Unresectable or metastatic HR+/HER2− (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Progressed on ≥1 endocrine therapy; previously treated with 1-3 prior lines of chemotherapy in the advanced setting
- Unselected for TROP2 expression[a]
- Age ≥18 years (US) or ≥20 years (Japan)
- ECOG PS 0-1
- Measurable disease per RECIST 1.1
- Stable, treated brain metastases allowed

→

NSCLC[b]
(0.27 to 10 mg/kg IV Q3W)

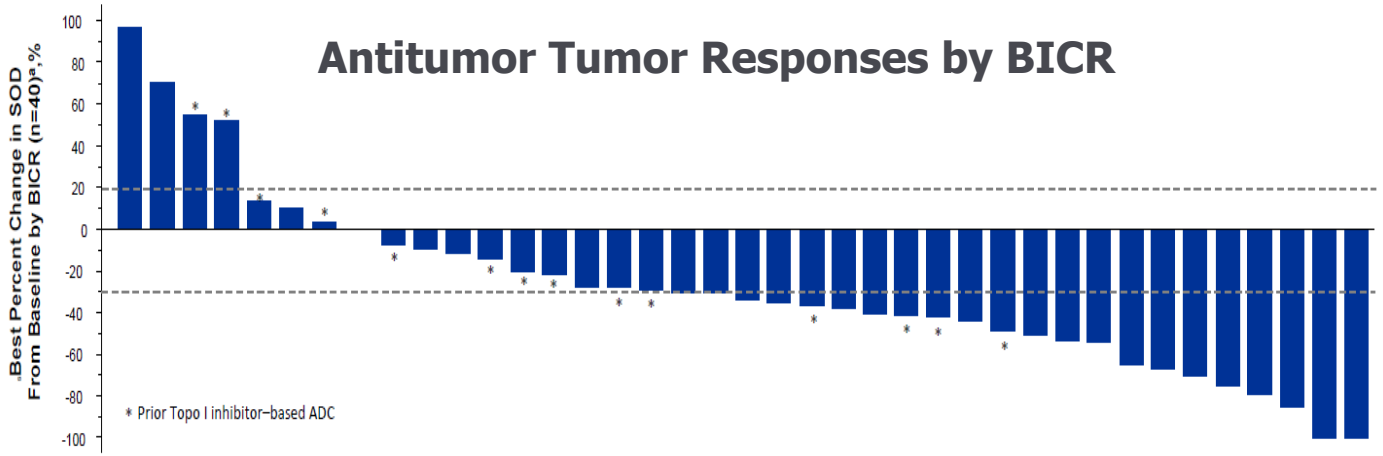
TNBC[c]
8 mg/kg IV Q3W (n=2);
6 mg/kg IV Q3W (n=42)

HR+/HER2− breast cancer
6 mg/kg IV Q3W (n=41)

Other tumor types
(SCLC, bladder, gastric, esophageal, CRPC, pancreas)

