UCSF Helen Diller Family Comprehensive Cancer Center

The New Wave: Antibody Drug Conjugates in the Treatment of Metastatic Breast Cancer

Hope S. Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center

ADCs: monoclonal antibody, conjugated drug, and stable linker

Monoclonal antibody

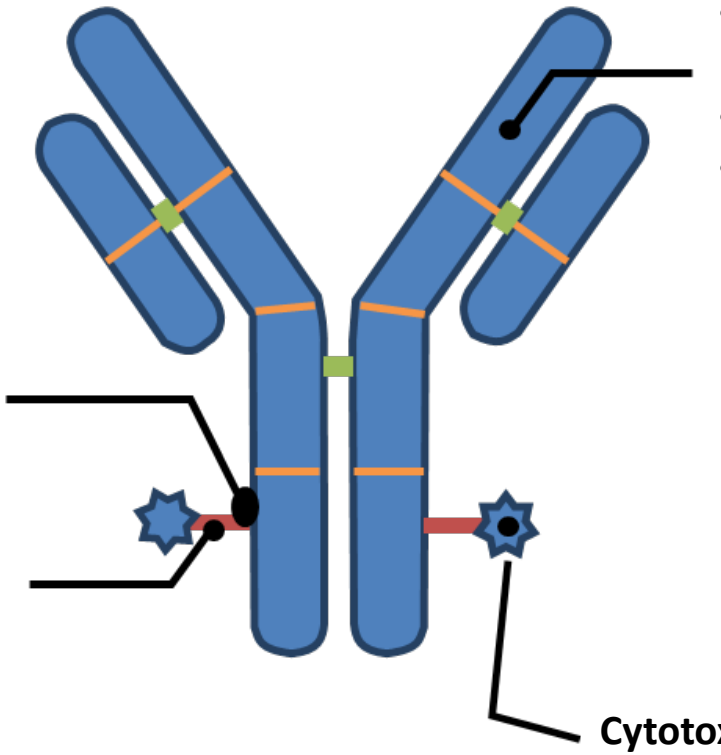
- Selective for an antigen with high copy numbers on the target tumour cell
- Internalises in target cell
- Minimal immunogenic response

Conjugation chemistry

- Lys or Cys residue of the mAb; controls drug distribution and DAR

Stable linker

- Selectively releases drug in target cell
- Long term stability



Linker Payload Disulphide bonds

Cytotoxic drug

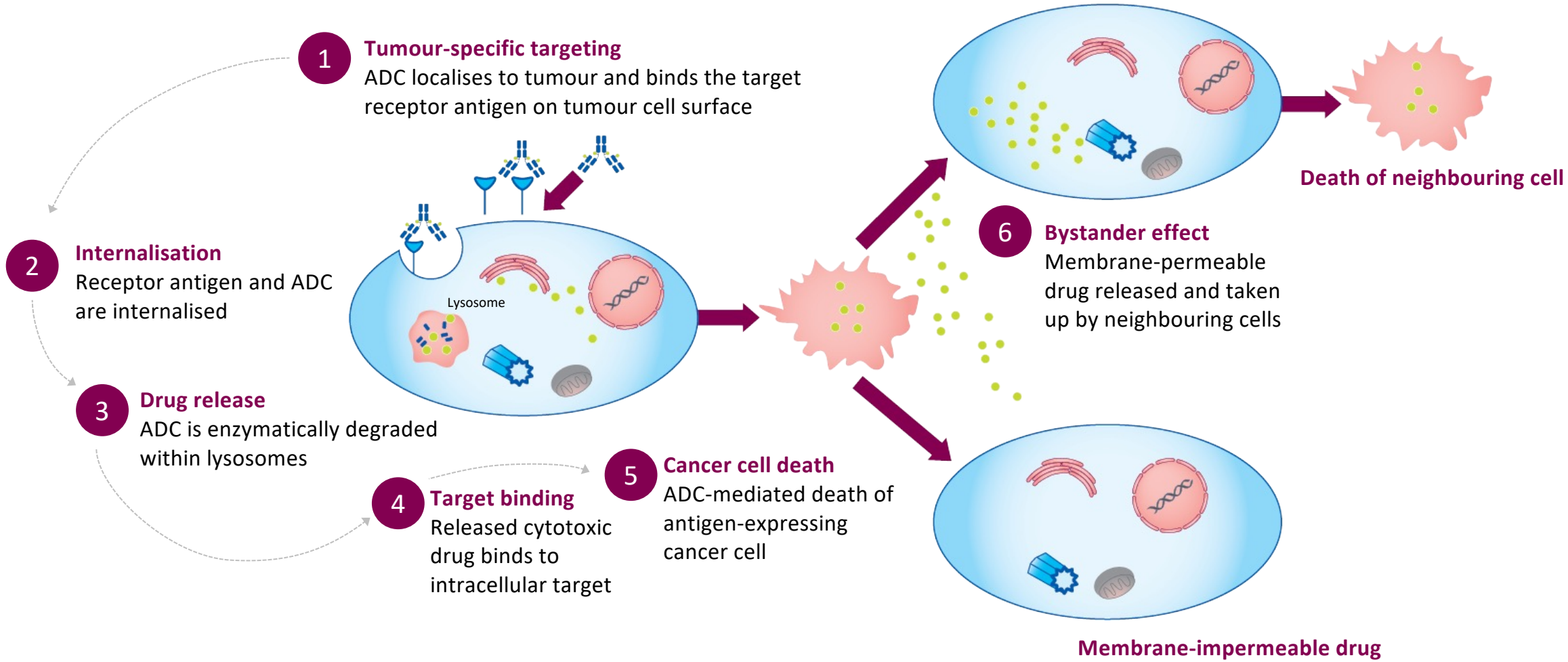
- Highly potent subnanomolar activity
- Functional groups for linking
- Lower hydrophobicity

Payload (chemotherapy)

Payloads	Auristatins	Maytansinoids	Calicheamicins	Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition
Examples:	MMAE MMAF	DM1 DM4	Ozogamicin	DXd SN-38

Nakada T, et al. *Chem Pharm Bull*. 2019;67:173–185; Drago, Modi, and Chandarlapaty; Nat Rev. Clin Onc. 2021

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+ mBC with prior therapy, multiple trials in mBC
vic-trastuzumab duocarmazine (SYD985)	HER2	Trastuzumab	Seco-DUBA	2.8	Phase 3 mBC reported
Sacitzumab govitecan (SG)	TROP2	RS7	SN-38	7.6	Approved in TNBC with at least one prior therapy, multiple trials in mTNBC, mBC
Datopotamab deruxtecan (Dato-DXd, DS-1062)	TROP2	Datopotamab	DXd	4	Phase 1 TNBC and HR+/HER2-; multiple trials in mBC
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	Phase III in HER2 positive and in HER2 low (China)
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

EMILIA: T-DM1: Historic Standard 2nd Line Therapy

But times have changed!

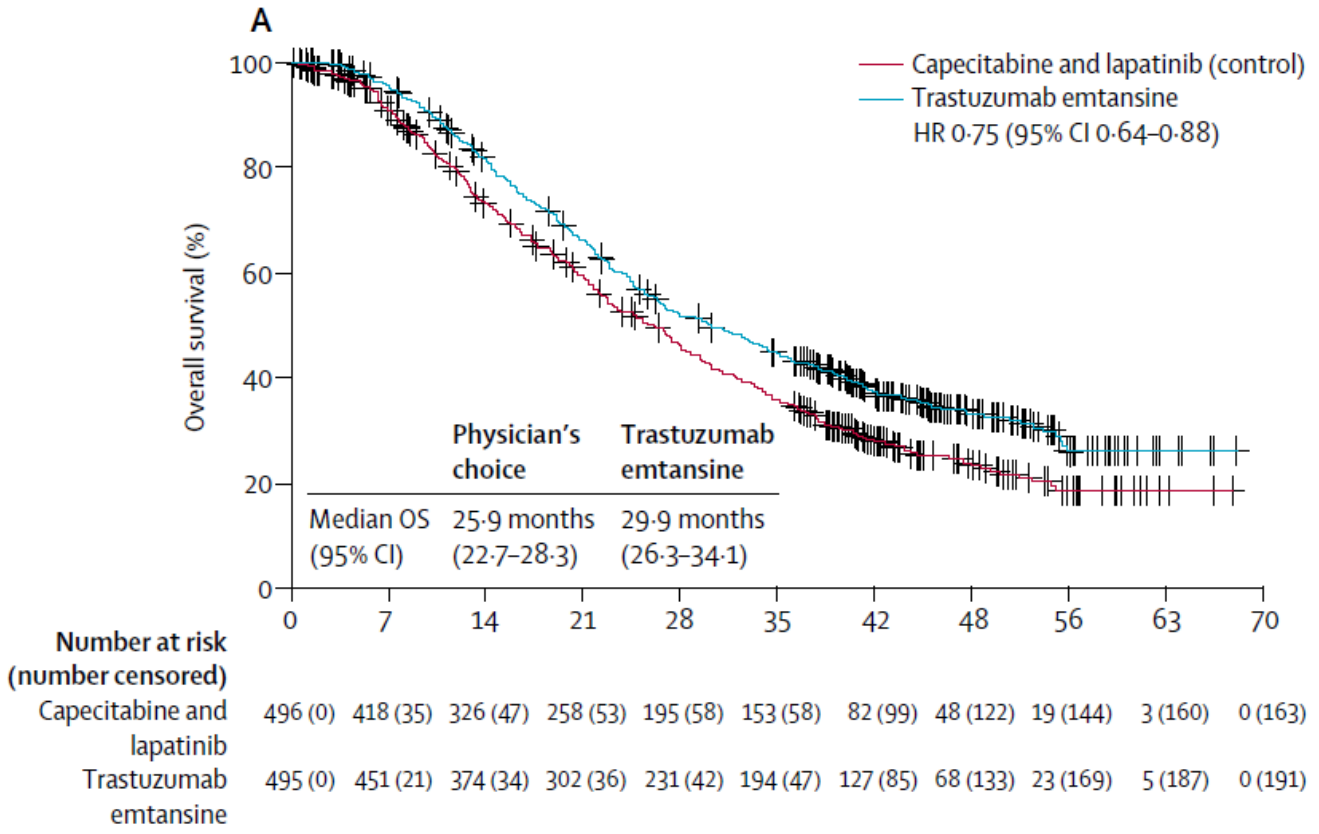
HER2+ LABC or MBC (N=980)

- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 mos of adjuvant tx

1:1

- T-DM1
- Capecitabine + Lapatinib

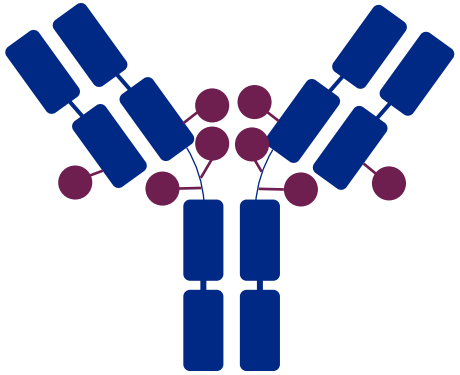
Overall



Dieras V et al, *Lancet Oncology;* 2017.

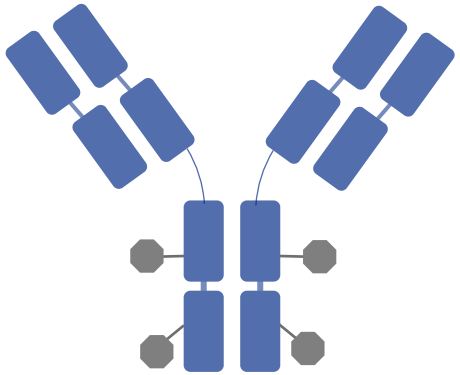
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4]	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%[6]
(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%)

[6]**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)

[7]**T-DXd in HER2-low mBC (N = 54)**
mPFS 11.1 months; ORR of 37.0%

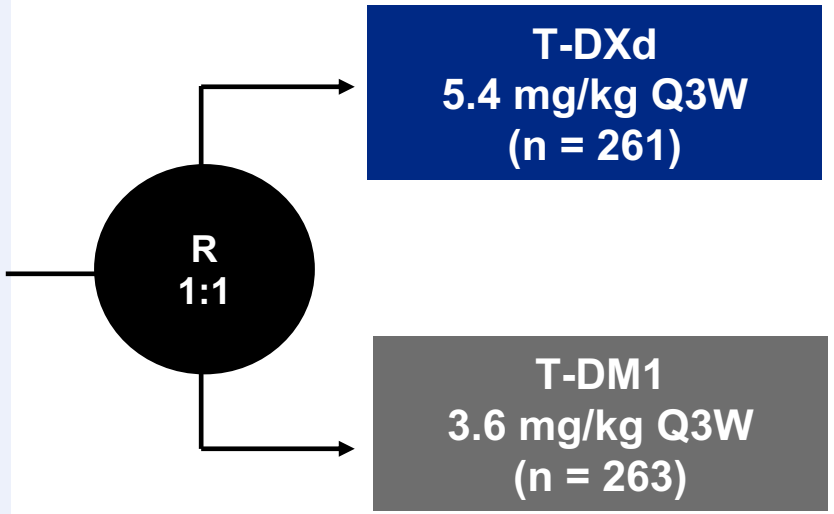
1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42.
4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res.* 2011;17:6437-47. 6. Modi et al, NEJM 2020. 7. Modi et al, JCO 2020

