UCSF Helen Diller Family Comprehensive Cancer Center

Antibody-Drug Conjugates for Breast Cancer: Current Clinical Evidence

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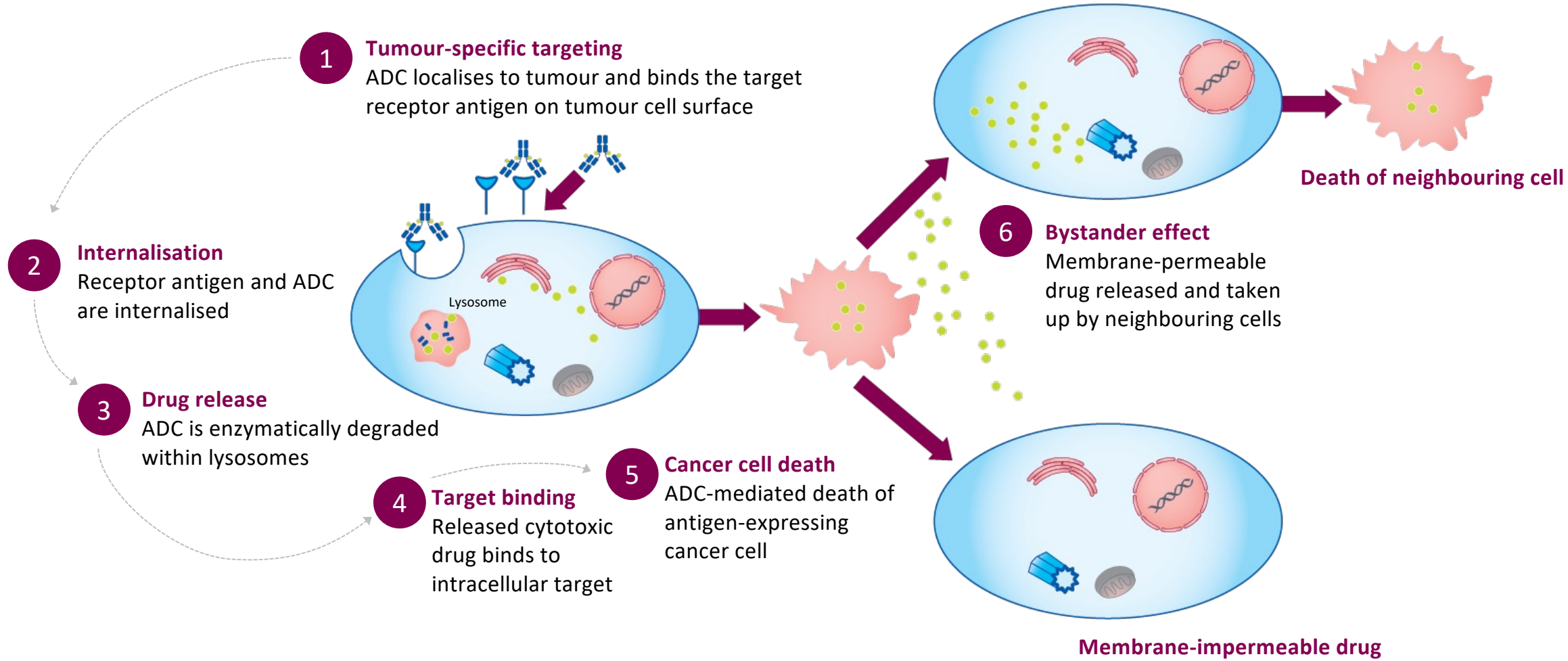
ADC technology enables tumour-specific targeting



ADC=antibody-drug conjugate

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

Overview of ADCs in Development for Breast Cancer

ADC	Target	Antibody	Payload	DAR	Clinical Status
Trastuzumab emtansine (T-DM1)	HER2	Trastuzumab	DM1	3.5	Approved in HER2+ mBC with prior therapy, multiple trials in mBC
fam-trastuzumab deruxtecan-nxki (T-DXd, DS-8201)	HER2	Trastuzumab	DXd	8	Approved in HER2+ and HER2 low mBC with prior therapy, multiple ongoing trials
vic-trastuzumab duocarmazine (SYD985)	HER2	Trastuzumab	Seco-DUBA	2.8	Phase 3 mBC in HER2+ reported
Sacituzumab govitecan (SG)	TROP2	RS7	SN-38	7.6	Approved in TNBC and HR+ MBC with prior therapy, multiple ongoing trials
Datopotamab deruxtecan (Dato-DXd, DS-1062)	TROP2	Datopotamab	DXd	4	Phase 3 TNBC and HR+/HER2- MBC, post NAC TNBC
Ladiratuzumab vedotin (SGN-LIV1A)	LIV1	hLIV22	Vc-MMAE	4	Phase 1b/II mTNBC (with pembro) and others
RC48-ADC (disitamab vedotin)	HER2	Hertuzumab	MMAE	4	Multiple trials in UC, gastric and other cancers (clinicaltrials.gov)
Patritumab deruxtecan (U3-1402)	HER3	Patritumab	DXd	8	Phase 1/2 mBC
A166	HER2	Trastuzumab	ND	ND	Phase 1/2 BC
ALT-P7 (HM2-MMAE)	HER2	HM2	MMAE	ND	Phase 1 mBC
ARX788	HER2	ND	Amberstatin269	1.9	Phase 1; phase III 3 HER2+ mBC
DHES0815A (anti-HER2/PBC-MA)	HER2	ND	PBD-MA	ND	Phase 1 mBC
MEDI4276	HER2	Trastuzumab scFv	AZI13599185	4	Phase 1 BC
XMT-1522 (TAK-522)	HER2	HT-18	AF-HPA	12	Phase 1 BC
AVID100	EGFR	MAB100	DM1	ND	Phase 1/2 TNBC
CAB-ROR2-ADC	Ror2	CAB	ND	ND	Phase 1/2 TNBC
Anti-CA6-DM4 immunoconjugate (SAR566658)	CA6	DS6	SPDB-DM4	1	Phase 2 TNBC

DAR: drug to antibody ratio

1. Nagayama A, et al. Ther Adv Med Oncol. 2020; 2. Rinnerthaler G, et al. Int J Mol Sci. 2019

Current Clinical Evidence: Antibody Drug Conjugates

- **An exciting and effective drug delivery system for the treatment of multiple subtypes of MBC**
- **Remarkable efficacy and established role in HER2+ disease**
- **Established role in TNBC**
  - Sacituzumab govitecan is a new standard of care for mTNBC
- **Established role in HER2 low and HR+ disease**
  - T-DXd is a new standard of care of HER2 ‘low’ disease
  - Sacituzumab govitecan an effective 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**

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

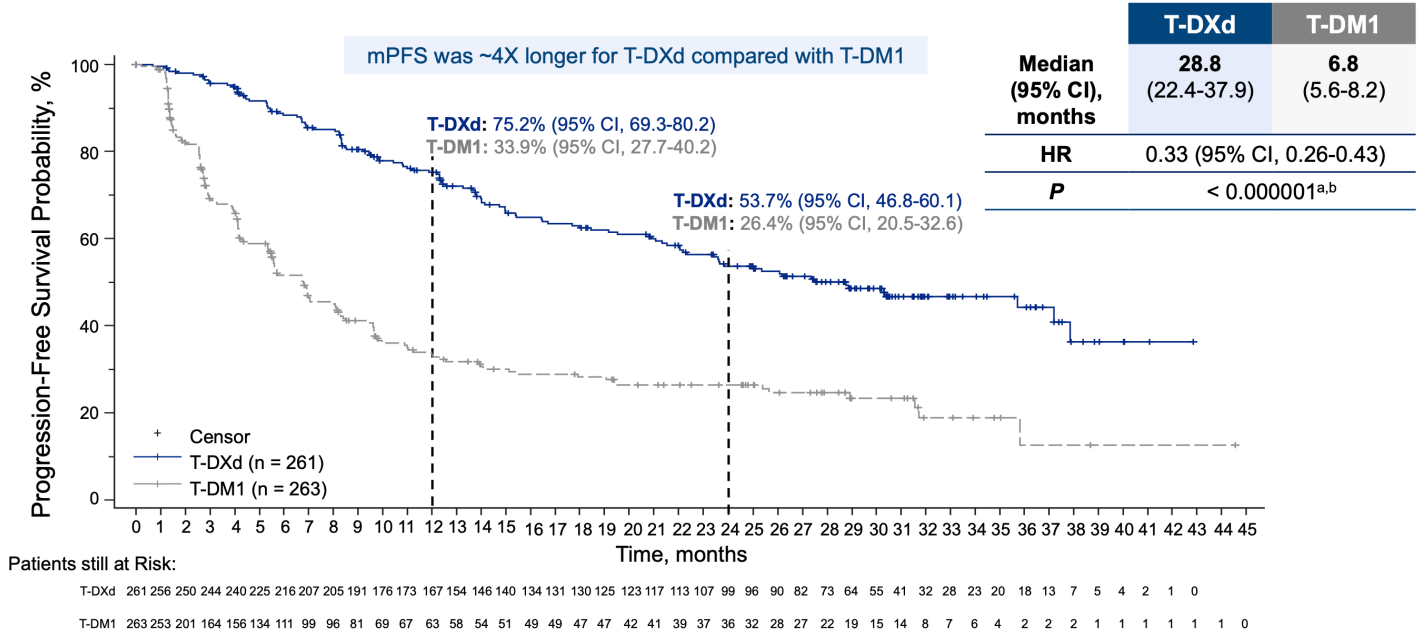
Updated AEs

- ILD: 15.2%, no grade 4 or 5

All grade AE

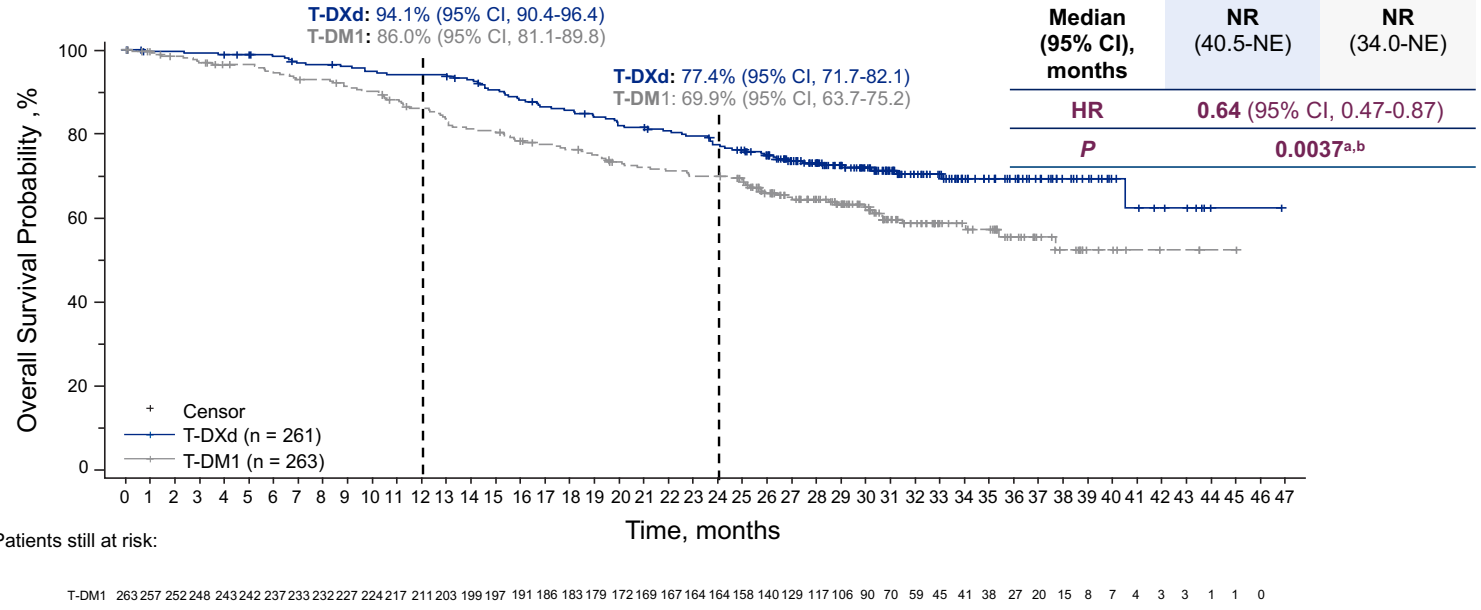
- Nausea: 77%
- Vomiting: 52%
- Alopecia 40%
- Neutropenia ≥grade 3: 16%

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



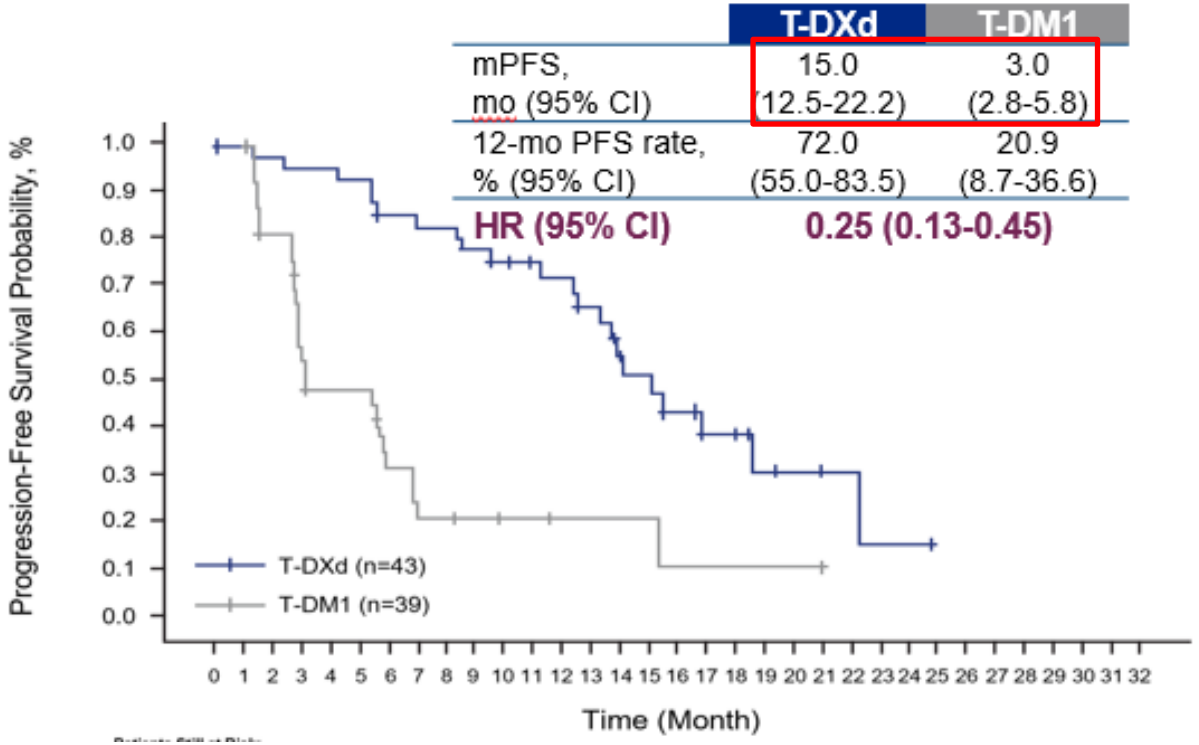
	T-DXd	T-DM1
Median (95% CI), months	NR (40.5-NE)	NR (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	