Primary objectives
- Safety
- Tolerability

Secondary objectives[d]
- Efficacy[e]
- Pharmacokinetics
- Antidrug antibodies



ORR by BICR:
- All patients: **32%**
- Topo I inhibitor-naive patients: **44%**

mDOR: 16.8 months in both groups

mPFS:
- All patients: 4.4 months
- Topo I inhibitor-naive patients: 7.3 months

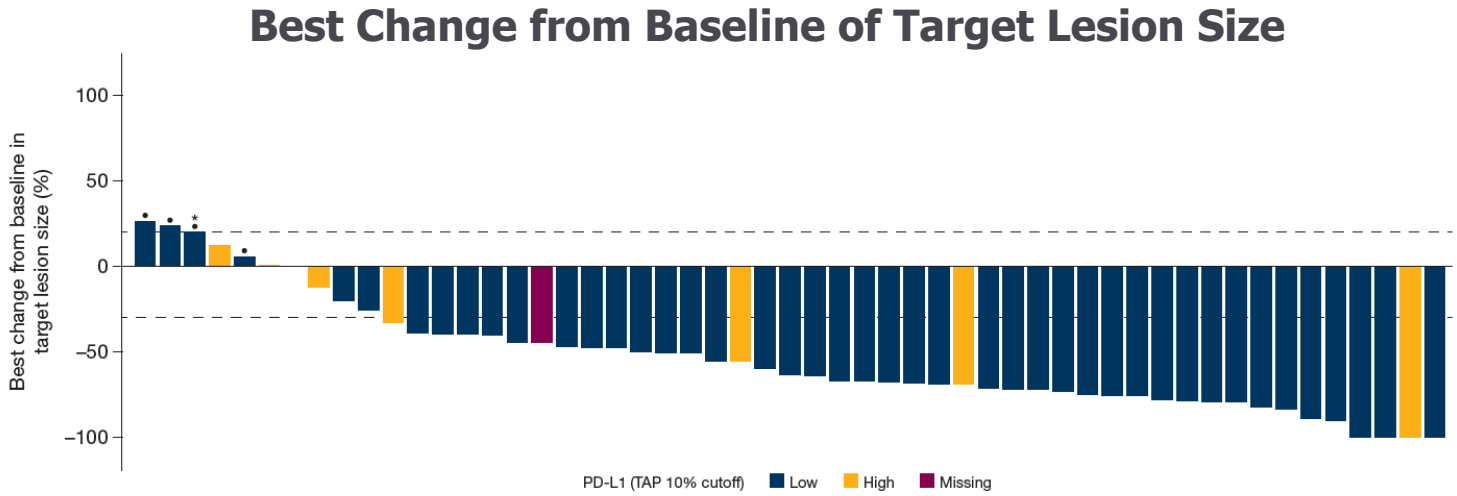
mOS:
- All patients: 13.5 months
- Topo I inhibitor-naive patients: 14.3 months

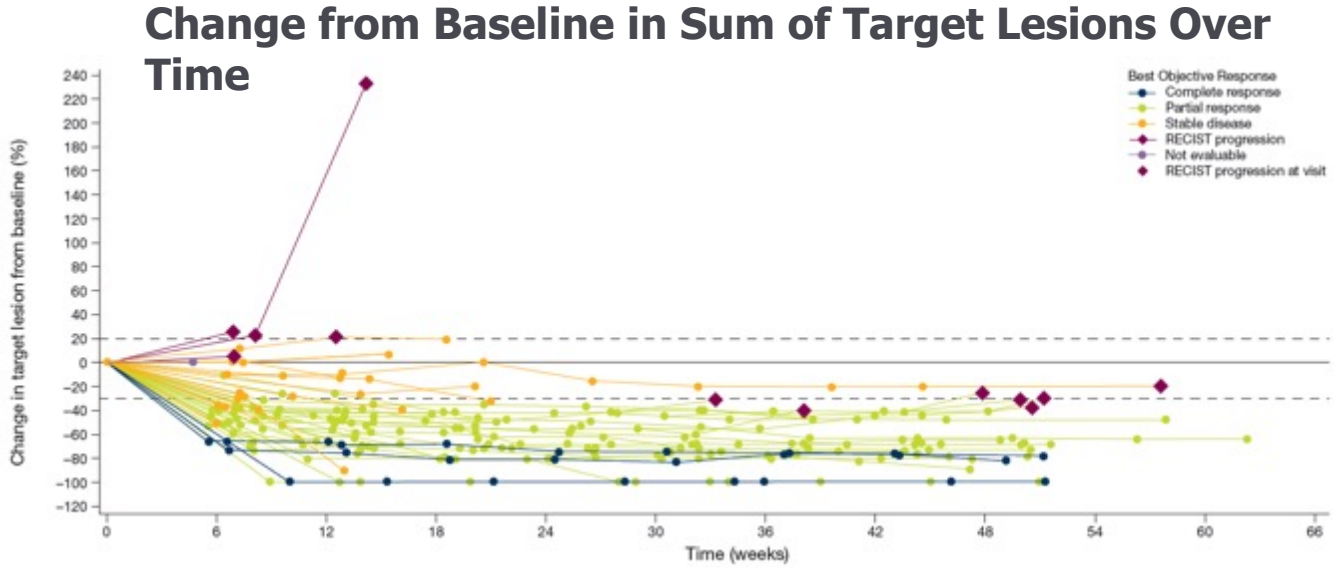
AEs:Most common TEAEs: stomatitis (73%), nausea (66%), vomiting (39%)

Bardia A, et al. SABCS 2022. Poster Presentation P6-10-03.