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

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



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

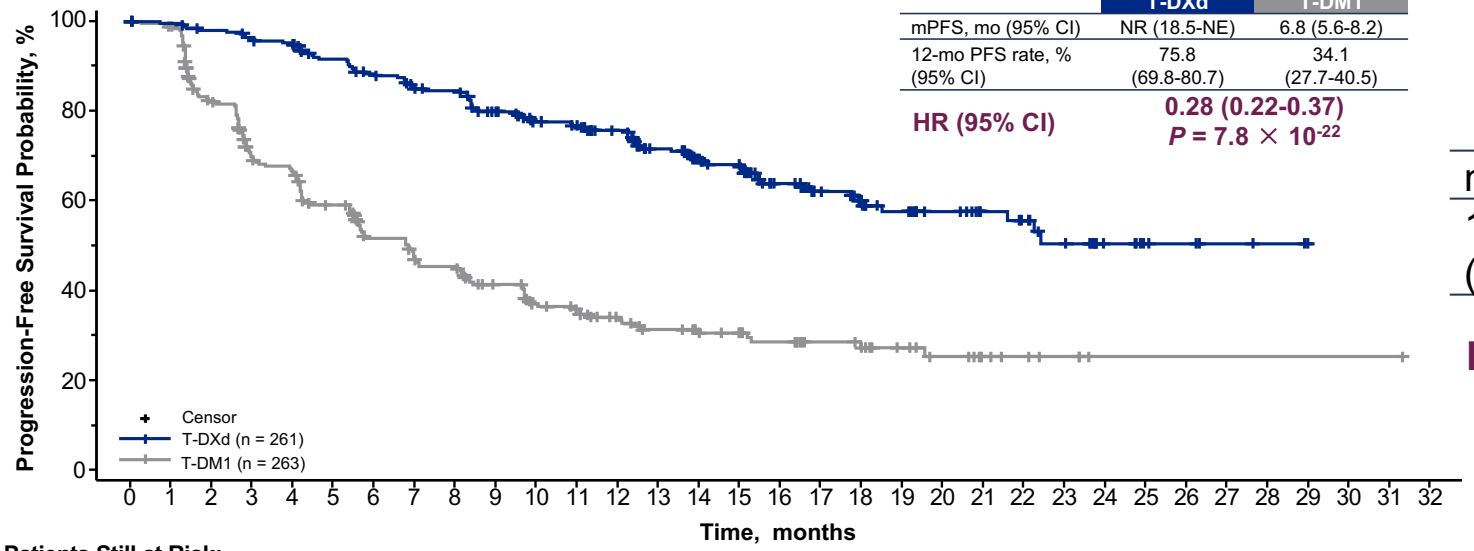
Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

Details:
- HR+: 50%
- Brain mets: 24 vs 20%
- Prior pertuzumab: 61%
- One line of piror rx: 50 vs 47%

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Cortes et al, NEJM 2022

Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

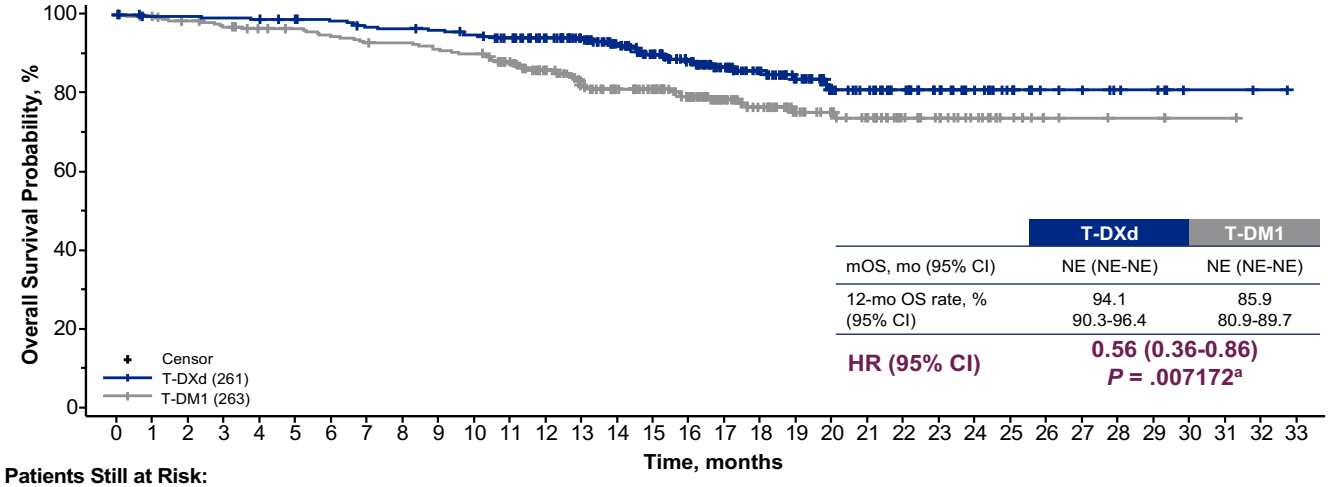
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	0

PFS by Investigator Assessment

	T-DXd	T-DM1
mPFS, mo (95% CI)	25.1 (22.1-NE)	7.2 (6.8-8.3)
12-mo PFS rate, % (95% CI)	76.3 (70.4-81.2)	34.9 (28.8-41.2)
HR (95% CI)	0.26 (0.20-0.35)	
	$P = 6.5 \times 10^{-24}$	

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	0.56 (0.36-0.86)	
	$P = .007172$[a]	

Patients Still at Risk:

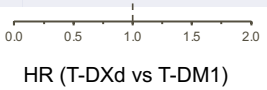
T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]$P = .007172$, but does not cross pre-specified boundary of $P < .000265$

PFS in Key Subgroups

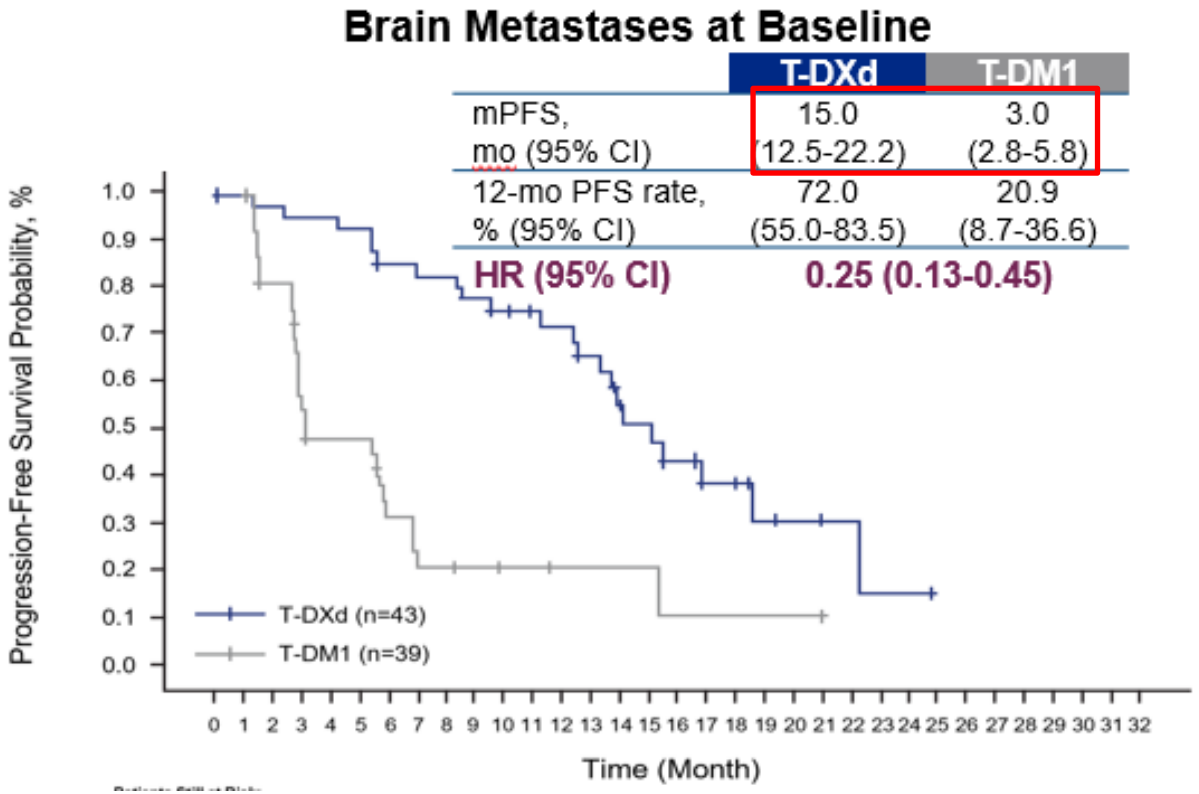
		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)