Hurvitz S et al. SABCS 2022; Lancet Oncology 2023

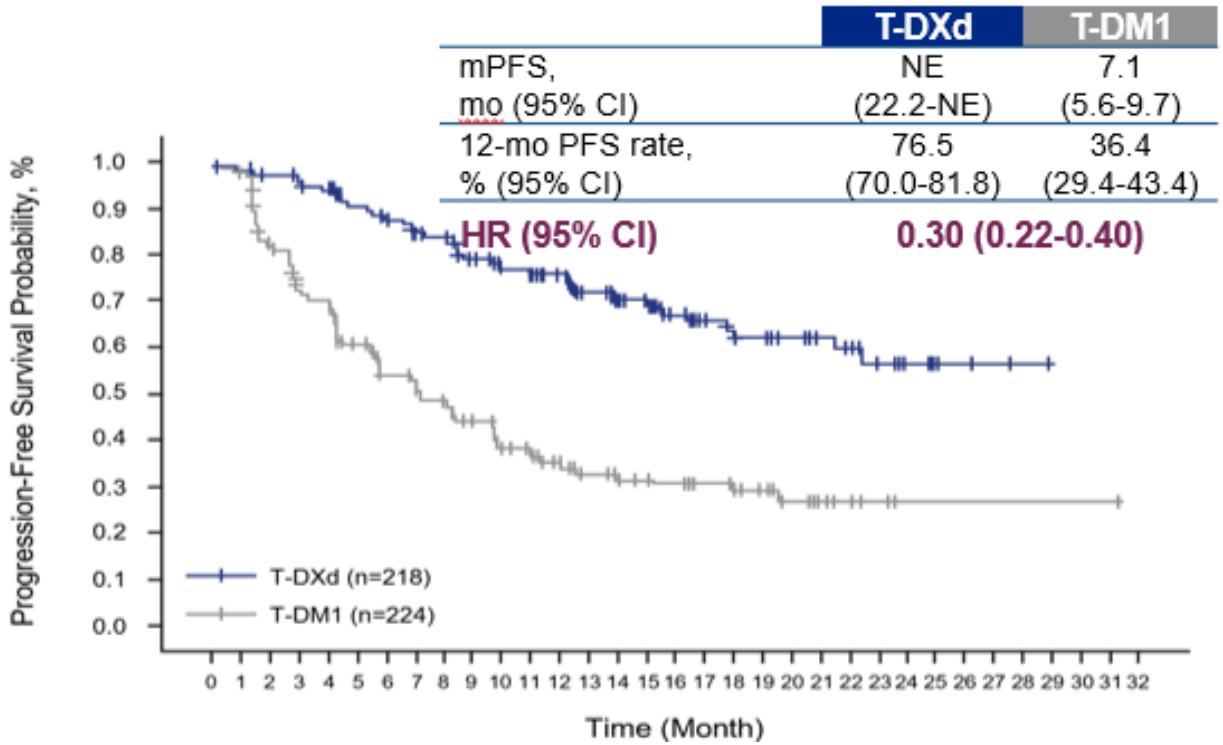
DESTINY Breast03

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

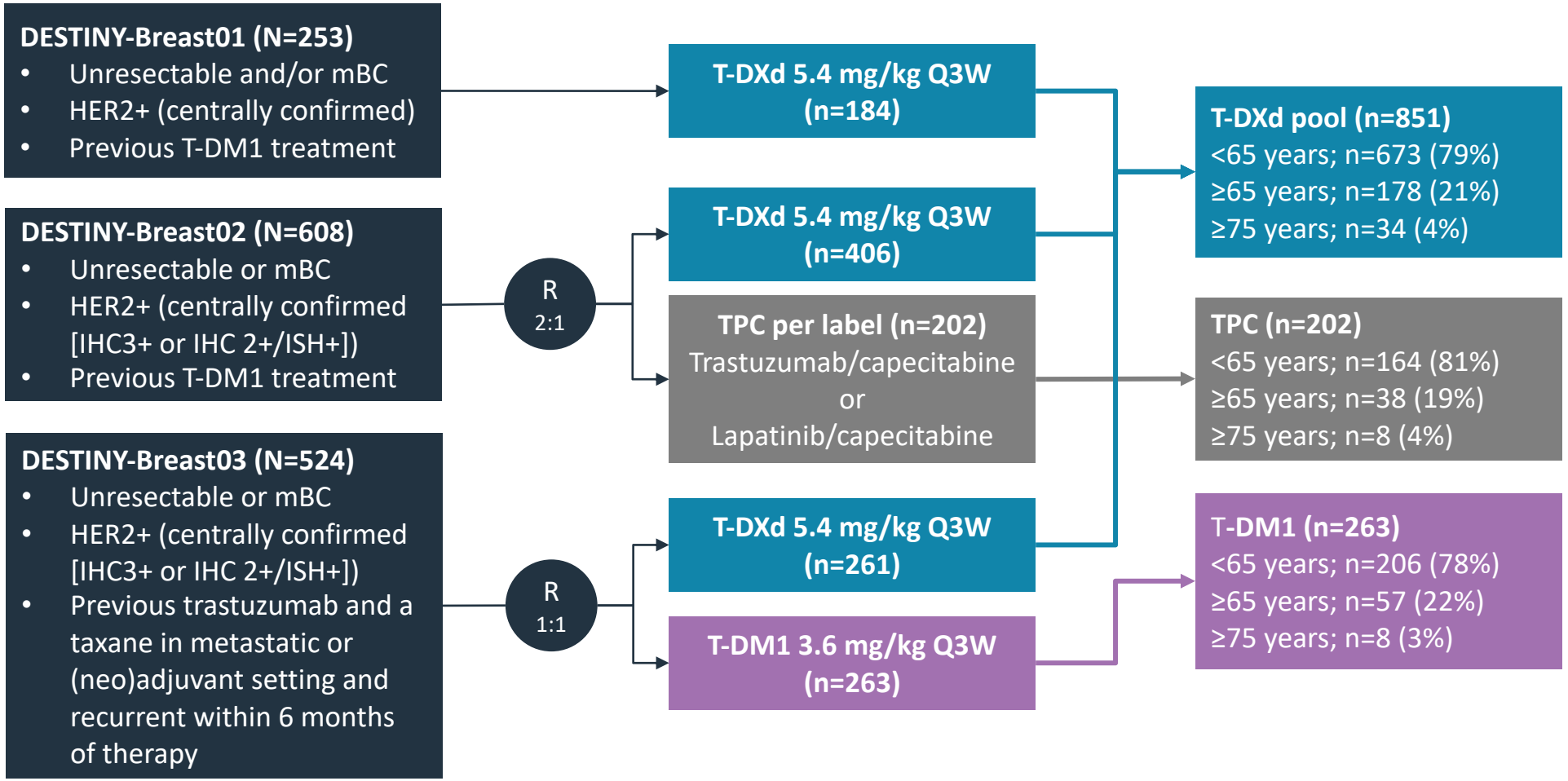
T-DXd	TPC
39.2 (32.7-NE)	**26.5** (21.0-NE)

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

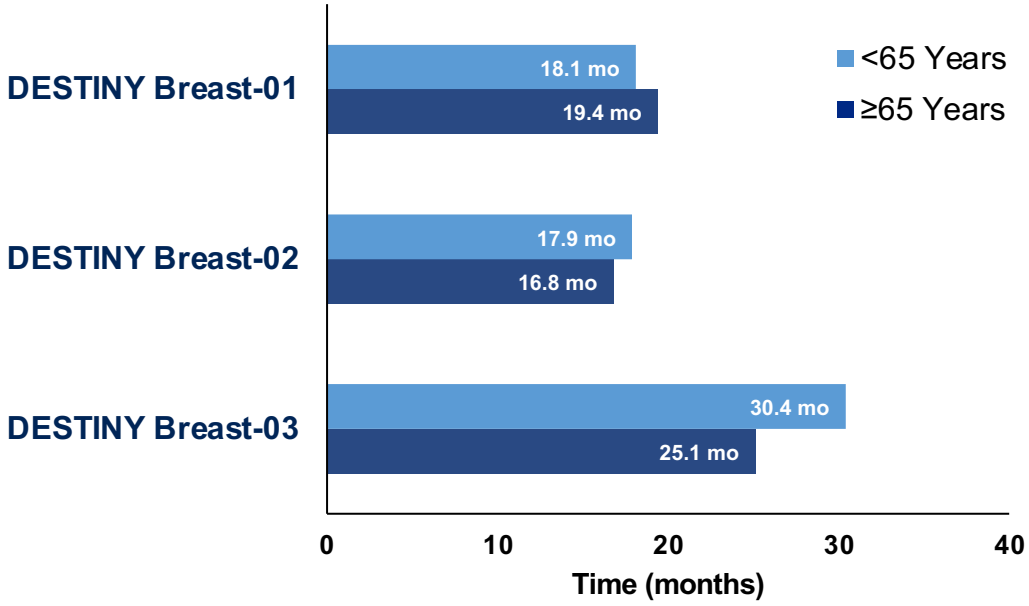
DESTINY-Breast01, 02, and 03: Age-Specific Pooled Analysis of T-TXd in Patients with HER2+ MBC



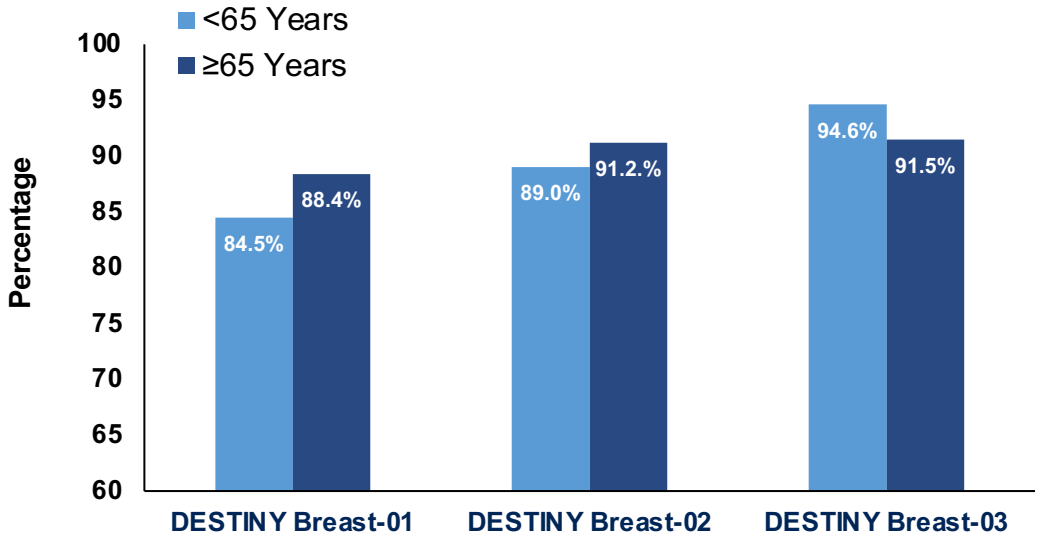
T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Krop I, et al. ASCO 2023. Abstract 1006.

Median Progression Free Survival



12-month Landmark Overall Survival

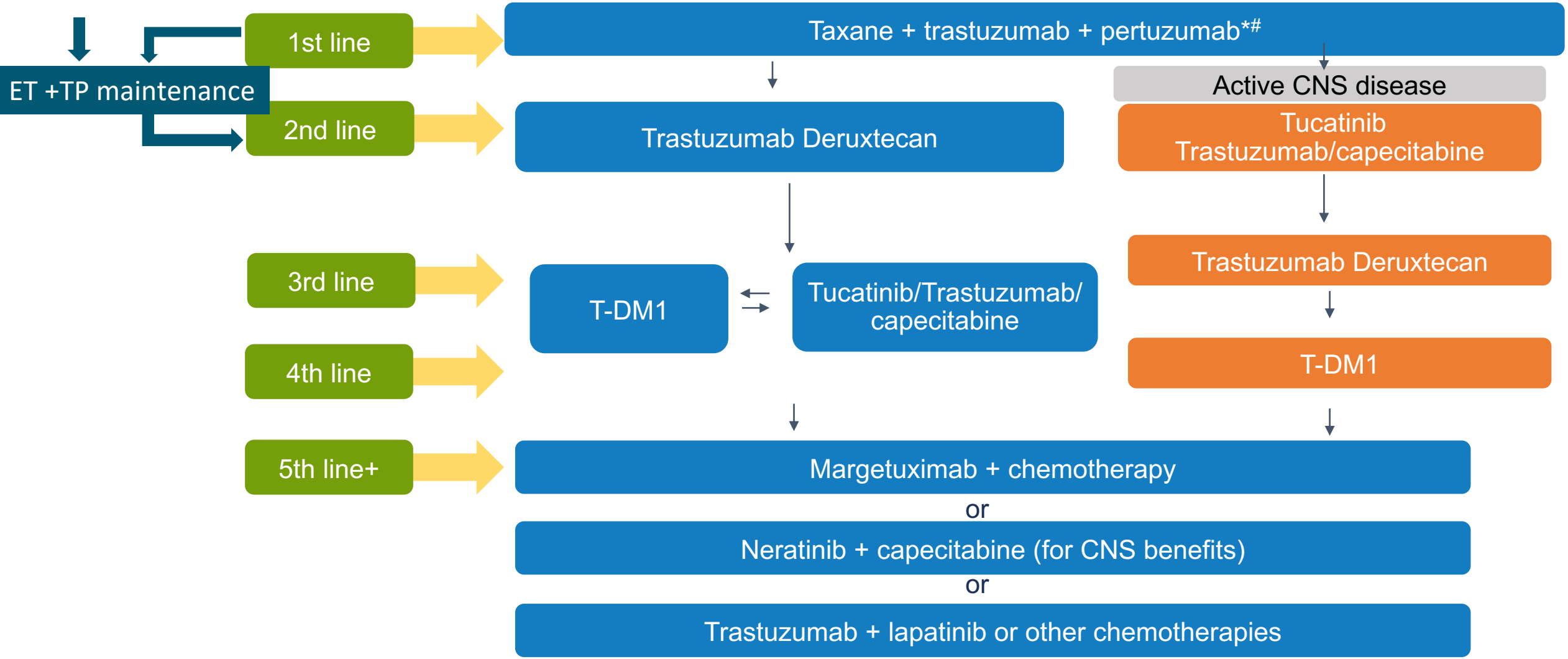


	DESTINY-Breast01		DESTINY-Breast02		DESTINY-Breast03	
	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
mOS, months (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)

- mPFS and confirmed ORR by BICR were similar with T-DXd in patients <65 and ≥65 years of age within each trial
- Patients ≥65 years of age experienced more grade ≥3 TEAEs across all trials
- Rates of adjudicated ILD/pneumonitis were generally higher in patients ≥65 years of age across all trials compared to patients <65 years of age
- Most drug-related ILD/pneumonitis cases were of low grade

Krop I, et al. ASCO 2023. Abstract 1006.