BEGONIA Trial: Dato-DXd + Durvalumab

- 1st line TNBC
  - N=61; 53 evaluable
  - ORR 73.6%
  - Durable responses
    - 82% remained in response at data cutoff
    - Responses in PD-L1 low and high tumors (SP263)
  - Previous data
    - 69% stomatitis, 14% grade 3
  - Current:
    - Stomatitis 55.7% no grade given
    - Alopecia 45.9%
    - Nausea 57.4%
    - ILD/pneumonitis in 3.3% (2)





Schmid et al, SABCS 2022; PD11-09

TROPION-Breast01

NCT05104866

- 2nd-3rd line therapy for HR+/HER2- mBC
- Completed accrual

Key Eligibility Criteria

- HR-positive, HER2-negative inoperable/ metastatic breast cancer with disease progression following 1 or 2 lines of chemotherapy (& progressed on, or not suitable for, endocrine therapy)
- Targeted agents (i.e., inhibitors of mTOR, PD-1/PD-L1, CDK4/6, PARP) and endocrine therapies do not count as prior lines of chemotherapy
- At least 1 measurable lesion
- FFPE tumor sample
- Adequate organ function

Stratification factors:

- 1 vs. 2 previous lines of chemotherapy in the inoperable/metastatic setting
- Geographic location (US/Canada/EU vs rest of world)
- Previous CDK 4/6 inhibitor use

1:1

Dato-DXd
6mg/kg IV Q3W
N=350

Investigator's Choice of Chemotherapy
(Eribulin, Vinorelbine, Capecitabine or Gemcitabine)
N=350

Dual primary endpoints
PFS (BICR), OS

Secondary endpoints
PFS (inv), ORR, DoR, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints
TROP2 IHC

Statistical Considerations:

To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses

Response assessment: Scan Q6W for 48 weeks, then Q9W until RECIST1.1 disease progression (as assessed by Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per Imaging schedule.

TROPION-Breast02

NCT05374512

- 1st line therapy for TNBC
- PD-L2 negative

Key eligibility criteria:

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1 / PD-L1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

- Geographic location
- DFI (*de novo* vs DFI ≤12 months vs DFI >12 months)

Dual primary endpoint:
PFS (BICR) and OS

Secondary endpoints:
PFS (inv), ORR, DoR, safety

1:1

Dato-DXd

Investigator's choice of chemotherapy

Results From the Phase 1/2 Trial of Patritumab Deruxtecan in HER3-Expressing MBC

Key Eligibility Criteria

- Advanced/unresectable or metastatic HER3+[a] BC
- Dose finding & expansion (HR+/HER2-): ≥2 and ≤6 lines of prior chemo; ≥2 for advanced disease
- Dose expansion (TNBC): 1-2 prior chemo regimens for advanced disease

Data for all 3 phases were pooled
Efficacy reported by BC subtype and safety reported for patients who received HER3-DXd 4.8mg/kg, 6.4mg/kg and all patients

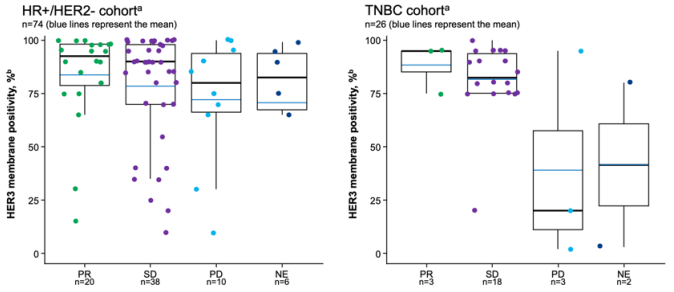
- Confirmed ORR for all patients (N=182): 28.6%
- (95% CI, 22.1-35.7)
- Median DOR: 7.0 months (95% CI, 5.5-8.5)
- In HER2+ disease, clinical activity was not associated with HER3 membrane expression