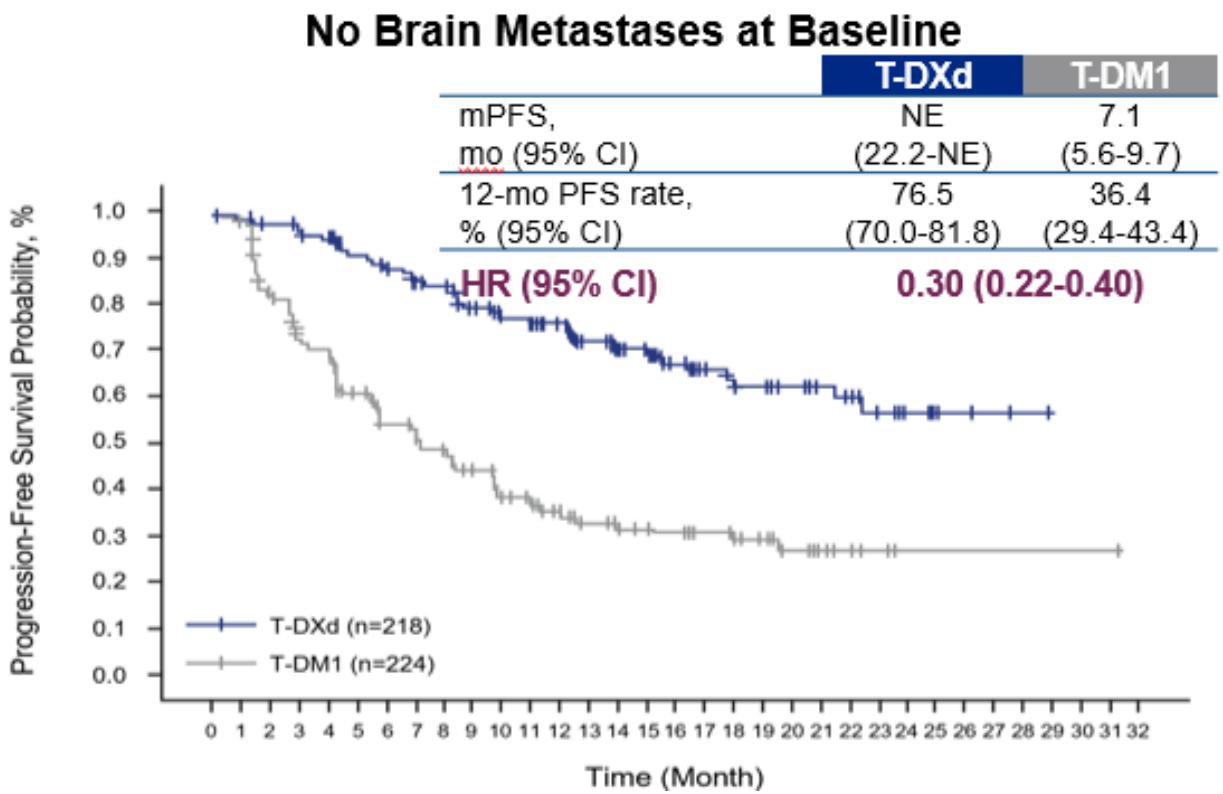


Cortes et al, NEJM 2022

DESTINY Breast03

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





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

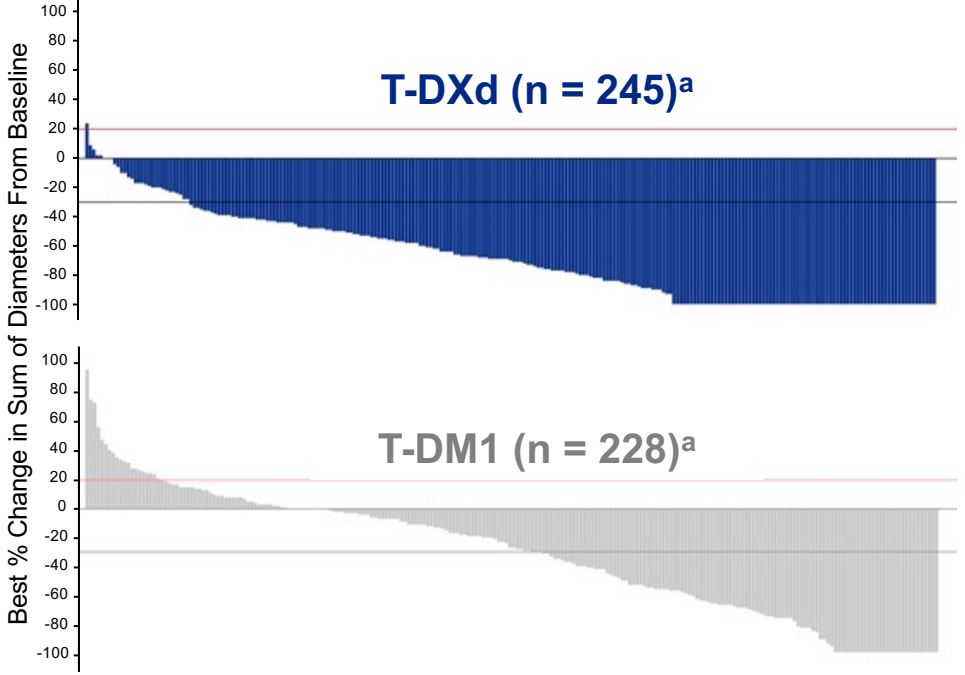
Confirmed ORR and Best Overall Response

- Study population

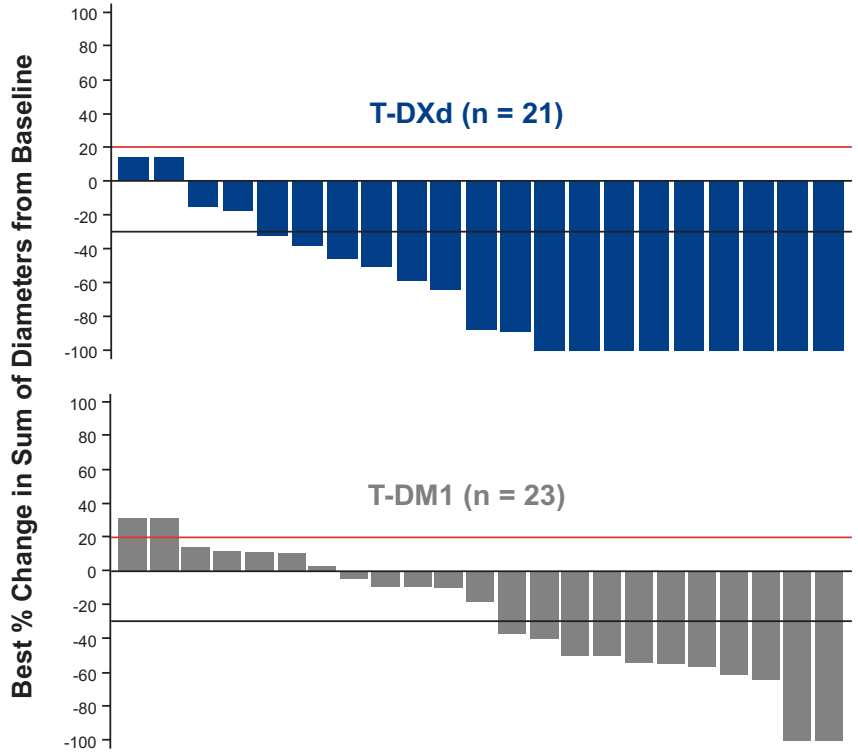
- Patients with brain mets

Toxicity

- ILD 10.5% (25/27 gr 1/2; no gr 4/5)
- No increase in LV dysfunction
- Nausea 76%; 6.6% gr 3



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)



	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)

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

Phase III TULIP Trial: Trastuzumab Duocarmazine (SYD985) in HER2+ MBC

HER2-positive LABC or MBC
≥2 therapies for metastatic disease, or T-DM1 for metastatic disease
Treated brain mets are allowed
N=437

R 2:1

SYD985 treatment
1.2 mg/kg IV every 21 days
N=291

Physician's choice treatment (PC)
N=146

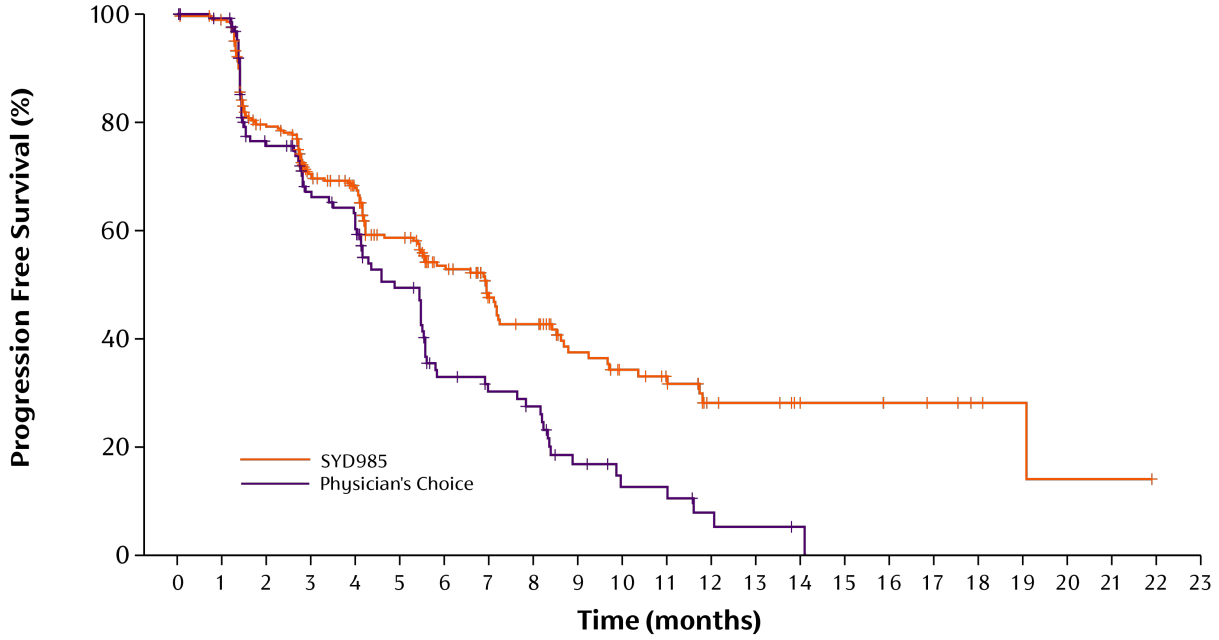
Continue treatment until progression or unacceptable toxicity

Primary Endpoint
- Centrally assessed PFS

Secondary Endpoints
- Investigator assessed PFS
- OS
- ORR
- HRQOL

SYD985: HER2-targeting ADC based on trastuzumab and a cleavable linker-duocarmycin (vc-*seco*-DUBA) payload:
- Active toxin (DUBA) alkylates DNA
- Drug to Antibody Ratio (DAR) from 2.4 to 2.8

Physician's choice
- Lapatinib + Capecitabine; Trastuzumab + Capecitabine; Trastuzumab + Vinorelbine; Trastuzumab + Eribulin



No. Patients at Risk																						
SYD985	291	278	208	167	150	109	83	59	51	35	28	24	13	12	9	8	6	5	3	2	1	1	0
Physician's Choice	146	125	86	69	64	44	26	22	19	10	6	6	3	2	1	0							

Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	**0.64 (0.49 – 0.84); p=0.002**	

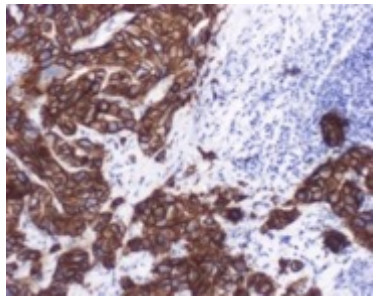
Eye toxicity: 78.1% SYD985, 29.2% physician's choice
Risk mitigation: prophylactic eye drops

ILD/pneumonitis: 7.6% (N=22/288); 4 fatal
Risk mitigation: hold for grade 1, stop for grade 2

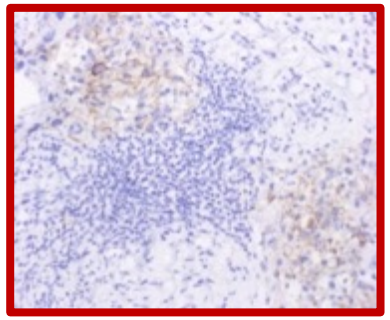
Prevalence of HER2 Low

HER2 IHC examples

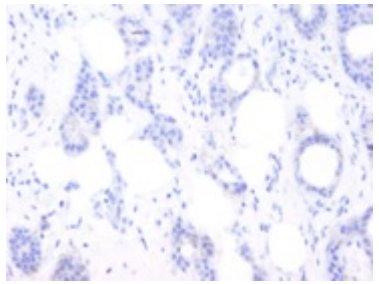
HER2+

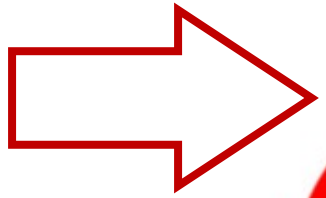


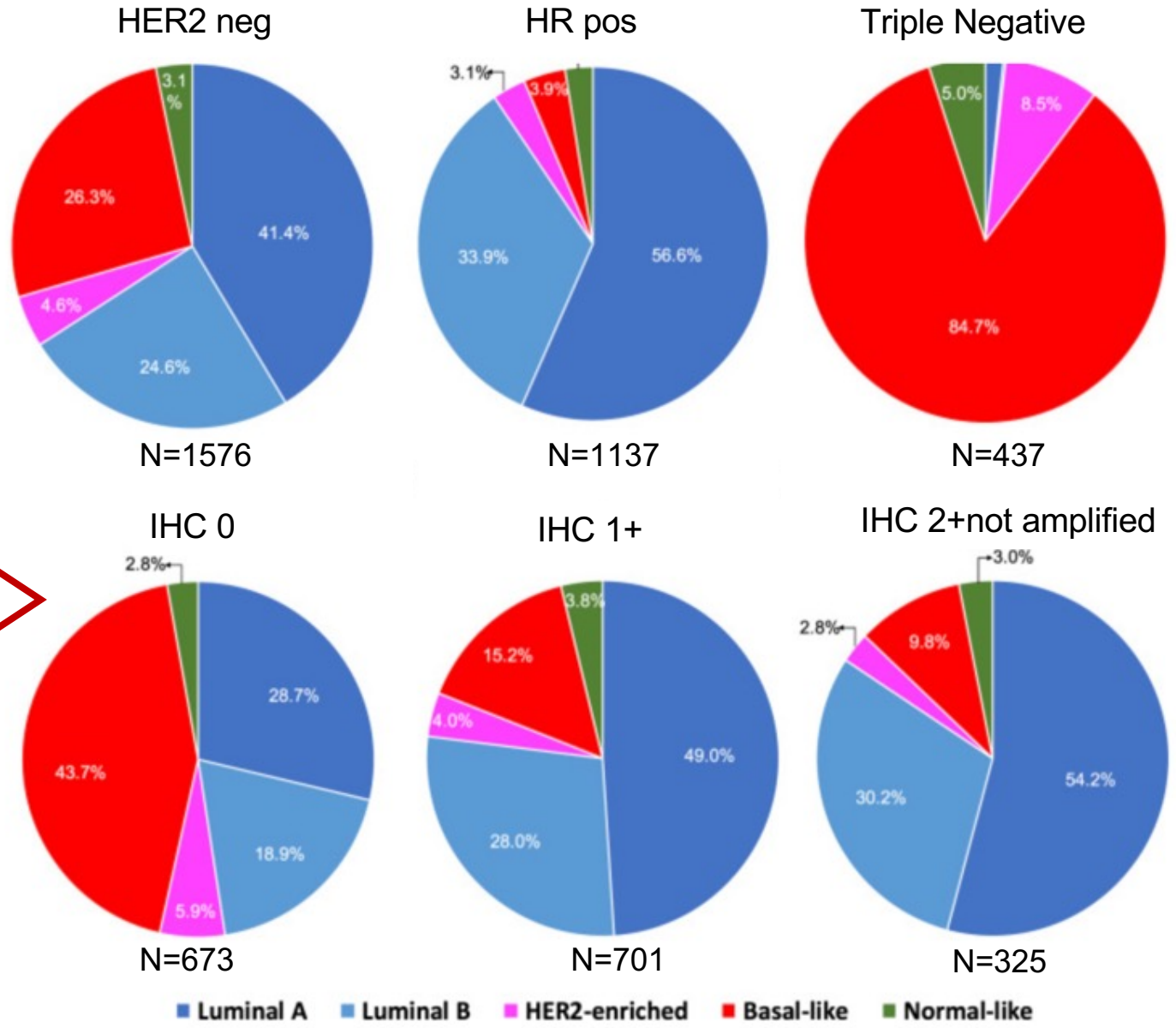
HER2-low



HER2-







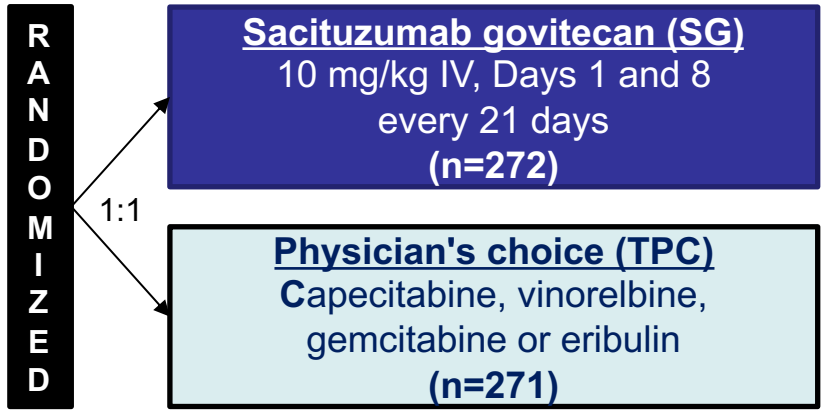
Schettini et al, NPJ Breast Cancer 2021

Proportion of HER2-low higher in HR+ BC (65%) compared to TNBC (37%)

Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: Study Design and Patients

Key Eligibility Criteria

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



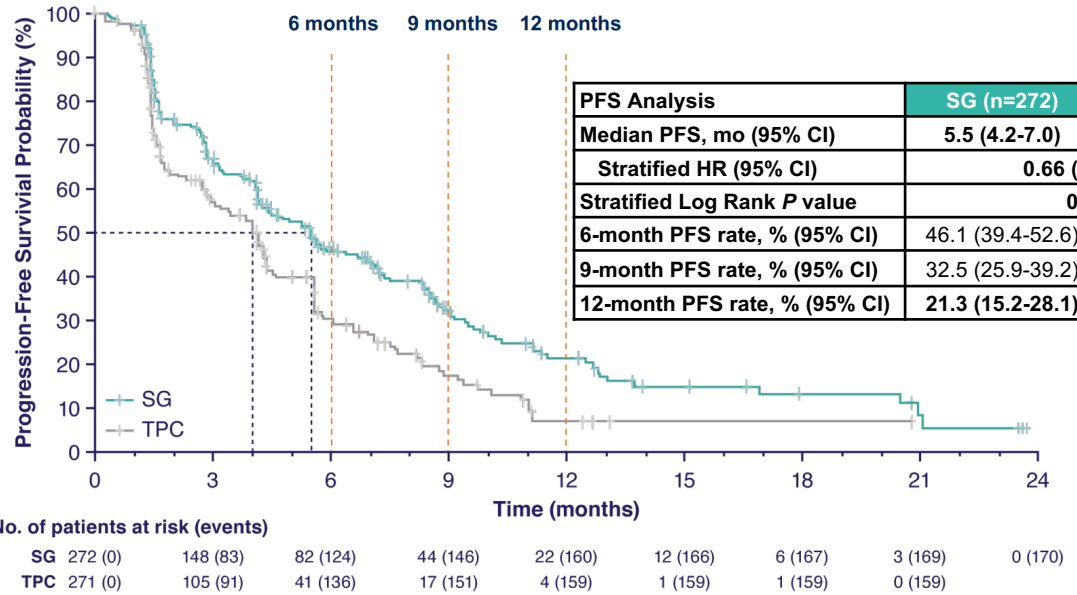
Primary endpoint: PFS by BICR
Secondary endpoints: OS, ORR, DOR, CBR by LIR and BICR, PRO, safety

Patient Characteristics		SG (n=272)	TPC (n=271)
Median age (range), years		57 (29-86)	55 (27-78)
ECOG PS, n (%)	0	116 (43)	126 (46)
	1	156 (57)	145 (54)
Visceral mets at baseline, n (%)		259 (95)	258 (95)
Liver mets, n (%)		229 (84)	237 (87)
Median time from initial MBC diagnosis to randomization (range), months		48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)		173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 months, n (%)		235 (86)	234 (86)
Prior CDK4/6i, n (%)	≤12 months	161 (59)	166 (61)
	>12 months	106 (39)	102 (38)
	Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting (range), n		3 (0-8)	3 (1-5)

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

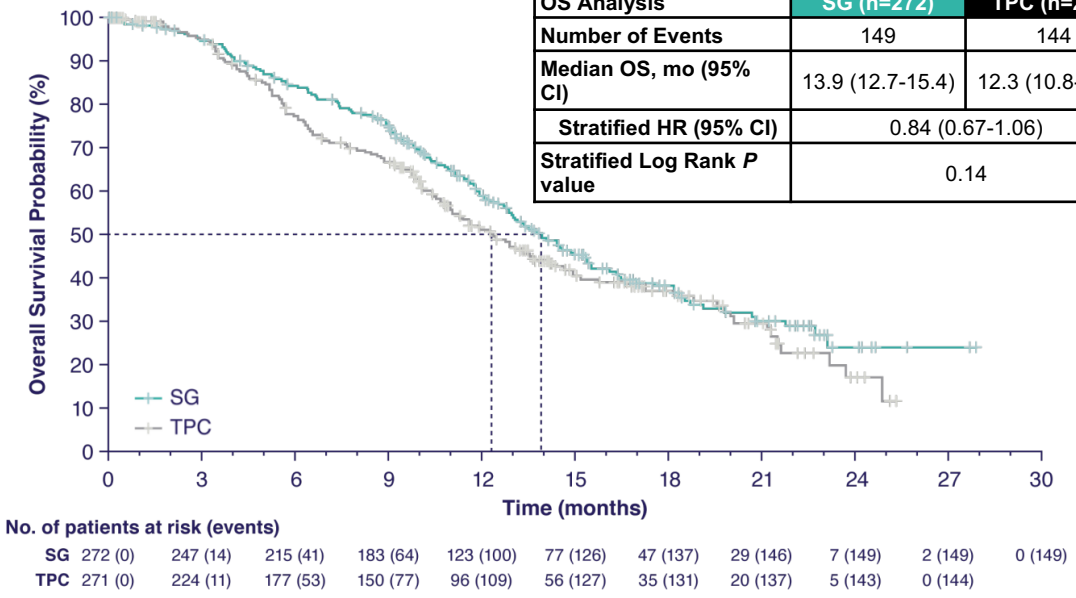
Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: Efficacy

BICR-Assessed PFS in the ITT Population



PFS Analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	0.66 (0.53-0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2-28.1)	7.1 (2.8-13.9)

OS in the ITT Population (First Planned Interim Analysis)



OS Analysis	SG (n=272)	TPC (n=271)
Number of Events	149	144
Median OS, mo (95% CI)	13.9 (12.7-15.4)	12.3 (10.8-14.2)
Stratified HR (95% CI)	0.84 (0.67-1.06)	
Stratified Log Rank *P* value	0.14	

- SG resulted in a 34% reduction in the risk of PD/death
- SG resulted in PFS benefit consistent across all subgroup analysis, including patients with
  - ≥3 prior chemotherapy regimens in the metastatic setting
  - Visceral mets
  - Endocrine therapy for MBC ≥6 months
- OS data was not mature and further follow-up is ongoing

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

Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: Efficacy (cont'd) and Safety

BICR Analysis		SG (n=272)	TPC (n=271)
ORR, n (%)		57 (21)	38 (14)
Odds ratio; nominal *P* value[a]		1.63; 0.03	
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[b], n (%)		92 (34)	59 (22)
Odds ratio; nominal *P* value		1.84; 0.002	
Median DOR, months (95% CI)		7.4 (6.5-8.6)	5.6 (3.8-7.9)

TEAEs, n (%)	SG (n=268)	TPC (n=249)
Grade ≥3	198 (74)	149 (60)
Leading to treatment discontinuation	17 (6)	11 (4)
Leading to dose delay	178 (66)	109 (44)
Leading to dose reductions	89 (33)	82 (33)
Serious	74 (28)	47 (19)
Leading to death[c]	6 (2)	0
Treatment-related	1 (<1)	0

- 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

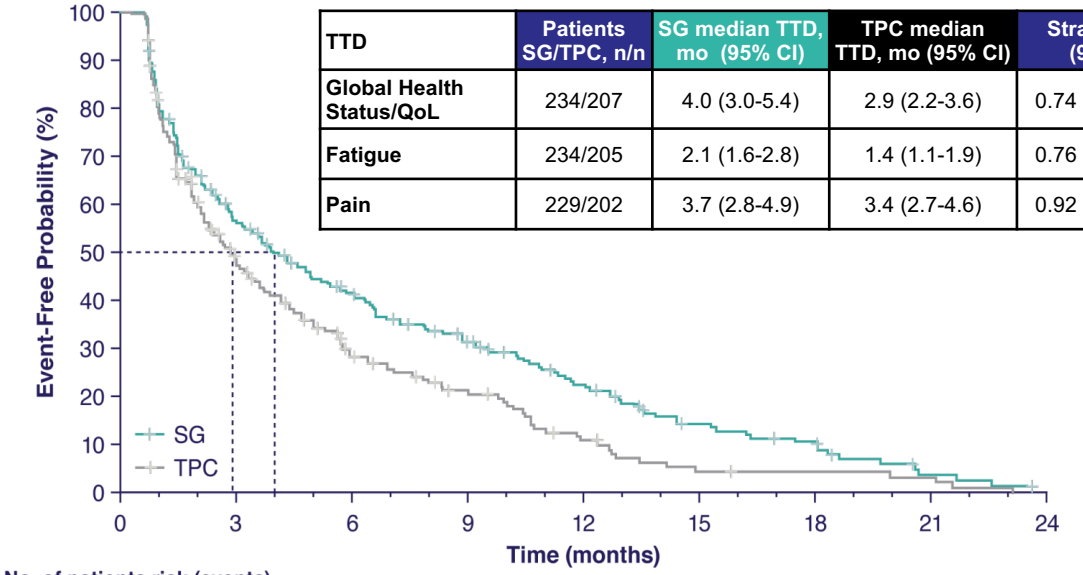
[a]Not formally tested because OS at interim analysis was not statistically significant. [b]CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR and SD ≥6 months. [c]Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment-related (septic 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.

Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: QoL and Summary

Time to Deterioration in Global Health Status/QoL Scale

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	4.0 (3.0-5.4)	2.9 (2.2-3.6)	0.74 (0.59-0.91)	0.005
Fatigue	234/205	2.1 (1.6-2.8)	1.4 (1.1-1.9)	0.76 (0.62-0.93)	0.007
Pain	229/202	3.7 (2.8-4.9)	3.4 (2.7-4.6)	0.92 (0.74-1.14)	0.45



No. of patients risk (events)

SG	234 (0)	125 (100)	84 (132)	59 (151)	36 (167)	19 (179)	13 (184)	3 (191)	0 (193)
TPC	207 (0)	87 (102)	43 (135)	28 (146)	13 (159)	5 (166)	4 (166)	3 (167)	0 (170)

Conclusions

- SG demonstrated PFS benefit over TPC in patients with HR+/HER2- advanced BC who received prior
  - Endocrine-based therapy
  - Prior CDK4/6i
  - ≥2 prior lines of chemotherapy
- OS results were not mature and further follow-up is ongoing
- SG demonstrated a benefit in HRQoL over TPC
- The safety profile with SG was consistent with that observed in previous studies[1-3]

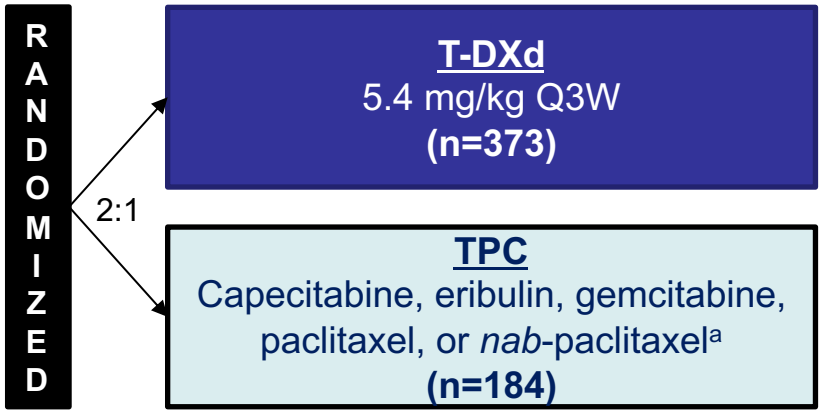
[a]Not formally tested because OS at interim analysis was not statistically significant.

1. Bardia A., et al. *Ann Oncol*. 2021;32:746-756. 2. Kalinsky K, et al. *Ann Oncol*. 2020;31(12):1709-1718.
3. Bardia A, et al. *New Engl J Med*. 2021;384:1529-1541.
Rugo H, et al. ASCO 2022. Abstract LBA1001.