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

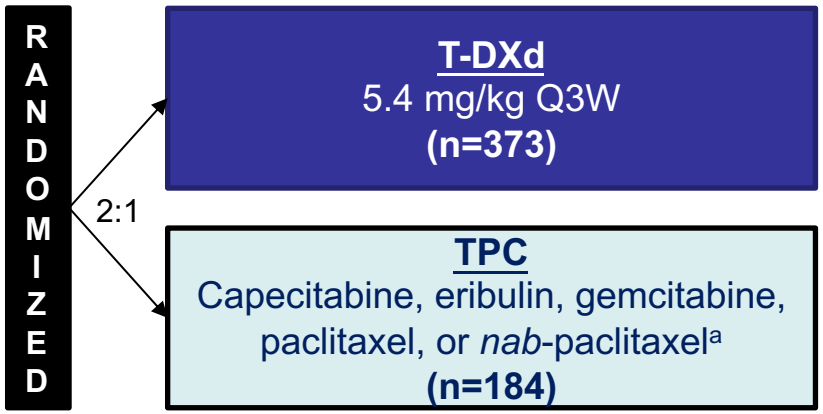
Select Trials in Progress with T-DXd: HER2+

- Early stage
  - Destiny Breast05 (NSABP B-60)
    - T-DM1 vs T-DXd as post neoadjuvant therapy (n=1600)
      - Question: Safety of concurrent radiation therapy?
        - Katherine trial: radiation pneumonitis 1.5 vs 0.7%, no difference in radiation skin injury
  - 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)

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
- 1-2 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



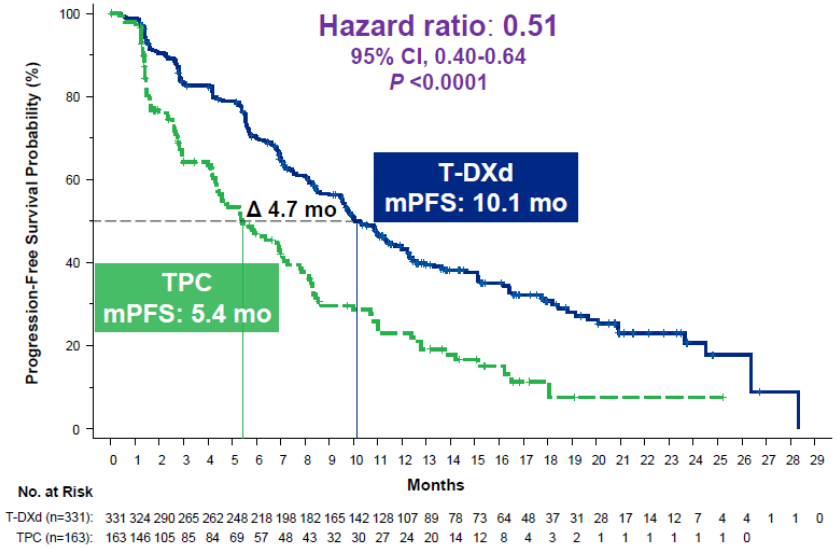
Primary endpoint: PFS by BICR (HR+)
Key secondary endpoints[b]: PFS by BICR (all patients), OS (HR+ and all patients)

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)

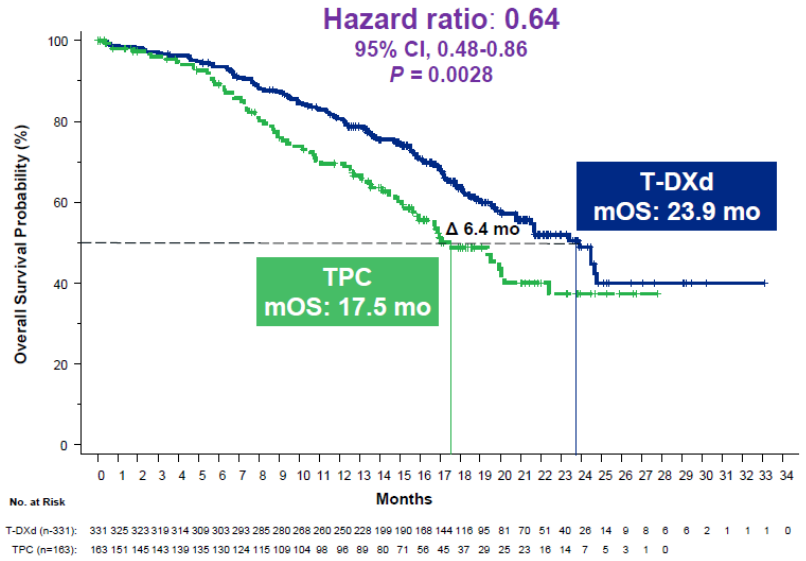
Data cutoff Jan 11, 2022.
[a] TPC was administered according to the label. [b] Other secondary endpoints included ORR (BICR and INV), DOR (BICR), PFS (INV), and safety. Efficacy in the HR- cohort was an exploratory endpoint. [c] HR status was based on data collected using interactive web/voice response system at randomization, which includes mis-stratified patients.
Modi S, et al. *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+		HR-		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=40)	TPC (n=18)	T-DXd (n=373)	TPC (n=184)
Median PFS, months	10.1	5.4	8.5	2.9	9.9	5.1
HR (95% CI); *P* value	0.51 (0.40-0.64); <0.0001		0.46 (0.24-0.89)		HR 0.50 (0.40-0.63); <0.0001	

OS	HR+		HR-		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=40)	TPC (n=18)	T-DXd (n=373)	TPC (n=184)
Median OS, months	23.9	17.5	18.2	8.3	23.4	16.8
HR (95% CI); *P* value	HR 0.64 (0.48-0.86); 0.0028		0.48 (0.24-0.95)		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., NEJM 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

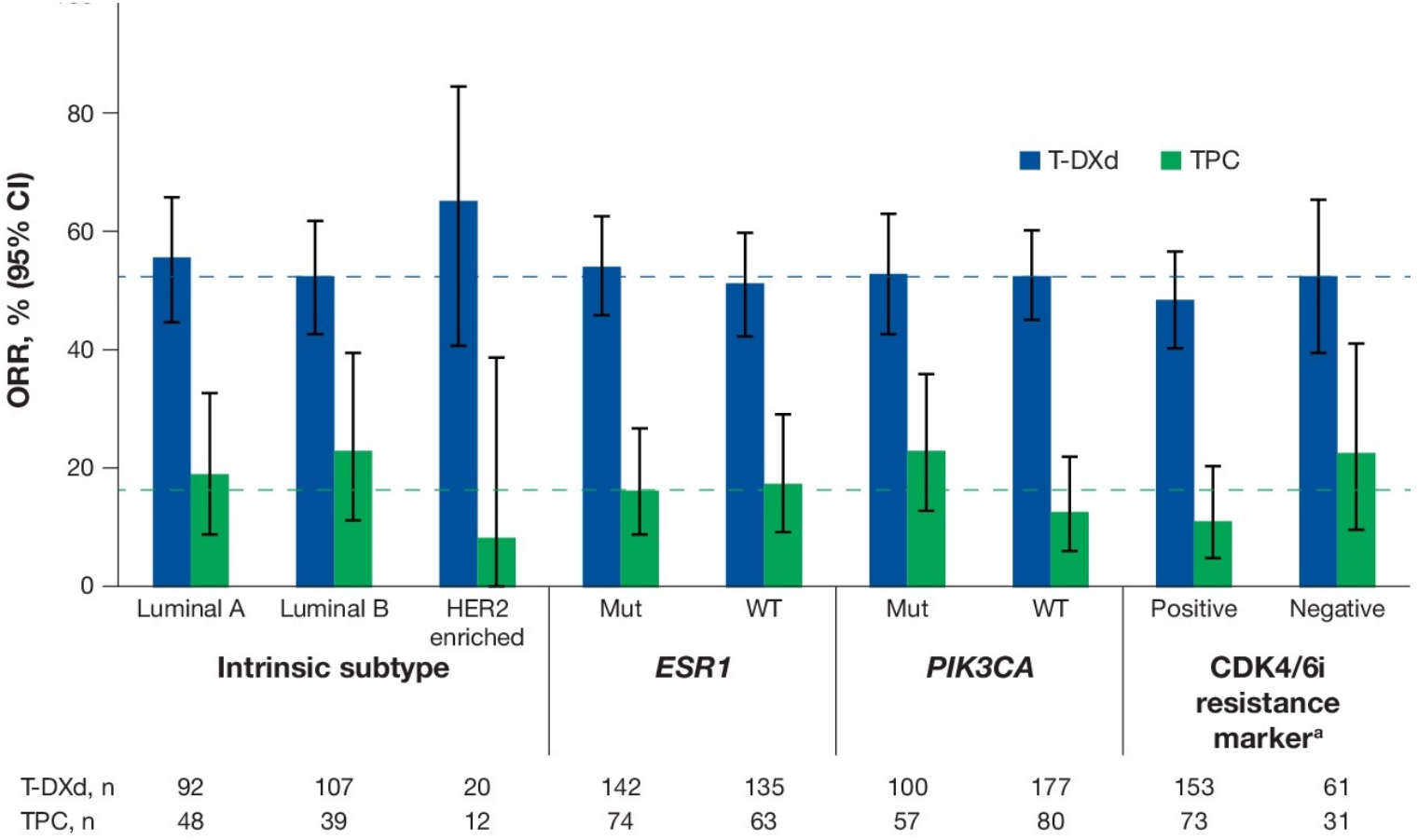
- **78% (823/1060) of samples designated as HER2-low by prior historical (local) result were confirmed as HER2-low by central testing using the PATHWAY HER2 4B5 assay** (and INFORM HER2 Dual ISH DNA Probe Cocktail when applicable)
- **Among the 22% (237/1060) of discordant samples**, **208/237 (88%) 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.

Biomarker Results From the Phase 3 DESTINY-Breast04 Trial of T-DXd in HR+/HER2-Low MBC

ORR According to Baseline Biomarker Status

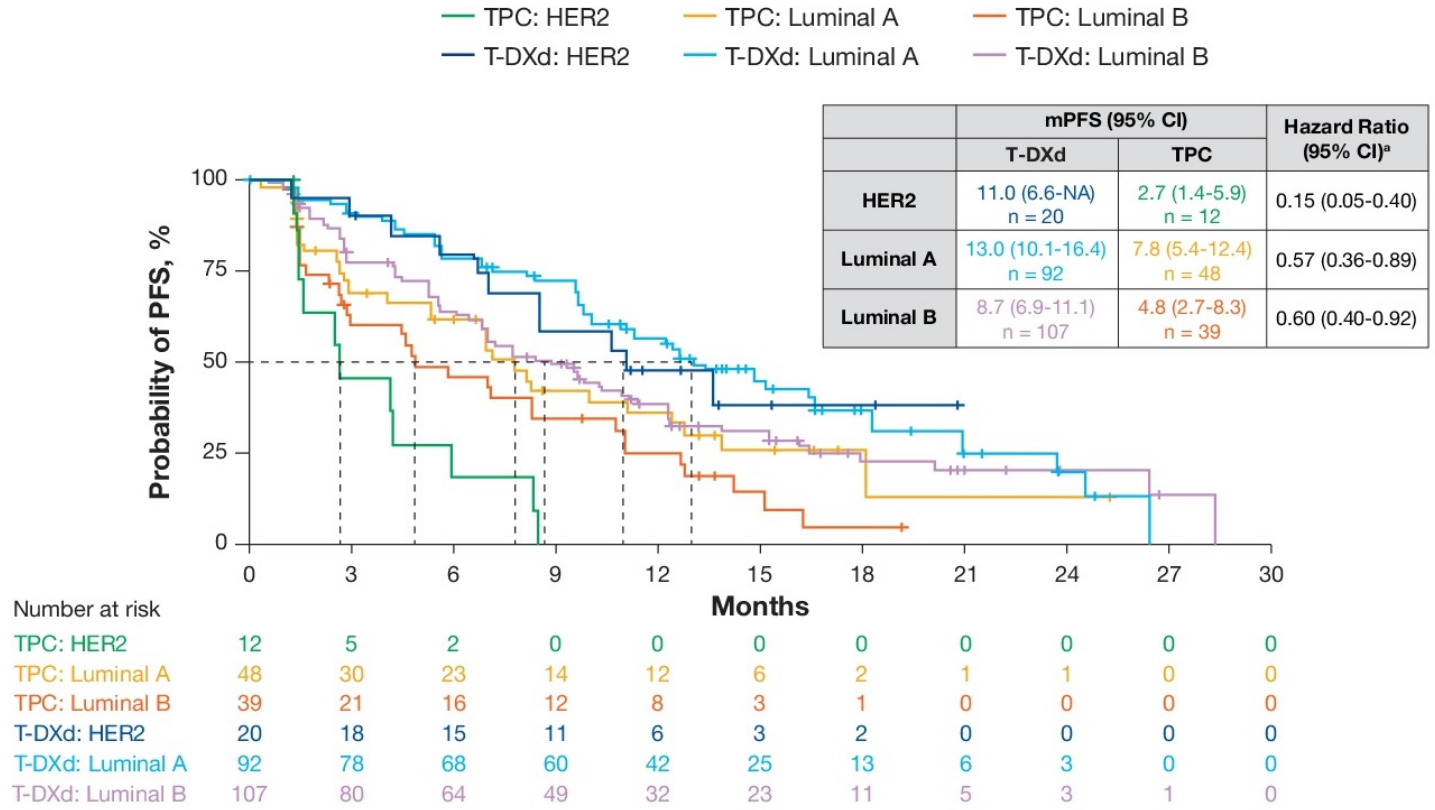


- Intrinsic subtypes estimated by PAM50 gene expression from sequencing of mRNA isolated from tumor tissue collected after prior treatment
- PIK3CA and ESR1 mutations and CDK4/6i resistance markers based on baseline ctDNA analysis on baseline blood samples (Guardant OMNI panel: alterations in approximately 500 genes)
- Known gene alterations associated with resistance to CDK4/6i included CCND1,CCNE1, CDK6, and FGFR1/2 amplification and RB1, PTEN, RAS, AKT1, ERBB2, and FAT1 mutations

[a] *CCDN1*, *CCNE1*, *CDK6*, *FGFR1/2* amplification; *RB1, PTEN, RAS, AKT1, ERBB2*, and *FAT1* mutations.