Safety similar between 4.6 and 6.4 mg/kg IV q3wk

- Most common toxicities: GI and heme
- 10% discontinuation due to AEs
- **27% grade 3 thrombocytopenia**
- **6.6% ILD; 1 death**

Outcomes (BICR per RECIST 1.1)		HR+/HER2- (n=113) HER3-High and Low	TNBC (n=53) HER3-High	HER2+ (n=14) HER3-High
Confirmed ORR, % (95% CI)		30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Best overall response (BOR), %[a]	PR	30.1	22.6	42.9
	SD	50.4	56.6	50.0
	PD	11.5	17.0	7.1
	NE	8.0	3.8	0.0
Median DOR (95% CI), months		7.2 (5.3-NE)	5.9 (3.0-8.4)	8.3 (2.8-26.4)
Median PFS (95% CI), months		7.4 (4.7-8.4)	5.5 (3.9-6.8)	11.0 (4.4-16.4)
Median OS (95% CI), months		14.6 (11.3-19.5)	14.6 (11.2-17.2)	19.5 (12.2-NE)

Pre-Treatment HER3 Membrane Expression by BOR



FDA Fast track designation for metastatic EGFR mutated NSCLC

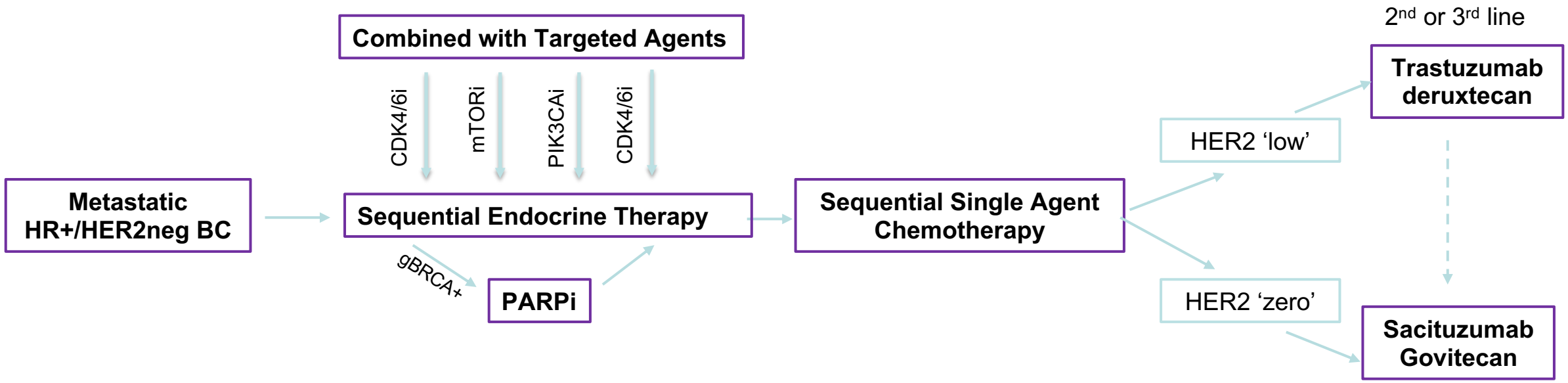
[a]HER3 status by IHC in archival tumor tissue; HER3-positive was defined as IHC 2+ and IHC 3+ for DE/DF cohorts and as ≥25% membrane positivity at 10x for DEXP cohorts. [b]Guided by mCRM with EWOC. [c]HER3-high = ≥75% membrane positivity at 10x; HER3-low = ≥25% and <75% membrane positivity at 10x. [d]HER2 status was defined as: zero, IHC 0; low, IHC 1+ or 2+ (ISH−); positive, IHC 2+ (ISH+), IHC 3+.

Krop IE, et al. ASCO 2022. Abstract 1002.