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



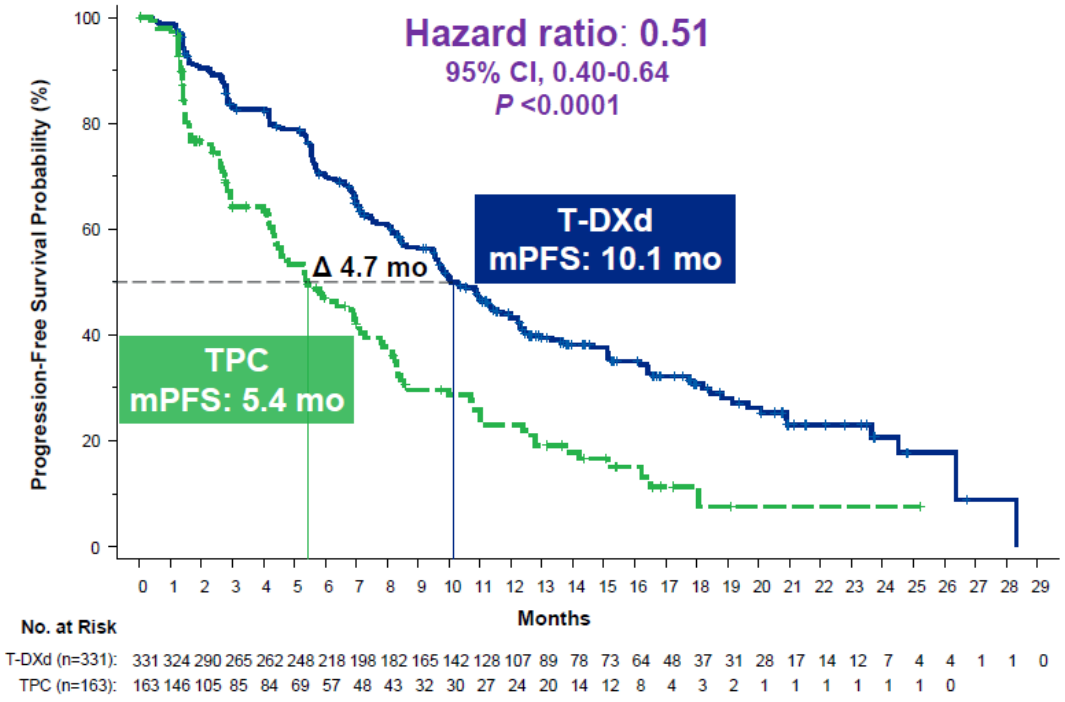
Primary endpoint: PFS by BICR (HR+)
Key secondary endpoints[b]: PFS by BICR (all patients), OS (HR+ and all patients)

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)

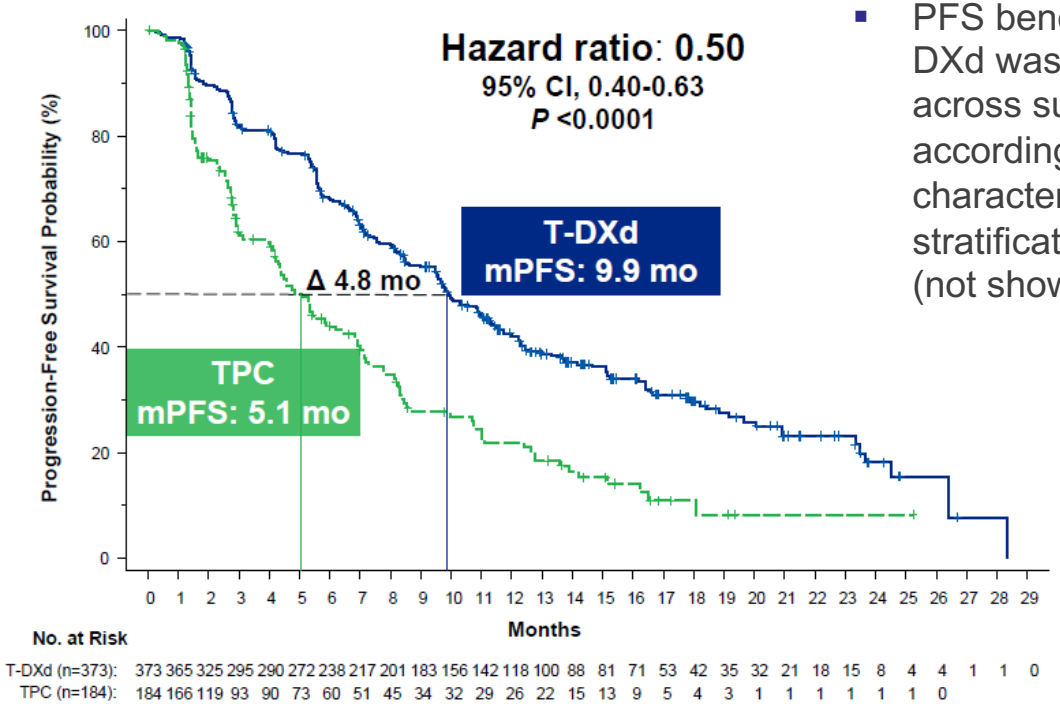
Data cutoff Jan 11, 2022.
[a] TPC was administered according to the label. [b] Other secondary endpoints included ORR (BICR and INV), DOR (BICR), PFS (INV), and safety. Efficacy in the HR- cohort was an exploratory endpoint. [c] HR status was based on data collected using interactive web/voice response 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+



PFS in All Patients



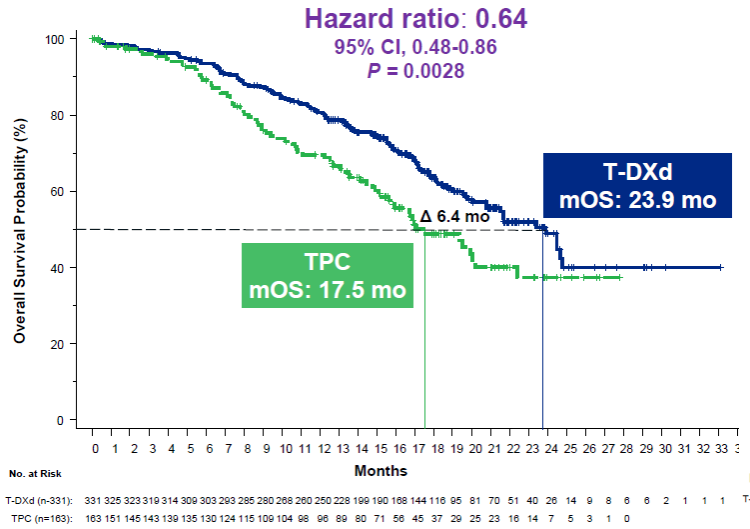
- PFS benefit with T-DXd was similar across subgroups according to baseline characteristics and stratification factors (not shown)

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	

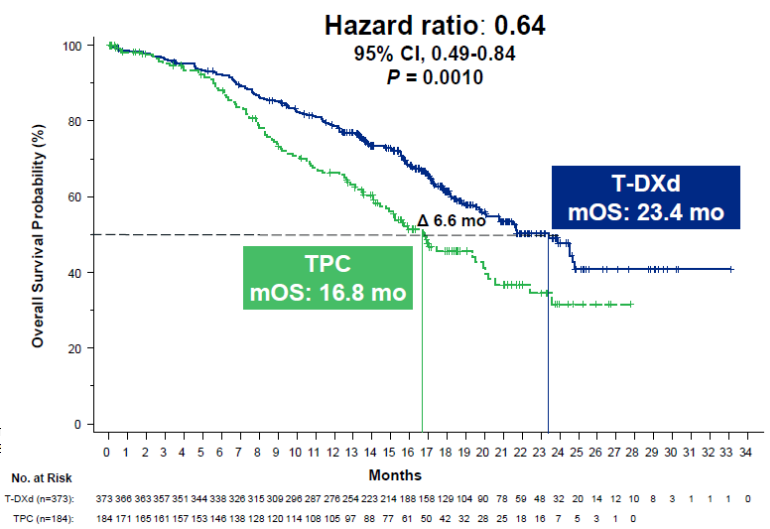
Modi S, et al. ASCO 2022. Abstract LBA3, NEJM 2022

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

OS in HR+



OS in All Patients



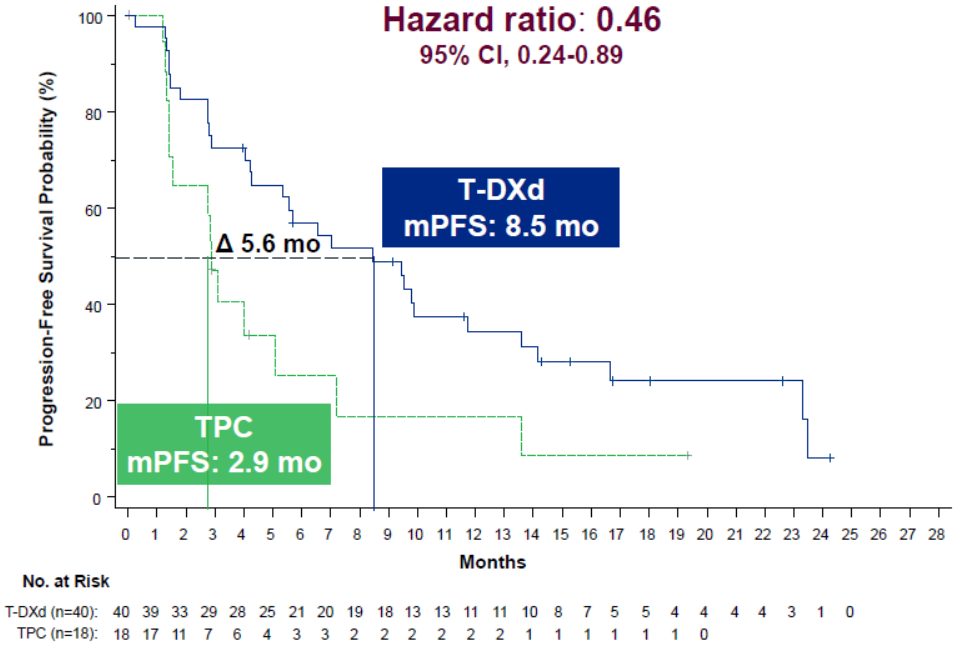
OS	HR+		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=373)	TPC (n=184)
Median OS, months	23.9	17.5	23.4	16.8
HR (95% CI); *P* value	HR 0.64 (0.48-0.86); 0.0028		HR 0.64 (0.49-0.84); 0.0010	

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, months	10.7	6.8	8.6	4.9

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

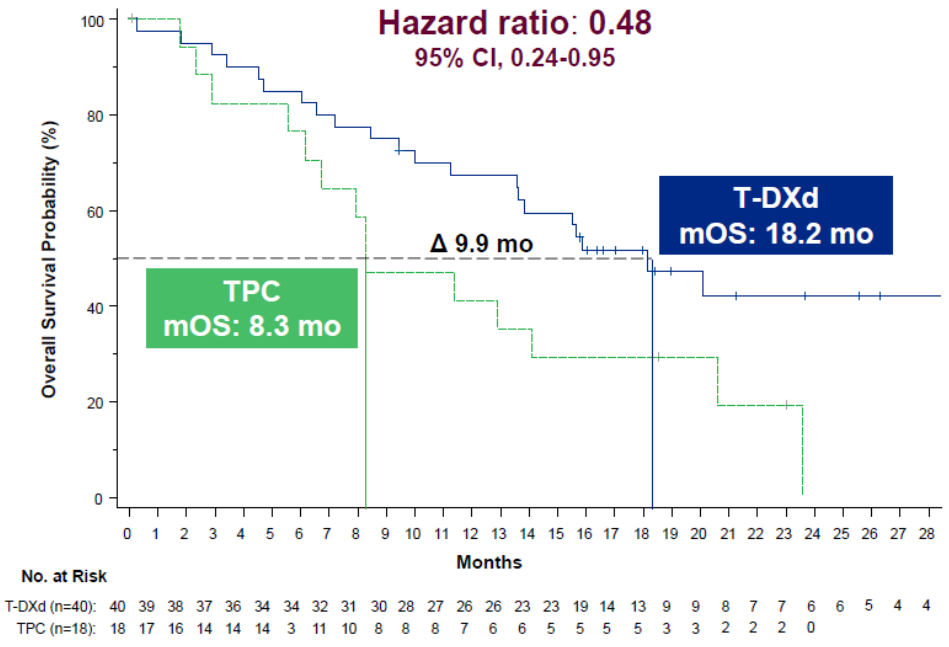
Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Efficacy in HRneg

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-

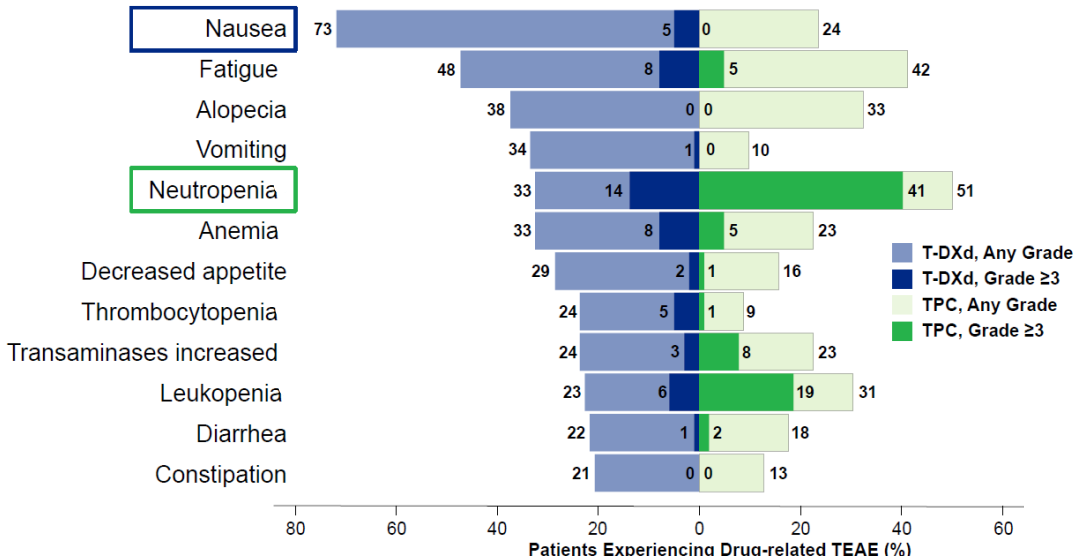


OS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median OS, months	18.2	8.3
HR (95% CI)	0.48 (0.24-0.95)	

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

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.

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.