Modi S, et al. ASCO 2023. Abstract 1020.

PFS by Intrinsic Subtype, PIK3CAm, ESR1m and CDK4/6i Resistance Markers



	mPFS (95% CI)		Hazard Ratio (95% CI)[a]
	T-DXd	TPC	
HER2	11.0 (6.6-NA) n = 20	2.7 (1.4-5.9) n = 12	0.15 (0.05-0.40)
Luminal A	13.0 (10.1-16.4) n = 92	7.8 (5.4-12.4) n = 48	0.57 (0.36-0.89)
Luminal B	8.7 (6.9-11.1) n = 107	4.8 (2.7-8.3) n = 39	0.60 (0.40-0.92)

PIK3CA	mPFS, mo (95% CI) T-DXd	TPC	Hazard Ratio (95% CI)
WT	10.0 (8.5-12.2)	4.8 (2.9-8.3)	0.50 (0.35-0.70)
Mut	9.7 (7.5-12.3)	6.2 (5.3-7.8)	0.60 (0.40-0.91)

ESR1	mPFS, mo (95% CI) T-DXd	TPC	Hazard Ratio (95% CI)
WT	10.0 (8.3-12.6)	5.3 (4.0-7.8)	0.43 (0.29-0.62)
Mut	9.8 (8.2-12.0)	6.9 (4.3-10.7)	0.67 (0.47-0.97)

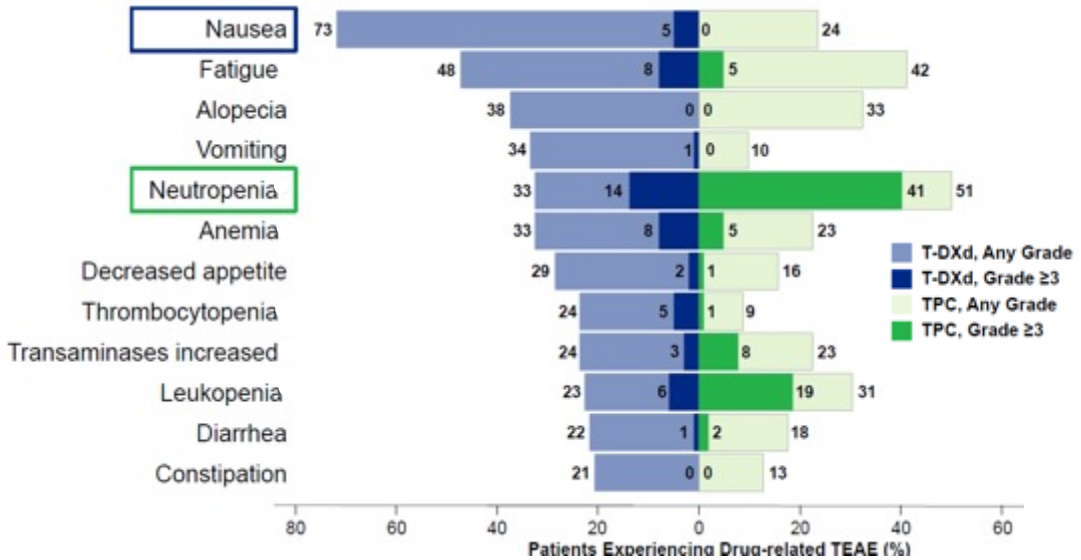
CDK4/6i Resistance[a]	mPFS, mo (95% CI) T-DXd	TPC	Hazard Ratio (95% CI)
Negative	12.3 (8.4-23.7)	8.4 (5.4-12.8)	0.57 (0.33-1.00)
Positive	9.5 (6.9-10.3)	5.3 (2.9-7.1)	0.56 (0.39-0.80)

CDK4/6i Resistance[a]	mPFS, mo (95% CI) T-DXd	TPC	Hazard Ratio (95% CI)
Negative	17.9 (9.0-NA)	7.1 (0.6-12.4)	0.26 (0.10-0.65)
Positive	9.7 (7.0-12.2)	4.8 (1.6-12.7)	0.55 (0.29-1.00)

Modi S, et al. ASCO 2023. Abstract 1020.

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

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

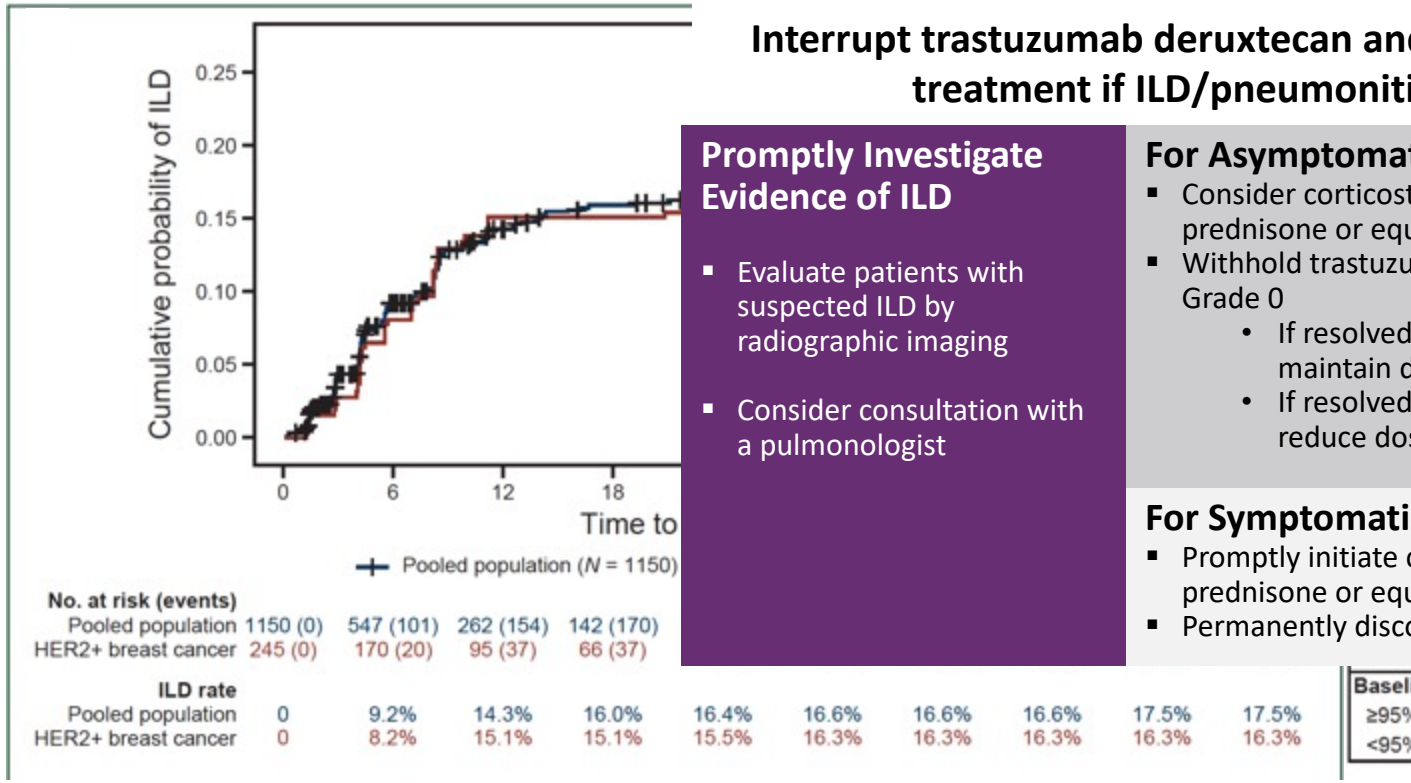
AEs of Special Interest, n (%)			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Adjudicated as drug-related ILD/pneumonitis[a]		**T-DXd (n=371)**	**13 (3.5)**	**24 (6.5)**	**5 (1.3)**	**0**	**3 (0.8)**	**45 (12.1)**
		TPC (n=172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction[b]	Ejection fraction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

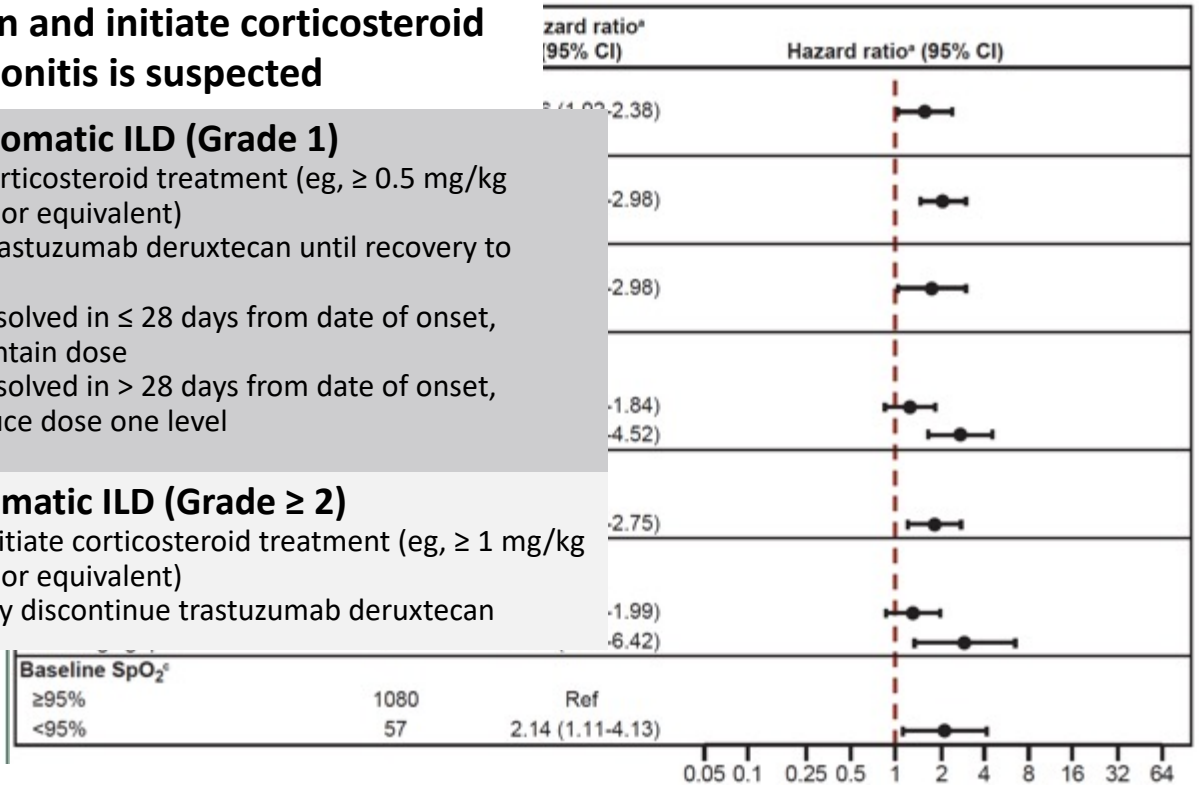
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

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

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

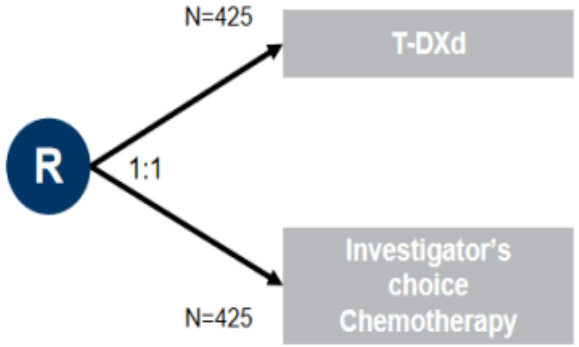
POPULATION

- 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

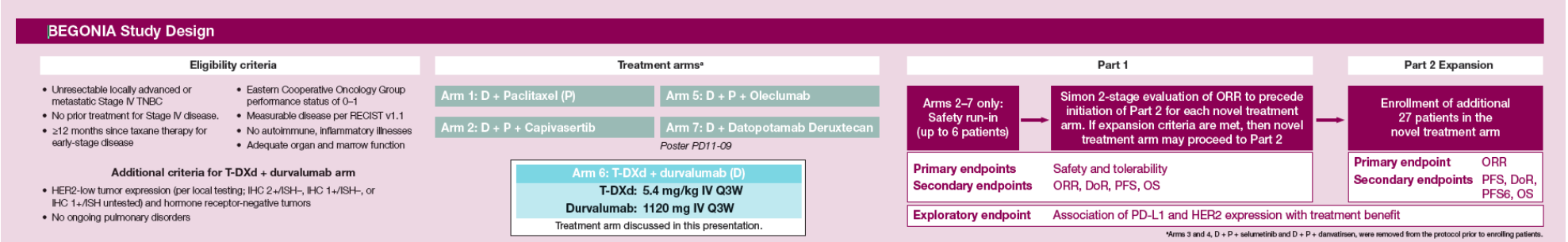
Secondary:

- 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

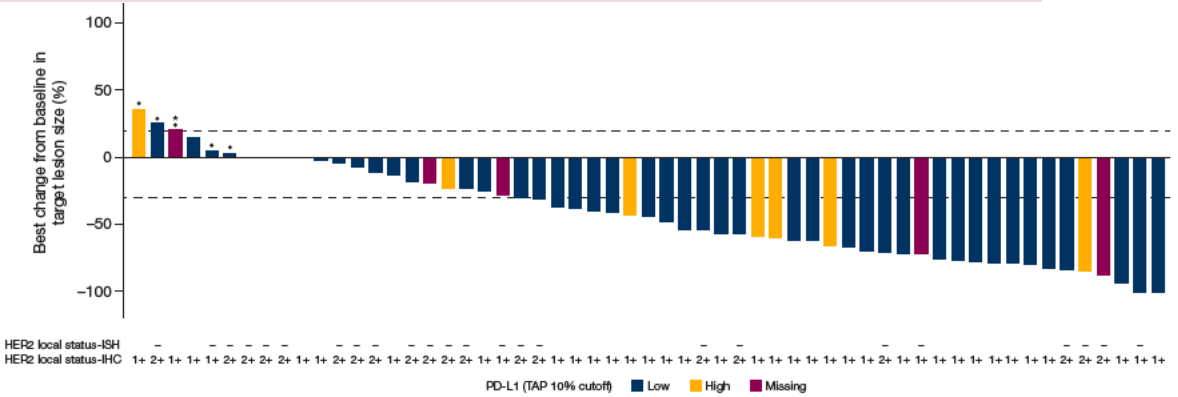
Exploratory:

- PRO
- Pharmacodynamic biomarkers

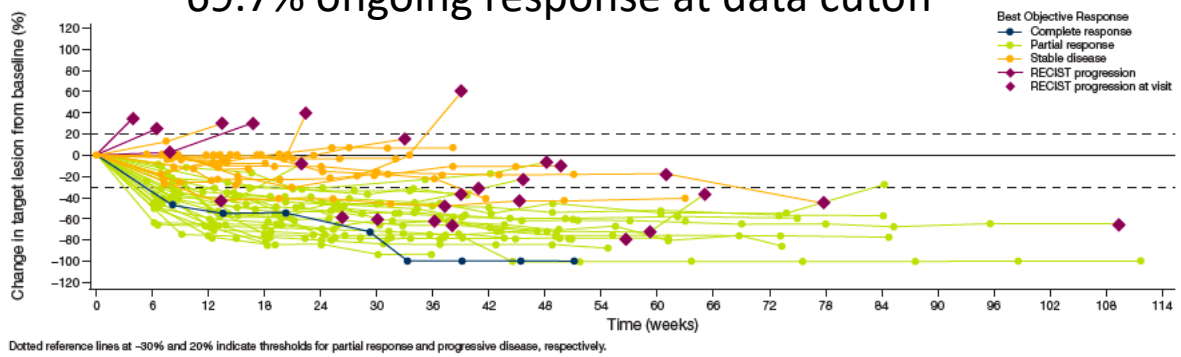
T-DXd + Durvalumab: The Begonia Trial



- 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

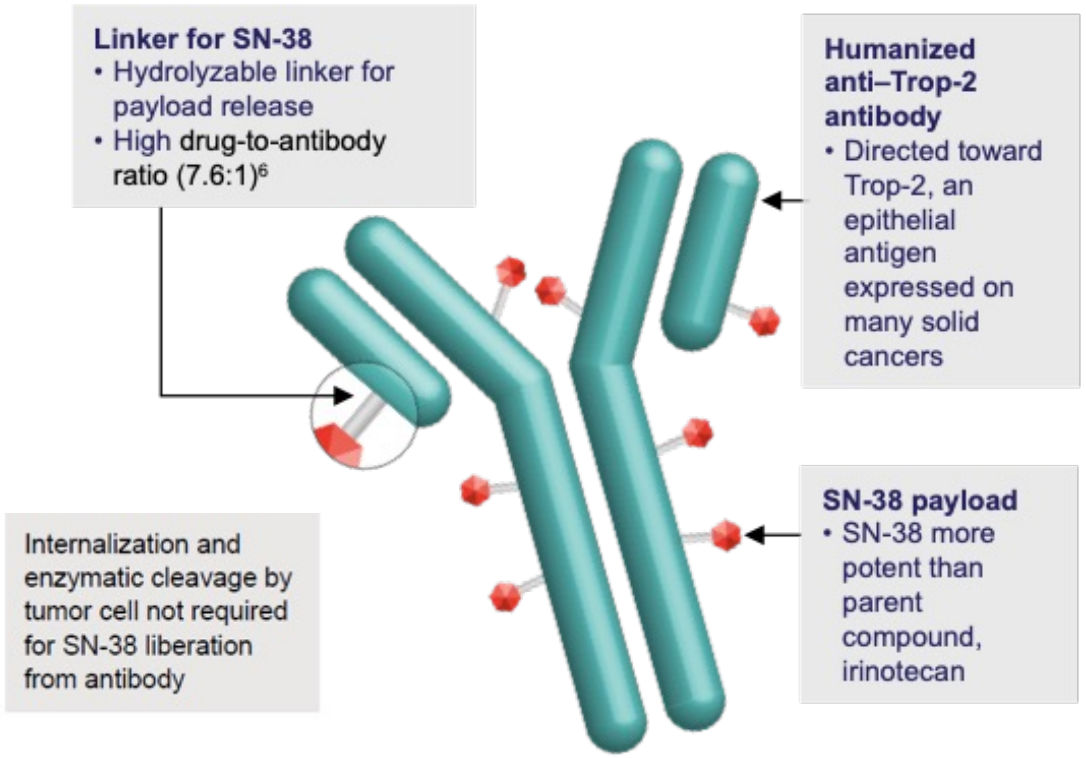


69.7% ongoing response at data cutoff



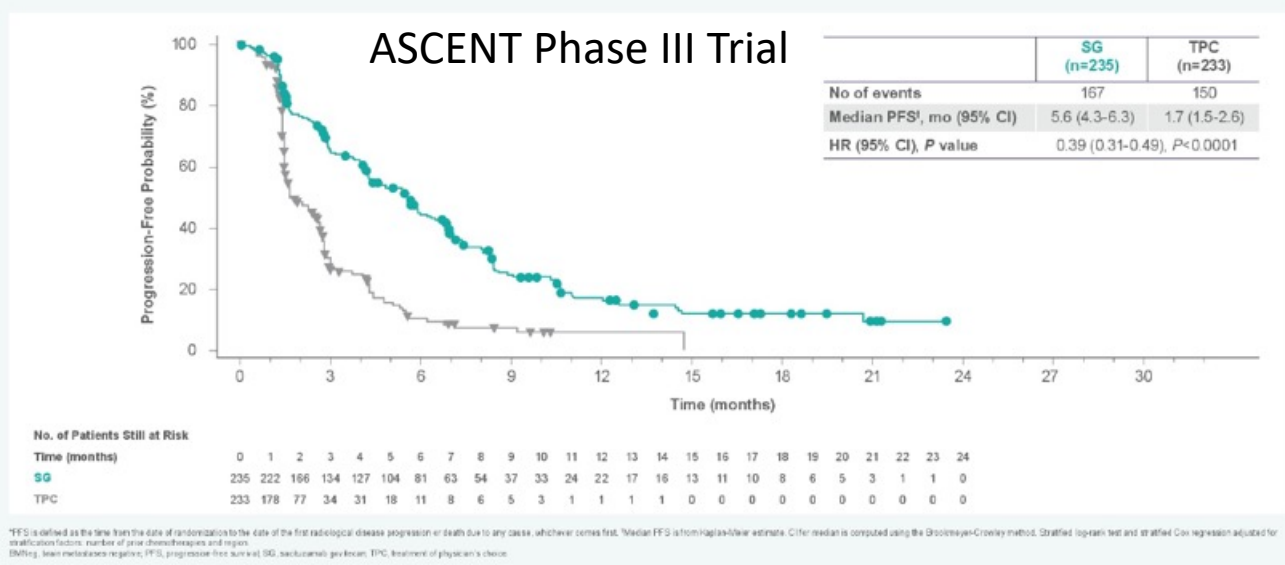
Schmid et al, SABCS 2022; PD11-08

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

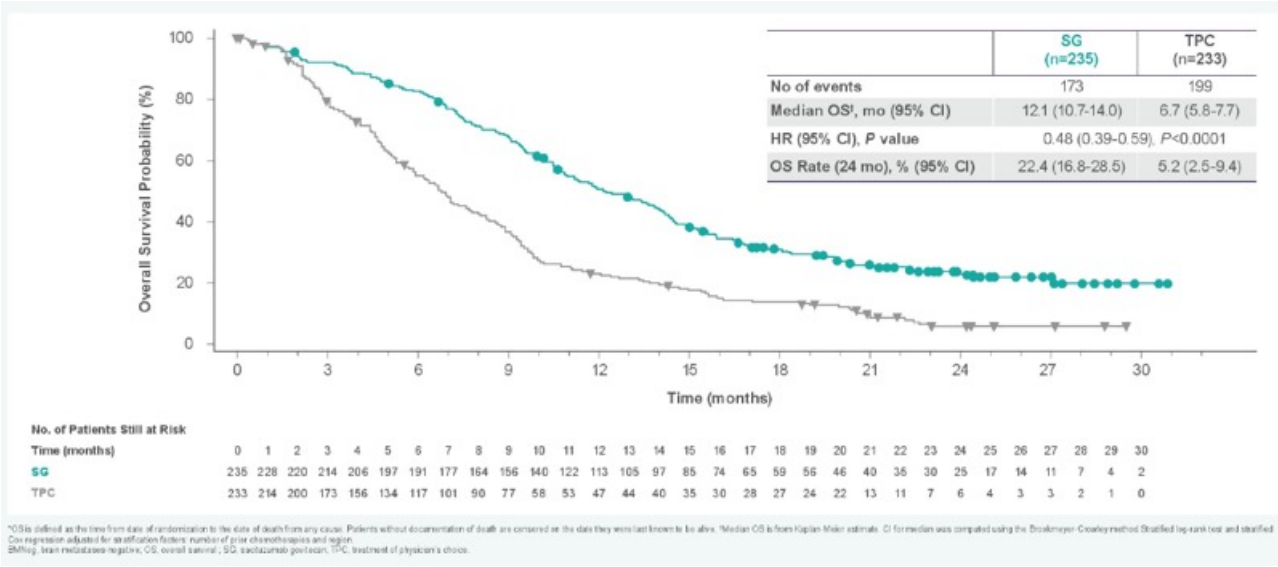


- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- **Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), FN (6% vs 2%)**
  - G-CSF: 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
  - No severe CV toxicity, no grade >2 neuropathy or grade >3 ILD with SG

ASCENT Phase III Trial



	SG (n=235)	TPC (n=233)
No of events	167	150
Median PFS[1], mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<0.0001	



	SG (n=235)	TPC (n=233)
No of events	173	199
Median OS[1], mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	0.48 (0.39-0.59), *P*<0.0001	
OS Rate (24 mo), % (95% CI)	22.4 (16.8-28.5)	5.2 (2.5-9.4)

Bardia et al. *NEJM*, 2021.

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

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan 10 mg/kg IV days 1 and 8, every 21 days n=272

Treatment of physician's choice[b] (capecitabine, vinorelbine, gemcitabine, or eribulin) n=271

Endpoints

Primary
- PFS by BICR

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

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

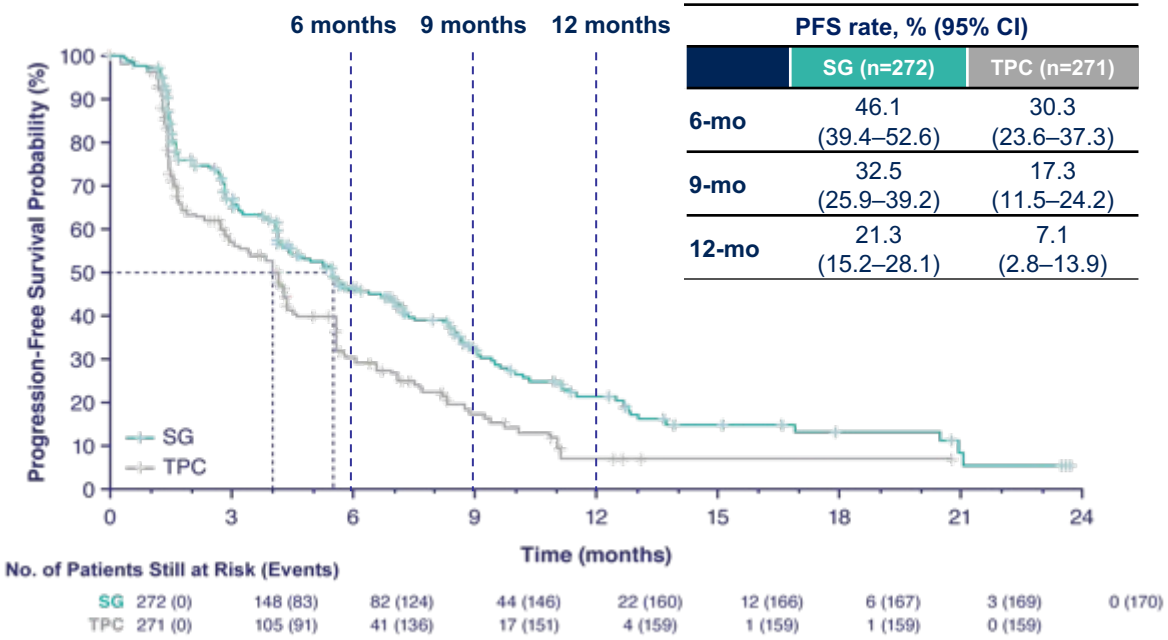
100% prior CDK4/6i
Median 3 lines of prior chemotherapy for MBC; median 4 years from diagnosis of MBC
95% visceral metastases

[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]

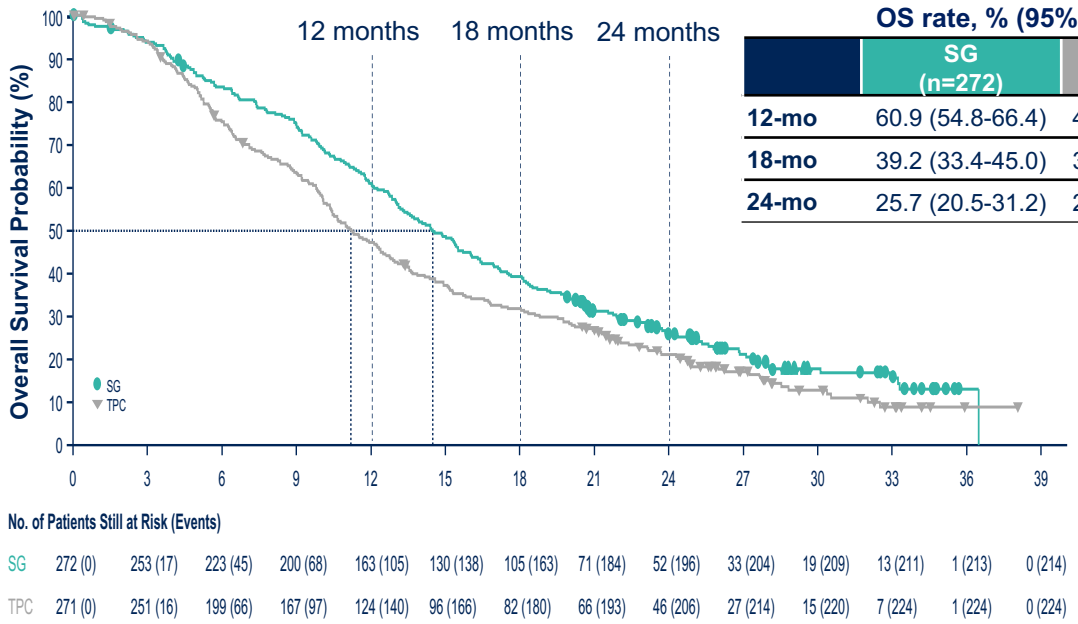
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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[2,3]

	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)	
Nominal *P* value	*P*=0.0133	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo	25.7 (20.5-31.2)	21.1 (16.3-26.3)

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.