Conclusion

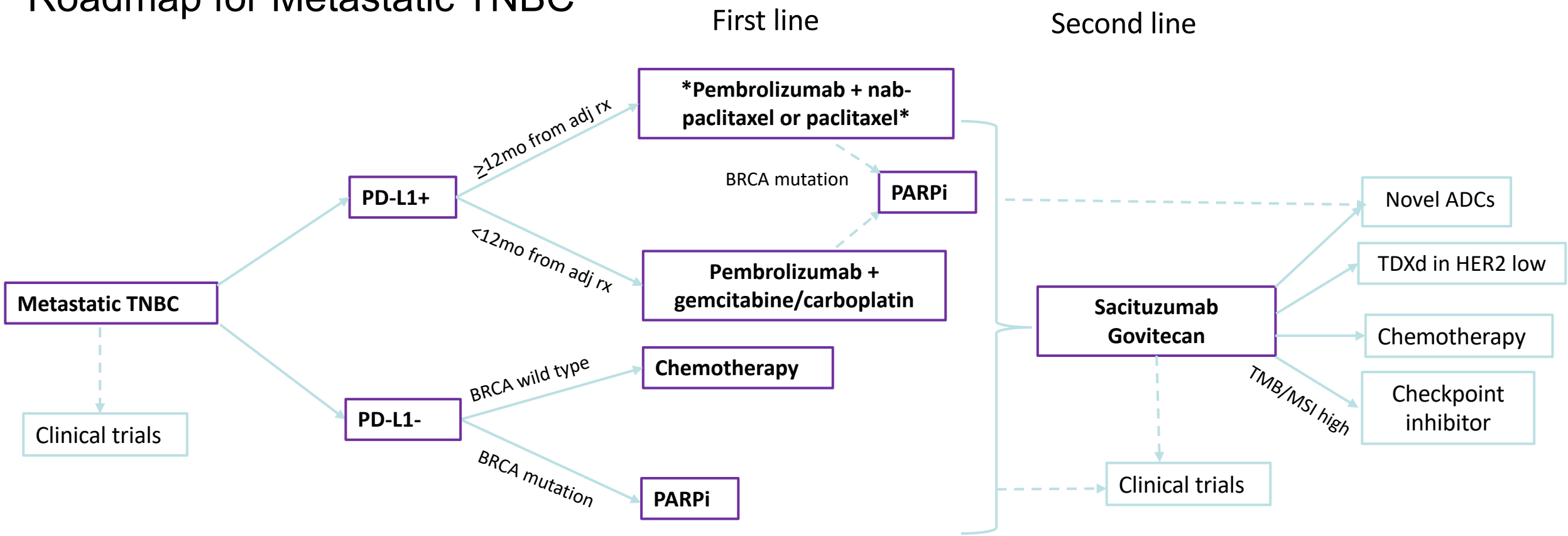
- **Antibody Drug Conjugates!**
  - **An exciting and effective drug delivery system for the treatment of multiple subtypes of MBC**
  - **Established role in HER2+ disease**
    - T-DXd is a new standard of care for mHER2+ BC
- **Established role in TNBC**
  - SG is a new standard of care for mTNBC
    - Post-neoadjuvant SASCIA and Optimice-RD/ASCENT-05 trials
- **Established role in HER2 low and HR+ disease**
  - T-DXd is a new standard of care of HER2 ‘low’ disease
  - Sacituzumab a treatment option for pre-treated HR+ disease
- **Ongoing trials in earlier lines, early-stage disease, and new ADCs in phase III trials**
- **Many questions remain!**
  - Defining HER2 low
  - Sequencing of ADCs
- **Toxicity management is critical**

Roadmap for HR+/HER2- Metastatic Breast Cancer



Multiple ADC trials in the neoadjuvant and post-neoadjuvant settings either accruing or to be opened soon!

Roadmap for Metastatic TNBC



**Pembrolizumab (CPS) or atezolizumab ex US (SP142), nab-paclitaxel only*)

PARPi: PARP inhibitor (olaparib, talazoparib)

Always consider clinical trials at each decision point


Thank you!