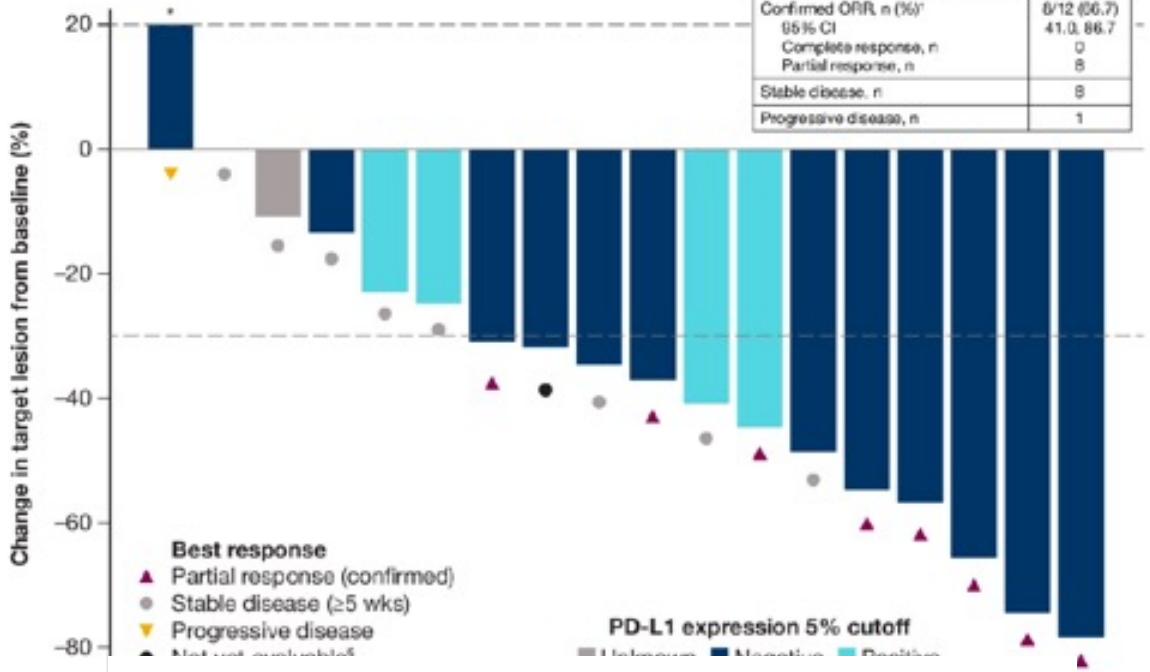
BEGONIA Trial

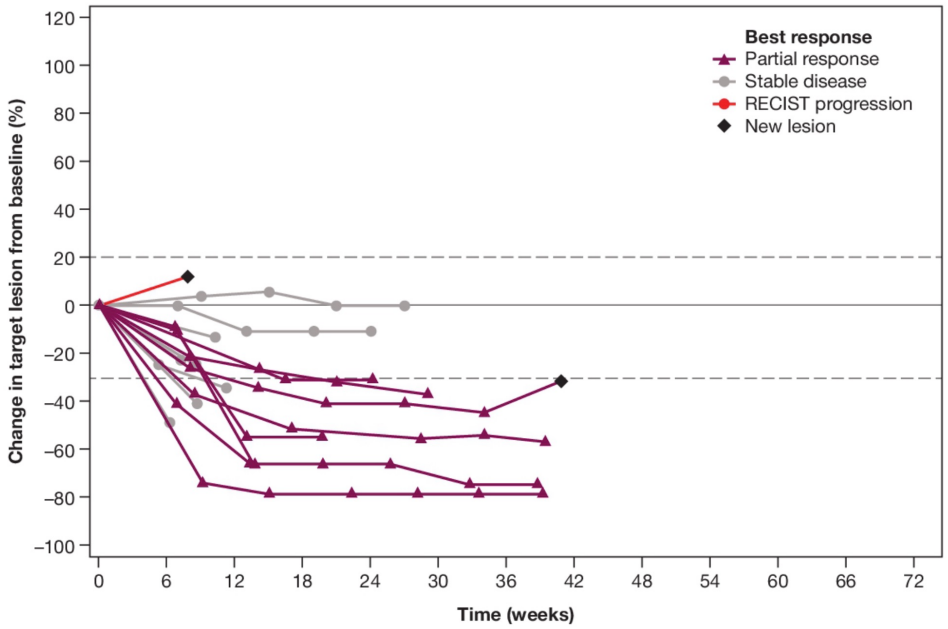
- First-line therapy for metastatic TNBC
- Basket trial
  - Arm 6: Durvalumab and T-DXd (also had to be HER2 low)
- PD-L1 testing using SP263
- ORR 66.7% (8/12)
- Safety
  - 2 cases of ILD
    - Grade 2 and 3
    - Both discontinued T-DXd

Schmid et al, Abstract 1023 ASCO 2021

ARM 6; n=18

Parameter	D+T-DXd
Patients who completed at least 1 on-treatment assessment, n	18
Response evaluable analysis set, n[a]	12
Confirmed ORR, n (%)[b] 95% CI Complete response, n Partial response, n	8/12 (66.7) 41.0, 86.7 0 8
Stable disease, n	3
Progressive disease, n	1



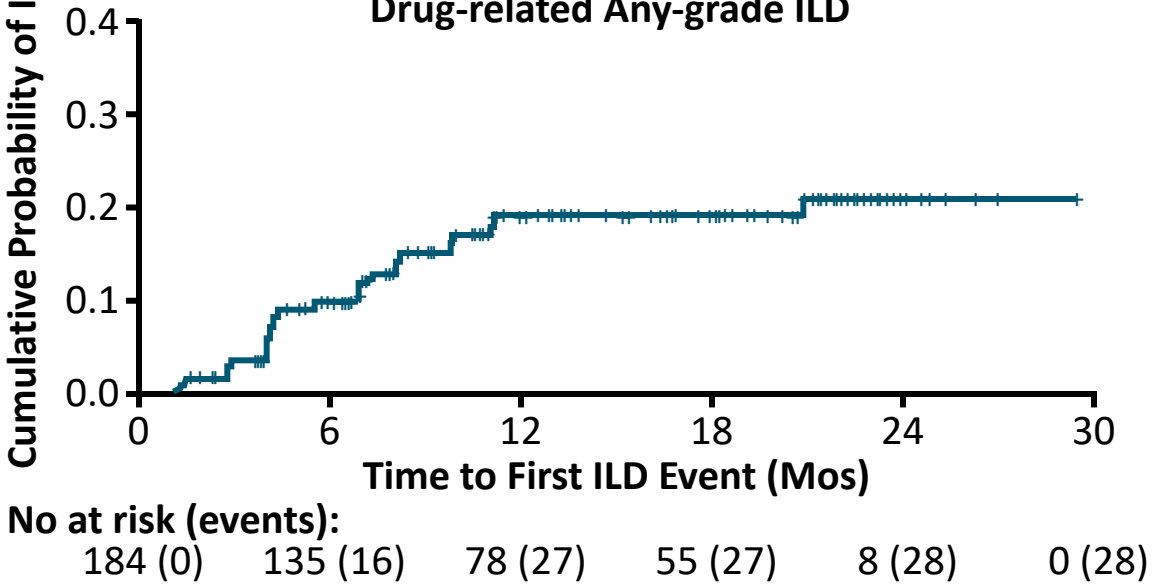


Warnings and Precautions: T-DXd ILD/Pneumonitis Monitoring and Management

Interstitial lung disease, n (%)	T-Dxd 5.4 mg/kg (N = 184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

Cumulative Probability of Adjudicated Drug-related Any-grade ILD



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

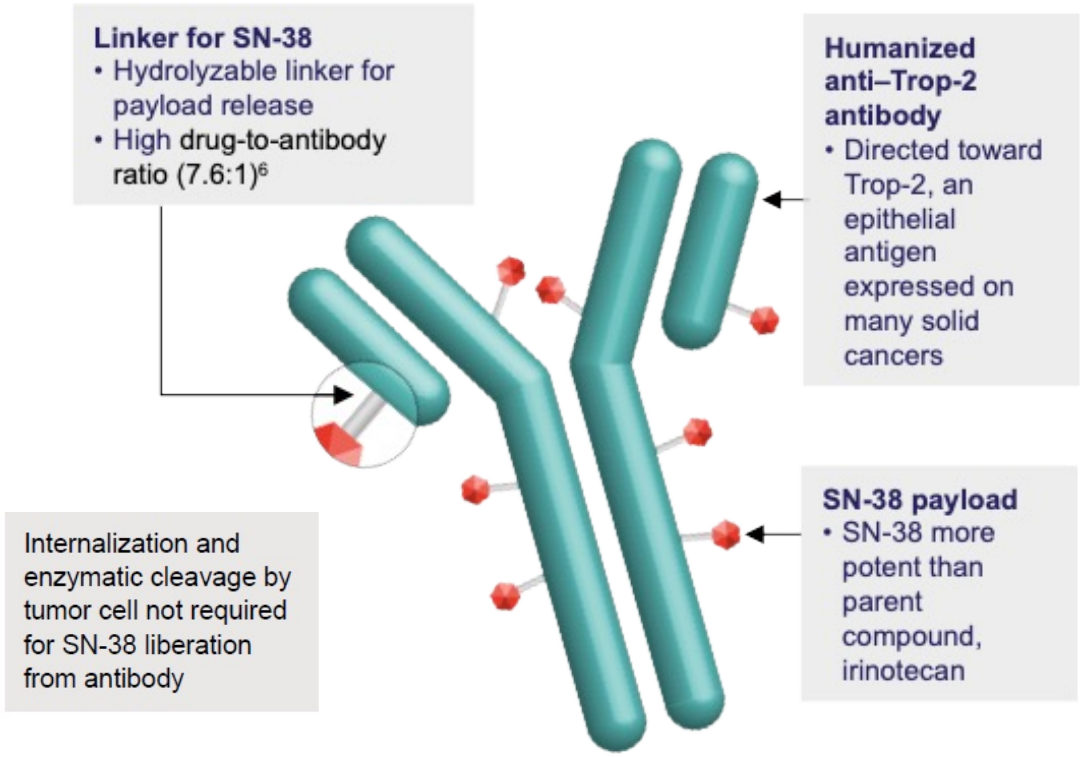
Modi et al, SABCS 2020

ENHERTU [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo Inc and Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.

Selected Ongoing Trials with ADC

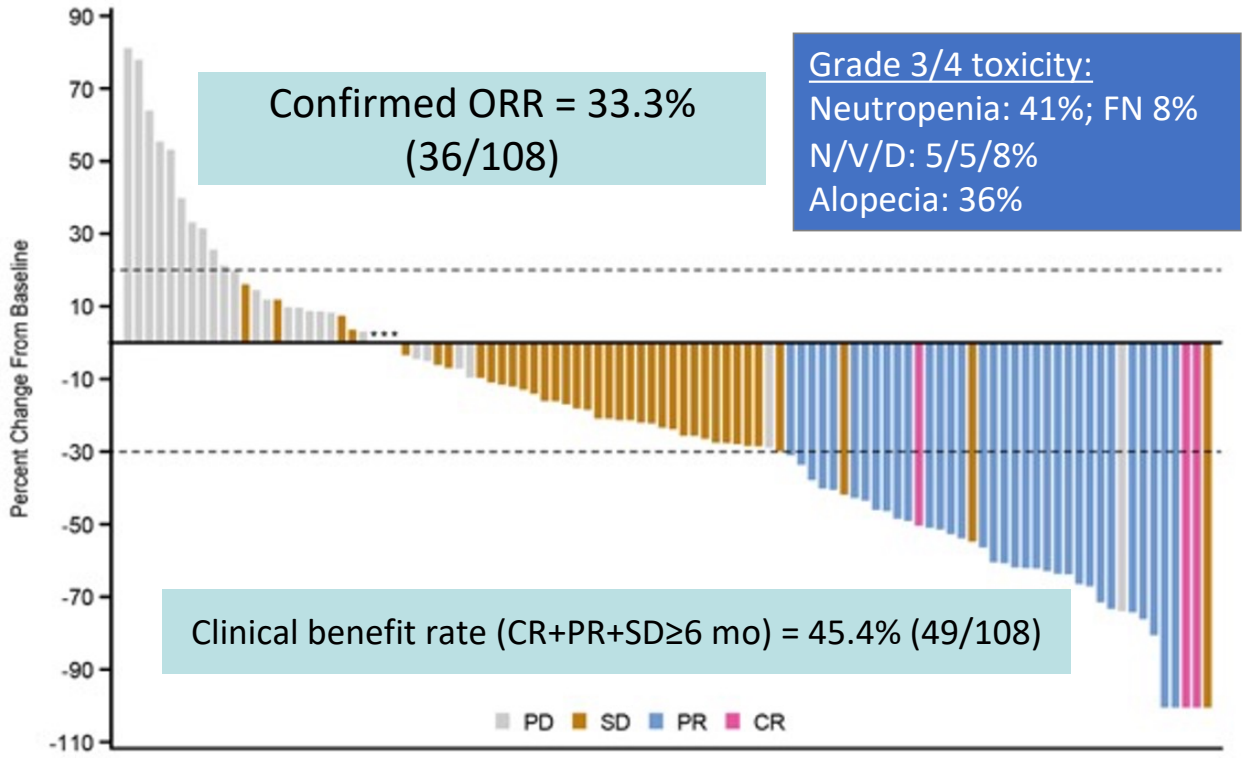
Trial	Design
HER2 positive	
DESTINY-Breast02 (NCT03523585)	T-DXd vs trastuzumab or lapatinib with capecitabine after T-DM1 (no brain mets) N=600
DESTINY-Breast12 (NCT04739761)	T-DXd in patients with previously treated MBC with and without brain mets N=500 (250 with brain mets)
DESTINY-Breast09 (NCT04784715)	First-line HER2+: THP vs T-DXd + placebo vs T-DXd + Pertuzumab N=1134
DESTINY-Breast05 (NCT04622319)	T-DXd vs T-DM1 for residual disease post neoadjuvant therapy N=1600
DESTINY-Breast11 (NCT05113251)	Neoadjuvant HER2+ therapy: T-DXd vs T-DXd-THP vs ddAC-THP N=624
HER2 low	
DESTINY-Breast06 (NCT04622319)	T-DXd vs chemotherapy (Cape or taxane) for HER2 0, 1 or 2+ (including 0-1+) N=850