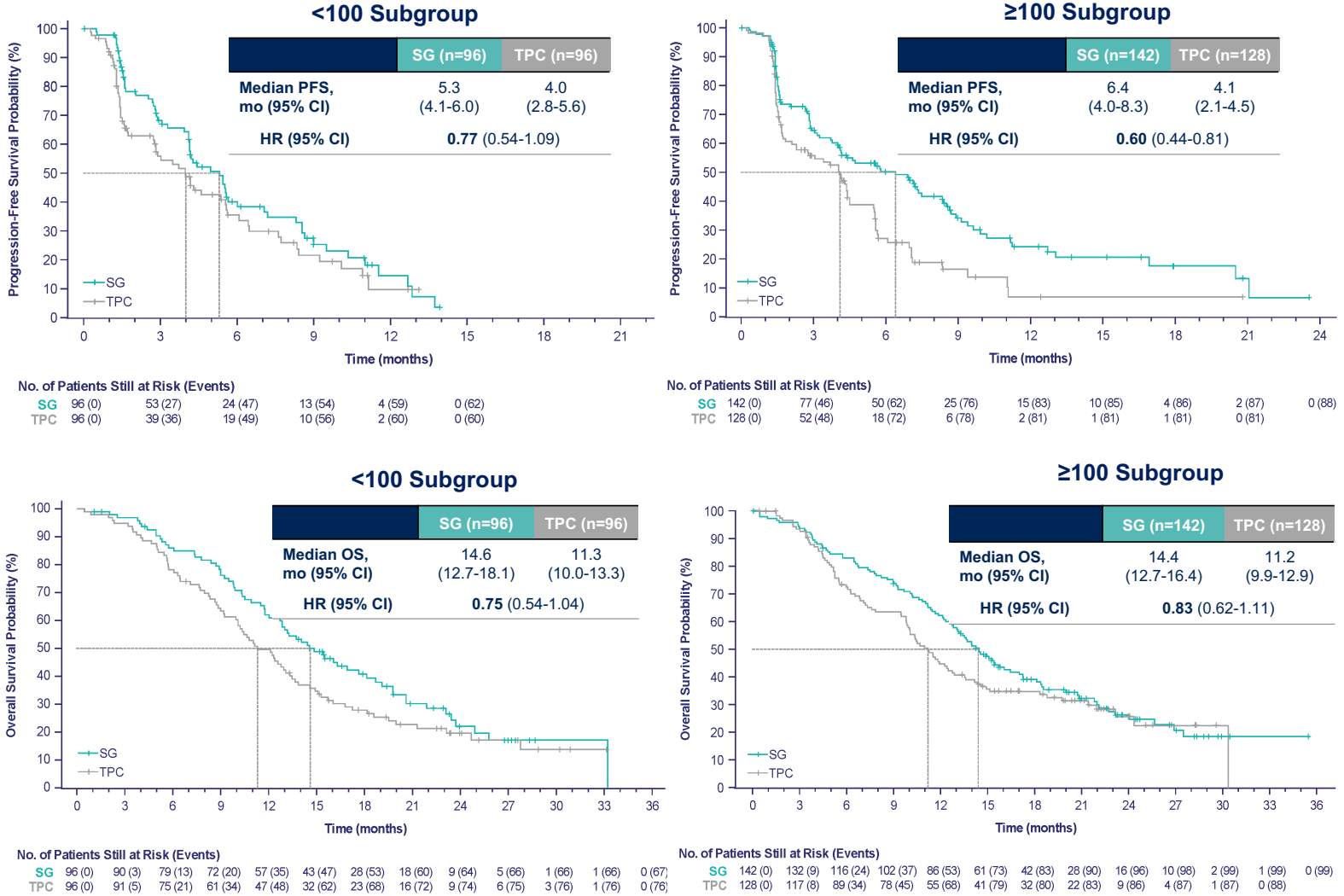
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol. 2022*. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76. 3. Tolaney et al, ASCO Abstract 1003

No new toxicity signals compared to ASCENT

Efficacy by Trop-2 Expression in the TROPiCS-02

- 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

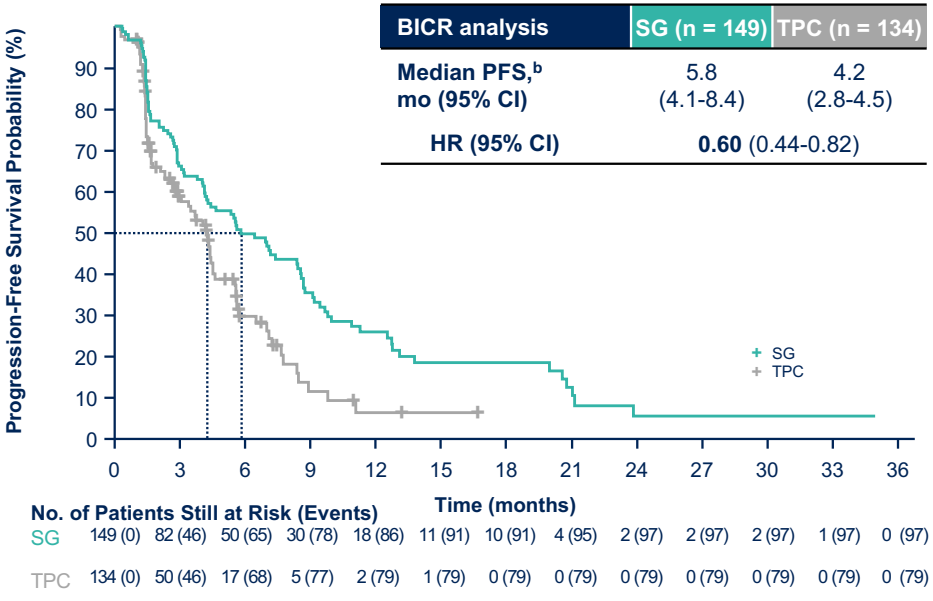
No Impact of TROP2 expression on efficacy



Rugo et al, SABCS 2022; GS5-11; similar data with mRNA from Bardia et al, ASCO 2023

Efficacy by HER-low Status in TROPiCS-02

HER2-low (IHC1+, IHC2+/ISH-)[a]

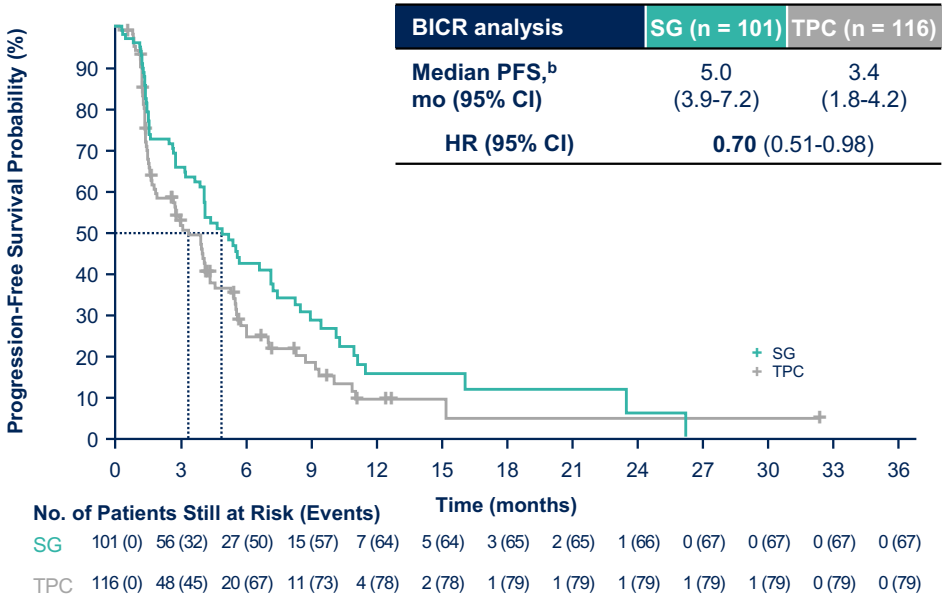


BICR analysis	SG (n = 149)	TPC (n = 134)
Median PFS,[b] mo (95% CI)	5.8 (4.1-8.4)	4.2 (2.8-4.5)
HR (95% CI)	**0.60** (0.44-0.82)	

No. of Patients Still at Risk (Events)

SG	149 (0)	82 (46)	50 (65)	30 (78)	18 (86)	11 (91)	10 (91)	4 (95)	2 (97)	2 (97)	2 (97)	1 (97)	0 (97)
TPC	134 (0)	50 (46)	17 (68)	5 (77)	2 (79)	1 (79)	0 (79)	0 (79)	0 (79)	0 (79)	0 (79)	0 (79)	0 (79)

HER2 IHC0[a]

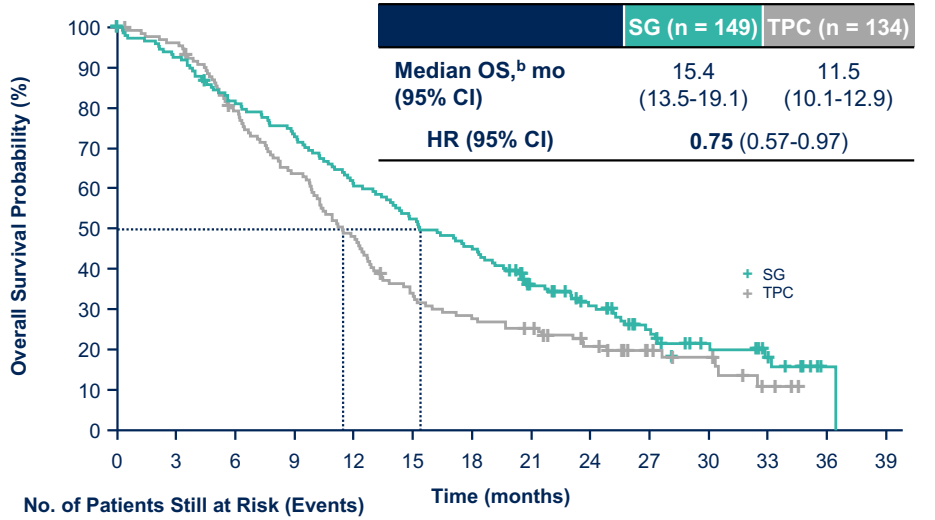


BICR analysis	SG (n = 101)	TPC (n = 116)
Median PFS,[b] mo (95% CI)	5.0 (3.9-7.2)	3.4 (1.8-4.2)
HR (95% CI)	**0.70** (0.51-0.98)	

No. of Patients Still at Risk (Events)

SG	101 (0)	56 (32)	27 (50)	15 (57)	7 (64)	5 (64)	3 (65)	2 (65)	1 (66)	0 (67)	0 (67)	0 (67)	0 (67)
TPC	116 (0)	48 (45)	20 (67)	11 (73)	4 (78)	2 (78)	1 (79)	1 (79)	1 (79)	1 (79)	1 (79)	0 (79)	0 (79)

HER2-low (IHC1+, IHC2+/ISH-)[a]

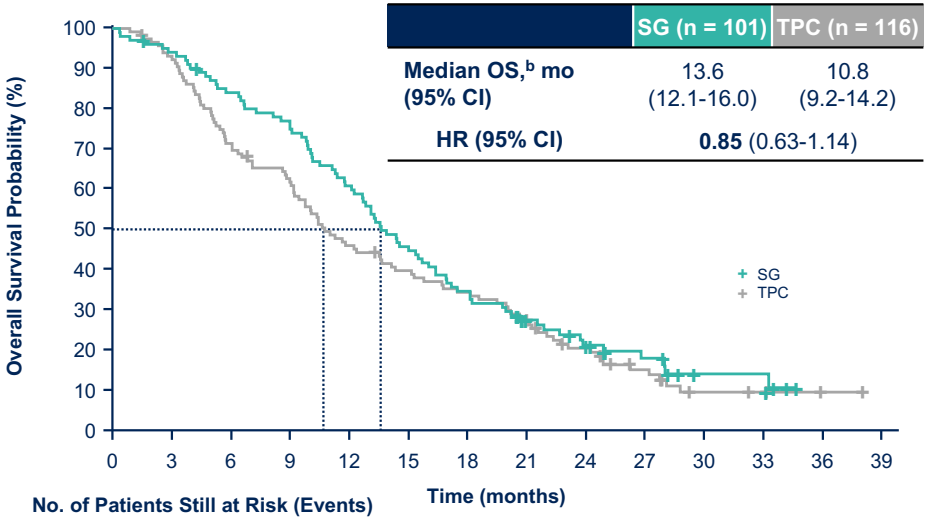


	SG (n = 149)	TPC (n = 134)
Median OS,[b] mo (95% CI)	15.4 (13.5-19.1)	11.5 (10.1-12.9)
HR (95% CI)	**0.75** (0.57-0.97)	

No. of Patients Still at Risk (Events)

SG	149 (0)	137 (11)	120 (27)	108 (39)	91 (56)	77 (70)	67 (80)	46 (94)	35 (100)	22 (106)	14 (109)	9 (111)	1 (112)	0 (113)
TPC	134 (0)	126 (5)	102 (27)	82 (47)	62 (67)	43 (85)	36 (92)	31 (96)	22 (101)	13 (102)	9 (103)	3 (106)	0 (106)	0 (106)

HER2 IHC0[a]



	SG (n = 101)	TPC (n = 116)
Median OS,[b] mo (95% CI)	13.6 (12.1-16.0)	10.8 (9.2-14.2)
HR (95% CI)	**0.85** (0.63-1.14)	

No. of Patients Still at Risk (Events)

SG	101 (0)	94 (6)	83 (16)	76 (23)	60 (39)	45 (54)	34 (65)	22 (72)	15 (77)	10 (79)	4 (81)	4 (81)	0 (82)	0 (82)
TPC	116 (0)	107 (8)	82 (33)	71 (43)	52 (62)	44 (69)	38 (75)	29 (83)	20 (90)	12 (95)	5 (99)	4 (99)	1 (99)	0 (99)

Tolaney et al, ASCO Abstract 1003

Safety Summary

TEAEs,[a] n (%)		SG (n = 268)		TPC (n = 249)	
		Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hematologic	Neutropenia[b]	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia[c]	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia[d]	17 (6)	1 (<1)	41 (16)	9 (4)
Gastrointestinal	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)
	Dyspnea	49 (18)	5 (2)	39 (16)	11 (4)
	Headache	44 (16)	1 (<1)	36 (14)	2 (1)
	Pyrexia	39 (15)	2 (1)	45 (18)	0
	AST increased	33 (12)	4 (1)	44 (18)	8 (3)

The most common grade ≥ 3 TEAEs were neutropenia (52%), diarrhea (10%), and anemia (7%) in the SG group, and neutropenia (39%), thrombocytopenia (4%), fatigue (4%), and dyspnea (4%) in the TPC group

UGT1A1 *28*28 homozygous (n=25/272; 9%): increased risk of diarrhea>neutropenia
Managed effectively by dose reduction/delay and antipropulsives

SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
TEAEs were defined as any AEs that began or worsened on or after the start of study drug through 30 days after the last dose of study drug.
[a]Key any-grade and grade ≥ 3 TEAEs were defined as those occurring in ≥ 15% or ≥ 10% of patients in 1 arm, respectively. [b]Combined preferred terms of "neutropenia" and "neutrophil count decreased." [c]Combined preferred terms of "anemia," "hemoglobin decreased," and "red blood cell count decreased." [d]Combined preferred terms of "thrombocytopenia" and "platelet count decreased."