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



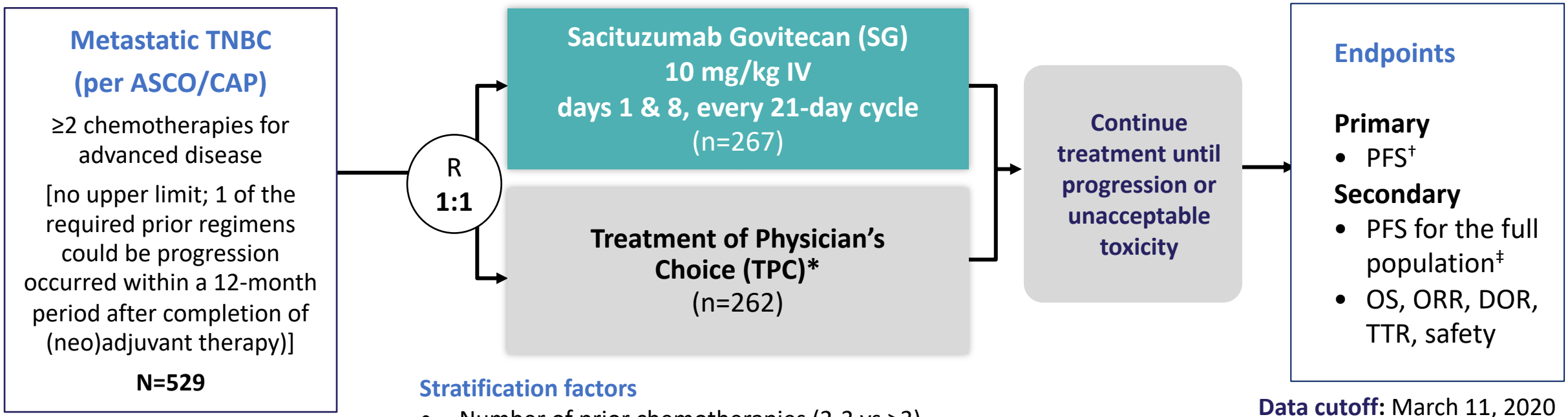
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- Full approval for the treatment of mTNBC and accelerated approval for advanced urothelial cancer

Phase I/II study in 108 patients with refractory mTNBC
Median of 3 prior lines of therapy (range 2-10) for MBC



Bardia et al. *NEJM*. 2019.

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



Stratification factors

- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

NCT02574455

Demographics:

TPC: 53% eribulin, 20% vinorelbine, 15% gemcitabine, 13% capecitabine; 70% TN at initial diagnosis

Median prior regimens 4 (2-17); ~88% with visceral disease

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

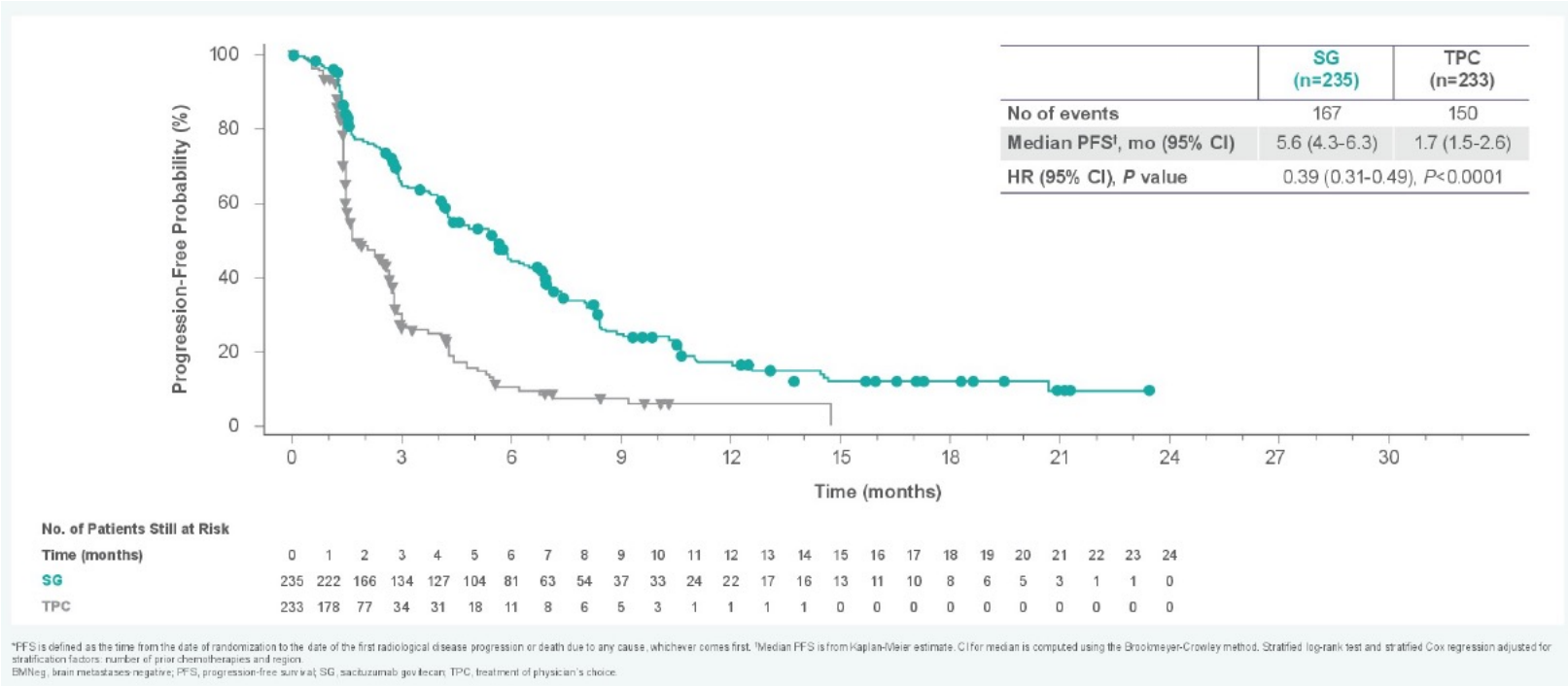
*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Bardia et al, NEJM 2021

ASCENT

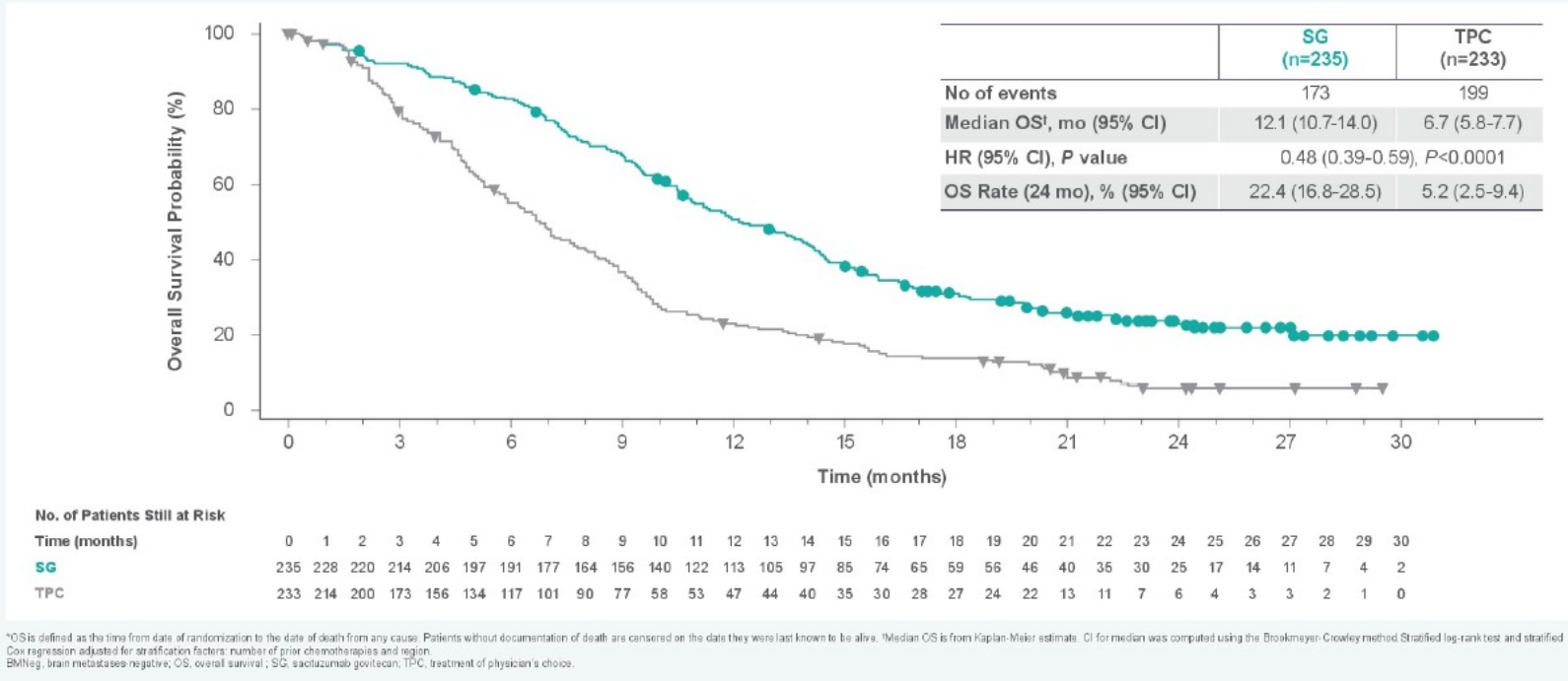
PFS and OS in the Bmneg Population



*PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first. †Median PFS is from Kaplan-Meier estimate. CI for median is computed using the Brookmeyer-Crowley method. Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies and region.
BMNeg, brain metastases-negative; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Efficacy in ITT population consistent with the BMNeg population

- Median PFS of 4.8 vs 1.7 mo (HR 0.41, p<0.0001)
- Median OS of 11.8 vs 6.9 mo (HR 0.51, P<0.0001)



*OS is defined as the time from date of randomization to the date of death from any cause. Patients without documentation of death are censored on the date they were last known to be alive. †Median OS is from Kaplan-Meier estimate. CI for median was computed using the Brookmeyer-Crowley method. Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies and region.
BMNeg, brain metastases-negative; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Bardia A, et al. N Engl J Med. 2021 and ASCO 2022

ASCENT Study: ORR, Additional Analyses, and Safety

	Patients without Brain Metastases	
	SG (N=235)	TPC (N=233)
Objective response — n (%)§	**82 (35)**	**11 (5)**
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
Clinical benefit — n (%)¶	105 (45)	20 (9)
SD — n (%)	81 (34)	62 (27)
SD for ≥6 mo	23 (10)	9 (4)
PD — n (%)	54 (23)	89 (38)
Response NE — n (%)‖	18 (8)	71 (30)
Median TTR (95% CI) — mo	1.5 (0.7–10.6)	1.5 (1.3–4.2)
Median DOR (95% CI) — mo	6.3 (5.5–9.0)	3.6 (2.8–NE)
HR (95% CI)	0.39 (0.14–1.07)	

Additional Analyses

- Activity consistent across medium and high TROP2 expression (too few with low/no expression and regardless of BRCA mutation status
- 14% treated in the first-line setting (≤12 mo from adj/neoadj rx)
  - PFS 5.7 vs 1.5 months (HR 0.41; 95% CI, 0.22-0.76)
  - OS 10.9 vs 4.9 months (HR 0.51; 95% CI, 0.28-0.91)

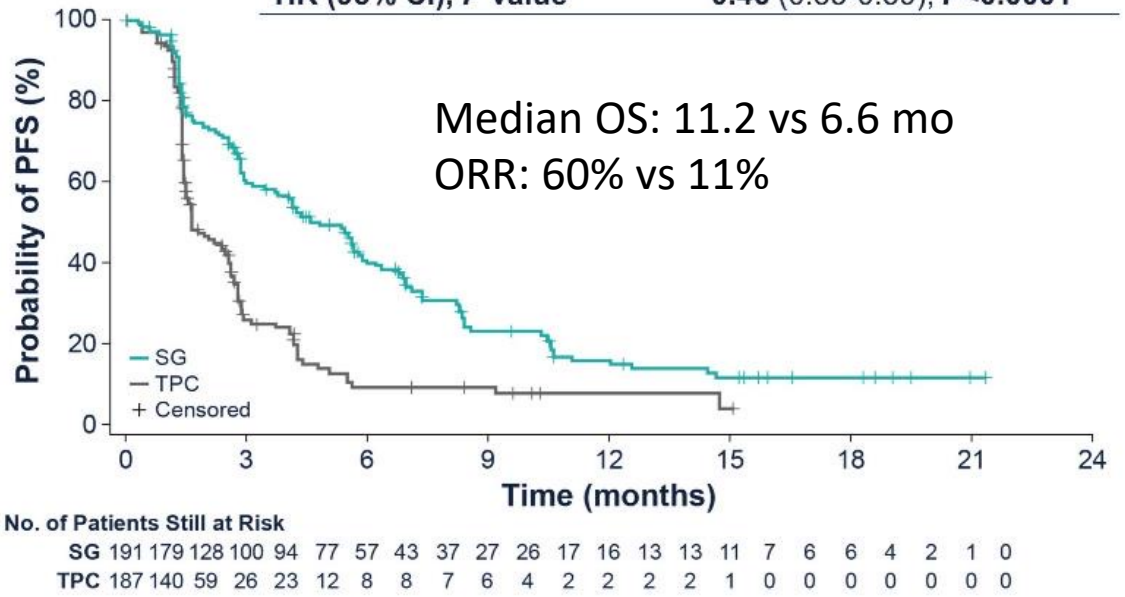
Most common toxicities

- Neutropenia, diarrhea, nausea, alopecia and fatigue
- 63 vs 40% grade 3 NTP; 59 vs 12% all grade diarrhea (10% grade 3)
- G-CSF: 49% (SC) and 23% (TPC)
- AEs leading to discontinuation: 4.7% (vs 5.4 % TPC), dose reductions due to TRAE similar (22 vs 26%)

Assessed by independent central review in brain met-neg population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo).
Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541; Bardia et al. Ann Oncol 2021; Carey et al NPJ BC 2022.