Rugo et al, JCO 2022, ESMO 2022; Tolaney et al, ASCO Abstract 1003; Marme et al, ESMO BC 2023

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

Endpoints
Primary
- PFS

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

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

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

N=1200
HER2-negative early breast cancer

- At least 16 weeks of taxane-based NACT
- No pCR:
  - TNBC
  - HR-positive and CPS-EG score ≥3 or 2 and ypN+

R 1:1

→ Sacituzumab govitecan (8 cycles d1, 8 q3w)

→ Treatment of physician´s choice*

Follow-up

Stratification factors:
- HR-positive vs HR-negative
- ypN+ vs ypN-0

Phase III Trial: Optimice-RD/ASCENT-05
Residual disease in TNBC

Residual invasive TNBC disease in breast or positive node(s) after anthracycline, taxane, and checkpoint inhibitor-based neoadjuvant therapy
N = 1514

R 1:1

→ A: Sacituzumab Govitecan x 8 cycles + Pembrolizumab x 8 cycles

→ B: Pembrolizumab x 8 cycles (add-on capecitabine per physician's choice)

Follow-up

PI: Sara Tolaney; Alliance Foundation Trial

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Invasive Breast Cancer

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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

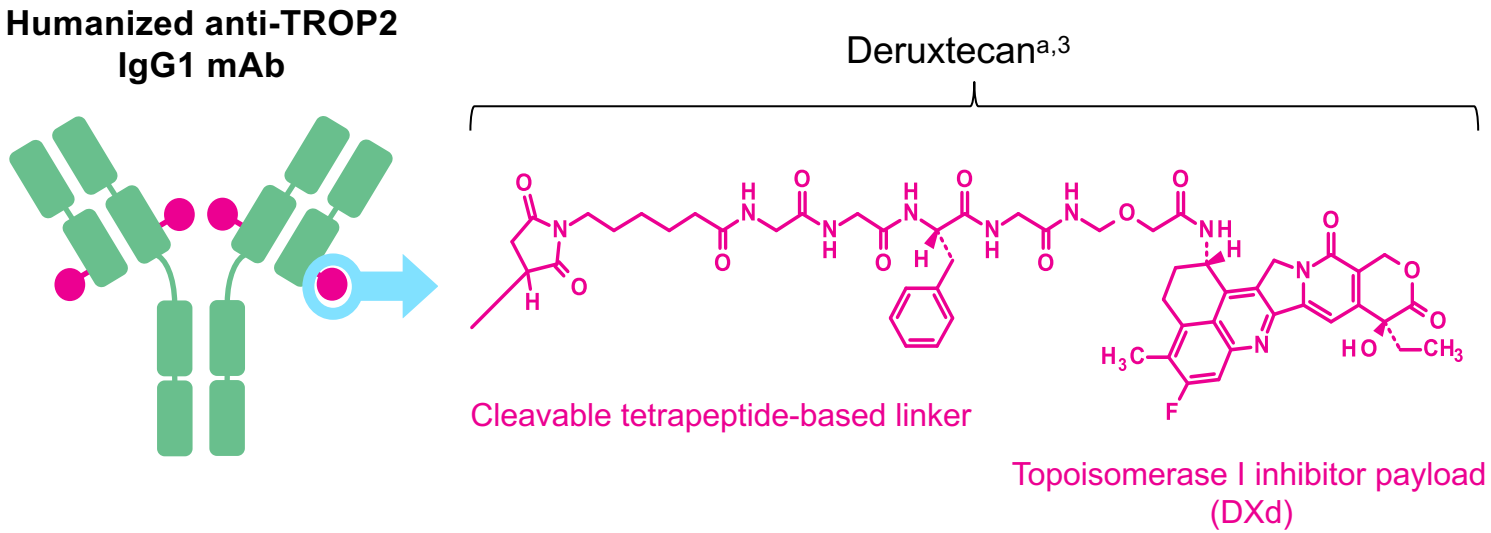
Sacituzumab FDA Approval

- 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 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,2,4]

[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. Krop I, et al. SABCS 2019; [abstract GS1-03]; 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

Phase 1 TROPION-PanTumor01: New Trop2 ADC Datopotomab Deruxtecan in HR+ and HR-/HER2- MBC

- 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)

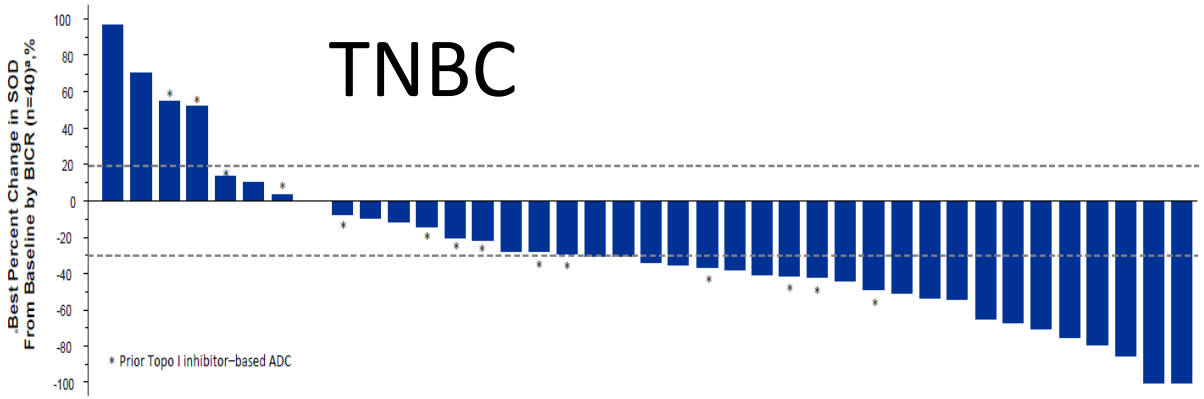
HR+/HER2− breast cancer 6 mg/kg IV Q3W (n=41)

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

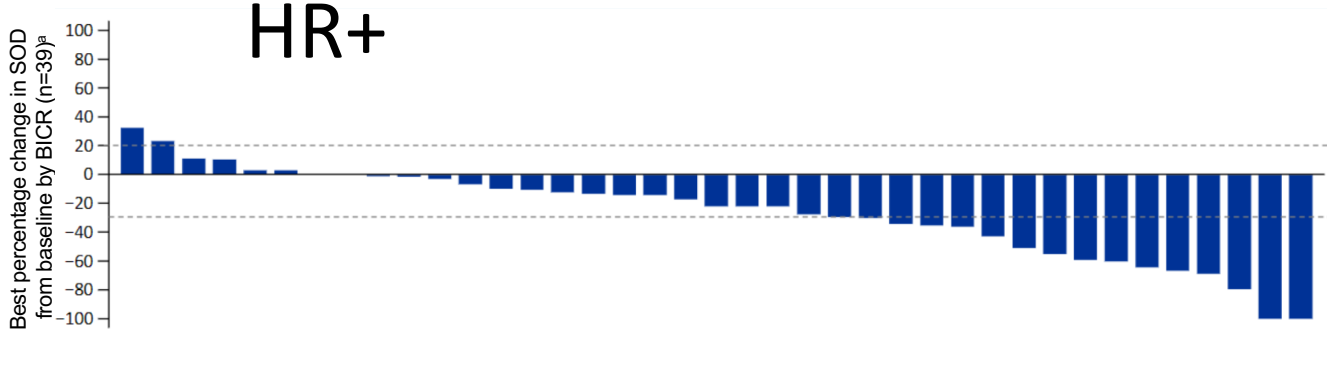
Primary objectives
- Safety
- Tolerability

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

TNBC



HR+



ORR by BICR:
- All patients: 32%
- Topo I inhibitor-naive patients: 44%
- Median PFS: 4.4-7.3 mo

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

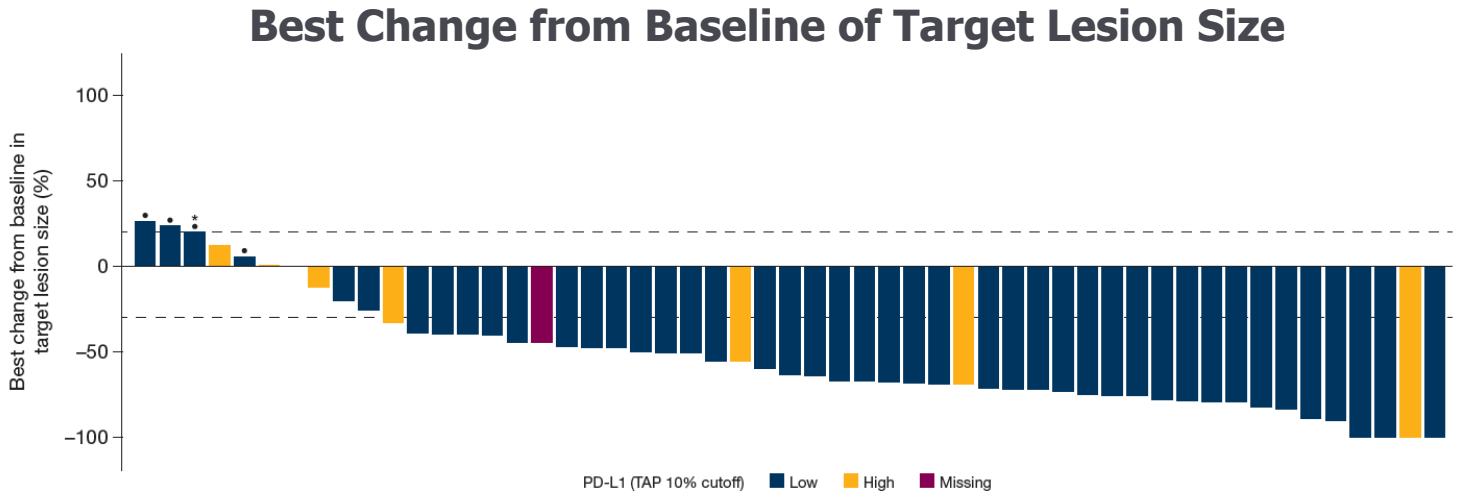
AEs:Most common TEAEs: stomatitis (73 -83%/grade 3 10%), nausea (66%), vomiting (39%)

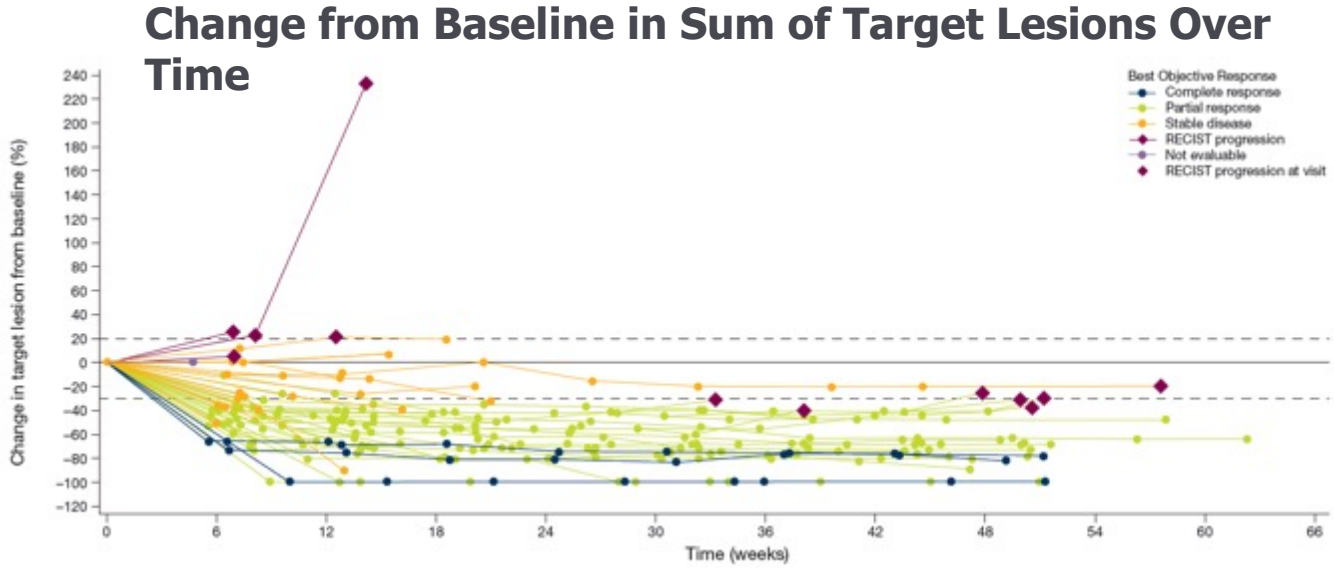
- ORR (all PR): 27%;
- CBR: 44%
- Med PFS 8.3 mo
- 59% alive for >1 year

Meric-Bernstam et al, SABCS 2022

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

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.

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

TROPION-Breast02

NCT05374512

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

- 1st line therapy for TNBC
- PD-L1 negative

Phase III TROPION Breast03

NCT05629585

N=1075
Stage I-III TNBC
Residual disease after at least 6 cycles of neoadjuvant chemotherapy

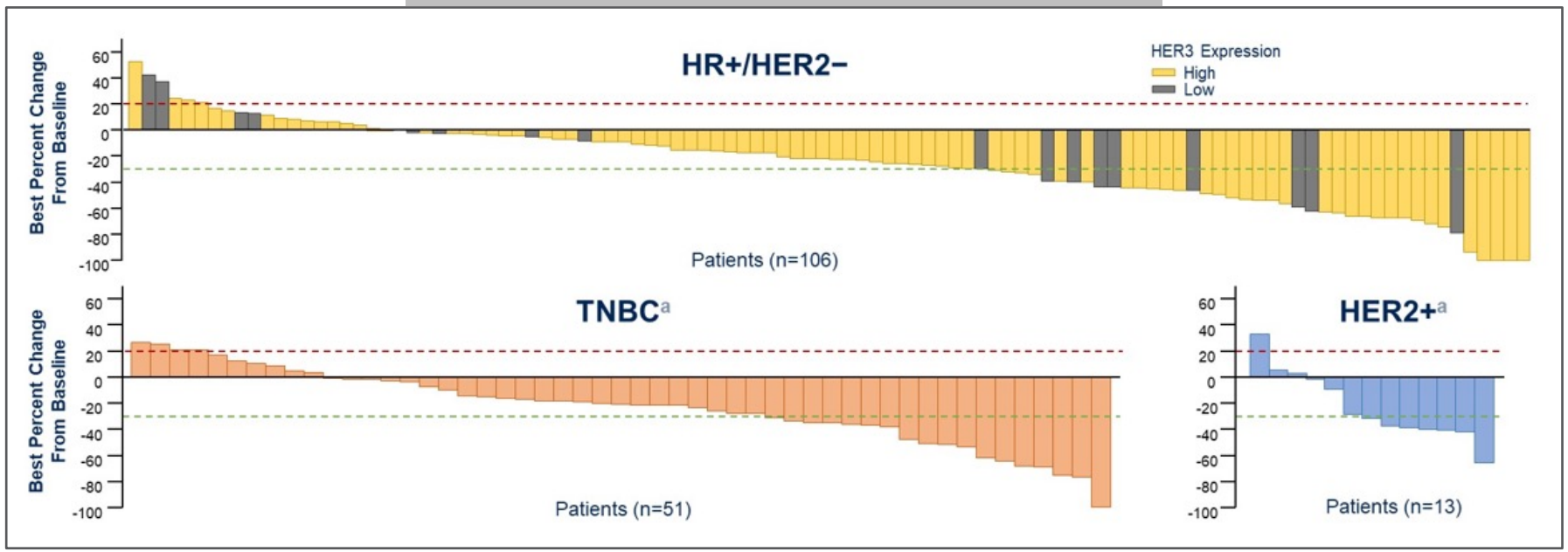
R
1:1:1

- Datopotamab deruxtecan x 8 cycles Durvalumab x 9 cycles
- Datopotamab deruxtecan x 8 cycles
- Capecitabine x 8 cycles OR Pembrolizumab x 9 cycles OR Cape + Pembro

Patritumab deruxtecan: Activity in HER3-expressing MBC

- Patritumab deruxtecan: Anti HER3 Ab (Patritumab) connected to a Topo I payload (DXd) via a cleavable linker
- Data from expansion of a phase 1/2 trial in HER3 expressing MBC
  - Heavily pretreated patient population with median priors ranging from 2-6 depending on subtype

Change in tumor size from baseline



Subtype	ORR	Median DoR
HR+/HER2-	30%	7.2 mo
HER2+	23%	5.9 mo
TNBC	43%	8.3 mo

FDA Fast track designation for metastatic EGFR mutated NSCLC

- ✓ **Durable antitumor activity in all BC subtypes across the range of HER3 expression**
- ✓ **Manageable safety profile with low rates of treatment discontinuation**
- ✓ **Most common toxicities: GI and heme**
  - **10% discontinuation due to AEs**
  - **27% grade 3 thrombocytopenia**
  - **6.6% ILD; 1 death**

Krop I et al. ASCO 2022, Abstract 1002

Results From a Phase 2 Study of HER3-DXd in MBC: Study Design and Patients

Key Eligibility Criteria

- ABC/MBC with ≥1 measurable lesion
- HER2– by ASCO/CAP (including HER2 zero and low expression)
- HR+ BC: ≤2 prior lines of Chemo in the metastatic setting; prior CDK4/6i required
- HR– BC (TNBC): 1-3 prior lines of Chemo in the metastatic setting

Part A (N=60) Activity and HER3 Expression
HER2– MBC
Patritumab deruxtecan 5.6 mg/kg IV q3w

Part B (N~20-40) Efficacy Analysis
Expansion in ≤3 select populations based on HER3 expression (25% to 74% and/or ≥75%) and ER expression (TNBC, low 1% to 10%, high >10%)

Part Z (N=21) Efficacy Analysis
HER2+ MBC post–T-DXd

Primary endpoint: ORR and 6-month PFS in HER2– MBC
Secondary endpoints: Safety, DOR, PFS, CBR in HER2– and HER2+ MBC

Patient Characteristics, n (%)		N=60
Sex/Age (years)	Male	1 (1.7)
	Female	59 (98.3)
	>18 to <65	43 (71.7)
	≥65 to <75	10 (16.7)
	≥75	6 (10.0)
ECOG	0	31 (51.7)
	1	29 (48.3)
Stage IV at diagnosis		13 (21.7)
BRCA1 mutated		2 (3.3)
BRCA2 mutated		1 (1.7)
Number of prior systemic regimens in metastatic setting	1-2	24 (40.0)
	≥3	36 (60.0)
	Median (range)	3 (1-9)
Type of prior regimen in metastatic setting	Chemotherapy	54 (90.0)
	PARPi	3 (5.0)
	Immunotherapy	12 (20.0)
	Sacituzumab govitecan	5 (8.3)

Hamilton EP, et al. ASCO 2023. Abstract 1004.

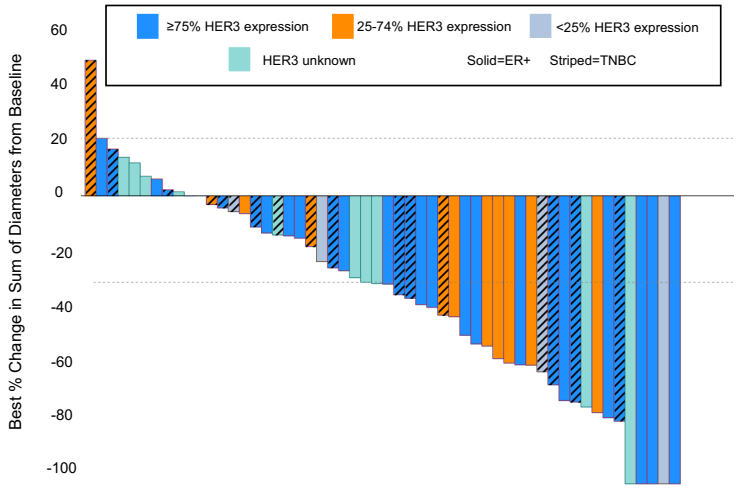
Data from Part A: HER3-DXd

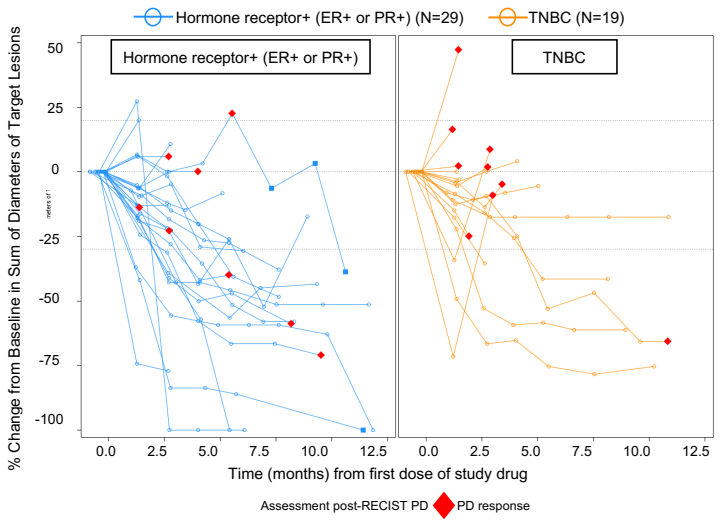
- 60 pts:
  - HR+: Prior CDKi, 0-2 chemo
  - TN: 1-3 chemo
  - 27 HR+/19 TN (n=48)
  - 64% HER3 ≥75%; 8% <25% (n=47)
- ORR 35%, CBR 43%,
  - No relationship to HER3 expression
- DOR ≥ 6mo: 47.6% in responders (n=10)
- Most common AE:
  - Nausea/diarrhea/fatigue
  - TEAE: 2 ILD, 1 low plt

	(N=60) n (%)
Number of Prior Systemic Regimens in Metastatic Setting	
1-2 prior regimens	24 (40.0)
3 or more prior regimens	36 (60.0)
Median (range)	**3 (1, 9)**
Type of Prior Regimens in the Metastatic Setting*	
Chemotherapy	54 (90.0)
PARP inhibitors	3 (5.0)
Immunotherapy	12 (20.0)
Sacituzumab govitecan	5 (8.3)

	HR+ (N=29)	TNBC (N=19)
ORR, n (%)	**12 (41.4)**	**4 (21.1)**
95% CI	(23.5, 61.1)	(6.1, 45.6)

	Any grade (N=60) n (%)	Grade 3/4 (N=60) n (%)
Any Adverse Event (AE)	56 (93.3)	19 (31.7)
Nausea	30 (50.0)	2 (3.3)
Fatigue	27 (45.0)	4 (6.7)
Diarrhea	22 (36.7)	3 (5.0)
Vomiting	19 (31.7)	1 (1.7)
Anemia	18 (30.0)	0
Alopecia	17 (28.3)	N/A
Hypokalemia	9 (15.0)	1 (1.7)
Decreased Appetite	8 (13.3)	0
Neutrophil Count Decreased**	7 (11.7)	3 (5.0)
White Blood Cell Count Decreased**	7 (11.7)	1 (1.7)



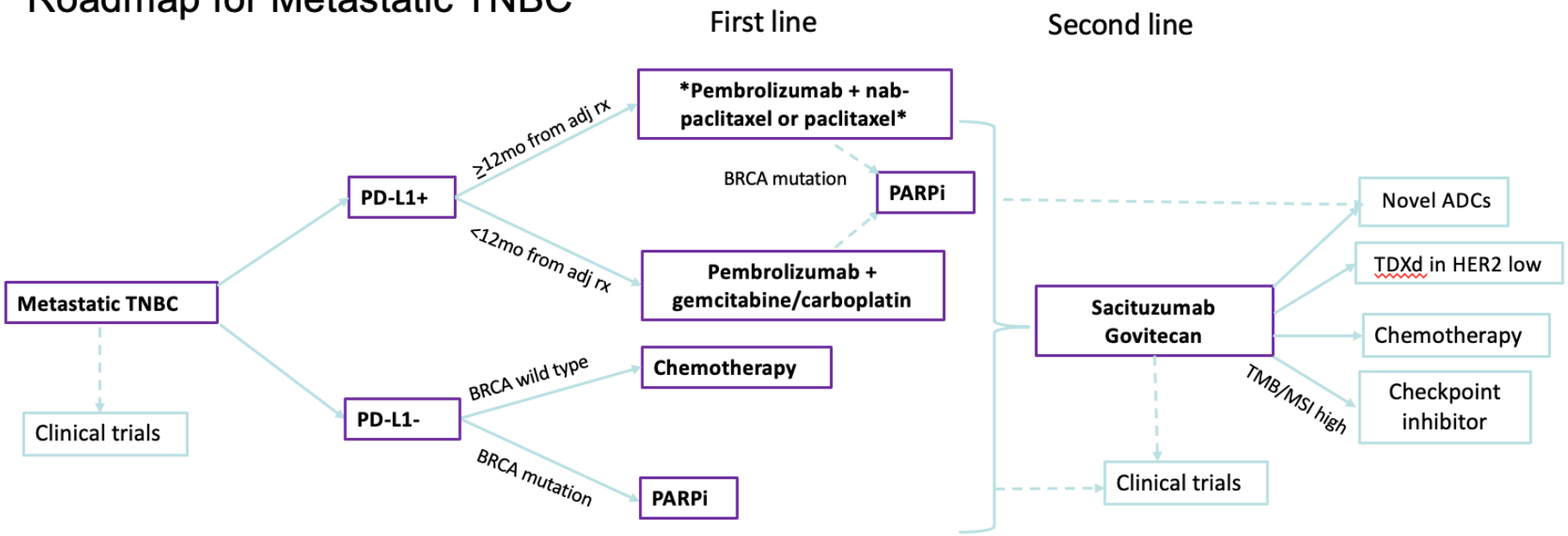


Hamilton et al, ASCO 2023

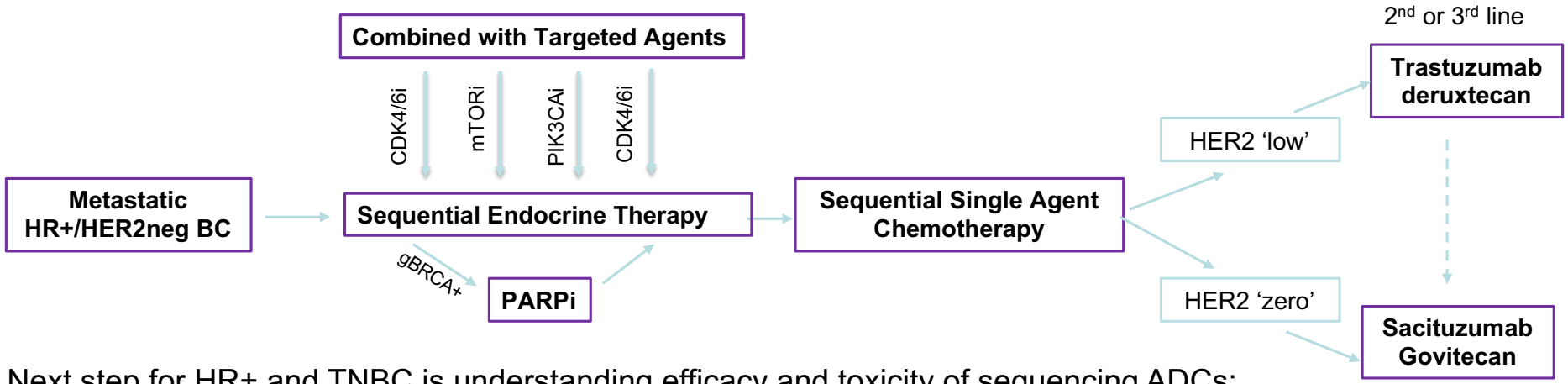
Conclusion

- **Antibody Drug Conjugates!**
  - **An exciting and effective drug delivery system for the treatment of multiple subtypes of MBC**
- **Remarkable efficacy in HER2+ disease**
  - Proven efficacy of sequential HER2 ADC with different payloads
- **Established role in TNBC**
  - SG is a new standard of care for mTNBC
- **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**
  - Combination data with radiation largely lacking

Roadmap for Metastatic TNBC



Roadmap for HR+/HER2- Metastatic Breast Cancer



Next step for HR+ and TNBC is understanding efficacy and toxicity of sequencing ADCs:

- TRADE-DXd (DFCI): DATO-Dxd and TDXd
- Sacituzumab sequenced registry trial (UCSF): SG and TDXd


Thank you!