ASCENT: Outcomes by Age—<65 Versus ≥65 Years

PFS BICR Analysis	<65 y SG (n=191)	<65 y TPC (n=187)
No. of events	136	117
Median PFS—mo (95% CI)	4.6 (3.7-5.7)	1.7 (1.5-2.5)
HR (95% CI), *P* value	**0.46** (0.35-0.59), ***P*<0.0001**	

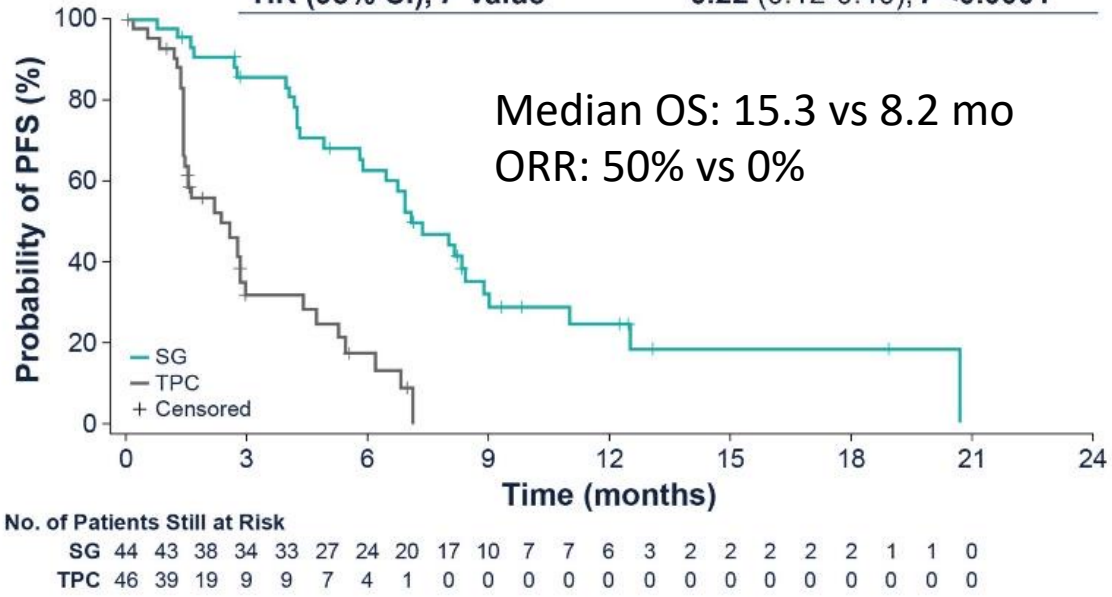


Median OS: 11.2 vs 6.6 mo
ORR: 60% vs 11%

No. of Patients Still at Risk

SG	191	179	128	100	94	77	57	43	37	27	26	17	16	13	13	11	7	6	6	4	2	1	0
TPC	187	140	59	26	23	12	8	8	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

PFS BICR Analysis	≥65 y SG (n=44)	≥65 y TPC (n=46)
No. of events	30	33
Median PFS—mo (95% CI)	7.1 (5.8-8.9)	2.4 (1.4-2.9)
HR (95% CI), *P* value	**0.22** (0.12-0.40), ***P*<0.0001**	



Median OS: 15.3 vs 8.2 mo
ORR: 50% vs 0%

No. of Patients Still at Risk

SG	44	43	38	34	33	27	24	20	17	10	7	7	6	3	2	2	2	2	2	1	1	0	
TPC	46	39	19	9	9	7	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

- Dose reductions: more frequent in patients ≥ 65 versus < 65 years; similar between SG and TPC treatment arms in all age groups, with no considerable impact on efficacy
- Treatment discontinuation due to TRAE: 2% each for ≥65-year versus < 65-year groups
- No treatment-related deaths
- Rates of AEs were similar for patients aged ≥ 75 years as observed in patients aged ≥ 65 years

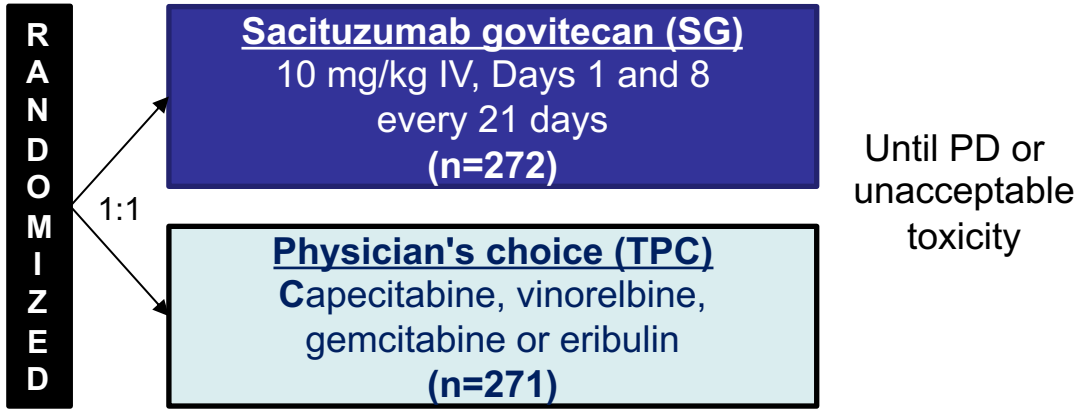
Kalinsky K, et al. ASCO 2021. Abstract 1011.

Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: Study Design and Patients

Phase I trial in HR+/HER21 MBC (n=54)
Median prior lines of chemo for MBC: 2
ORR 31%, CBR 48% (Kalinsky et al, Ann Onc 2020)

Key Eligibility Criteria

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



N=543

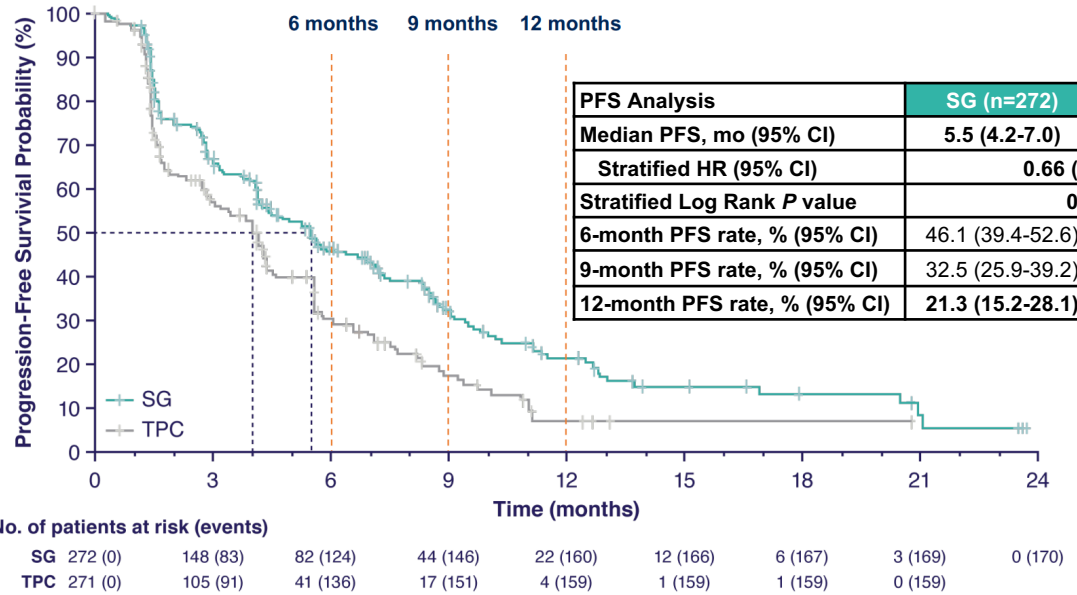
Primary endpoint: PFS by BICR
Secondary endpoints: OS, ORR, DOR, CBR by LIR and BICR, PRO, safety

Patient Characteristics		SG (n=272)	TPC (n=271)
Median age (range), years		57 (29-86)	55 (27-78)
ECOG PS, n (%)	0	116 (43)	126 (46)
	1	156 (57)	145 (54)
Visceral mets at baseline, n (%)		259 (95)	258 (95)
Liver mets, n (%)		229 (84)	237 (87)
Median time from initial MBC diagnosis to randomization (range), months		48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)		173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 months, n (%)		235 (86)	234 (86)
Prior CDK4/6i, n (%)	≤12 months	161 (59)	166 (61)
	>12 months	106 (39)	102 (38)
	Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting (range), n		3 (0-8)	3 (1-5)

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

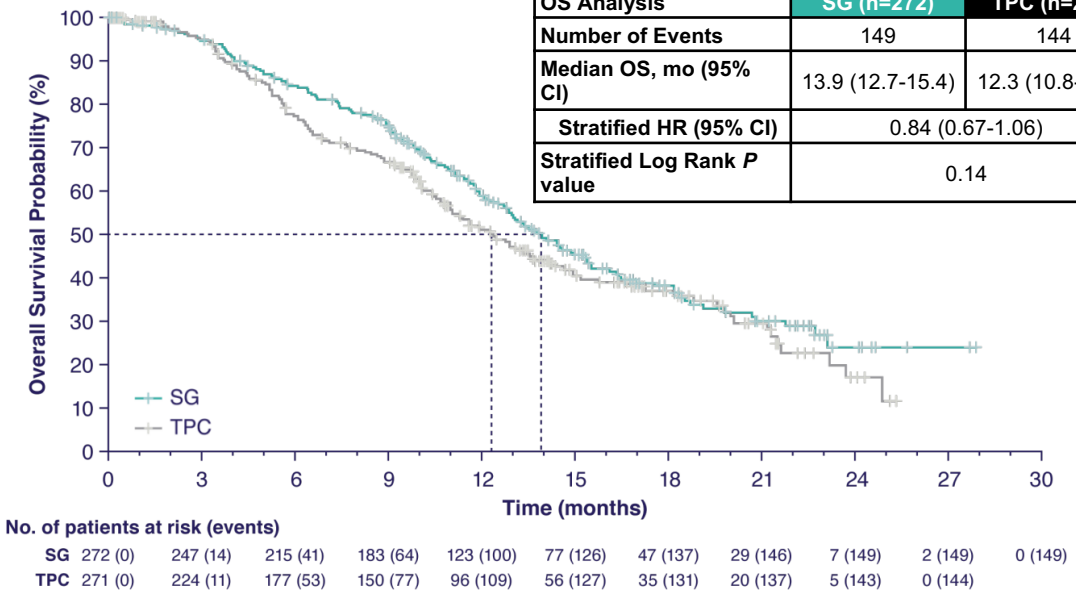
Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: Efficacy

BICR-Assessed PFS in the ITT Population



PFS Analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	0.66 (0.53-0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2-28.1)	7.1 (2.8-13.9)

OS in the ITT Population (First Planned Interim Analysis)



OS Analysis	SG (n=272)	TPC (n=271)
Number of Events	149	144
Median OS, mo (95% CI)	13.9 (12.7-15.4)	12.3 (10.8-14.2)
Stratified HR (95% CI)	0.84 (0.67-1.06)	
Stratified Log Rank *P* value	0.14	

- SG resulted in a 34% reduction in the risk of PD/death
- SG resulted in PFS benefit consistent across all subgroup analysis, including patients with
  - ≥3 prior chemotherapy regimens in the metastatic setting
  - Visceral mets
  - Endocrine therapy for MBC ≥6 months
- OS data was not mature and further follow-up is ongoing

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

Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: Efficacy (cont'd) and Safety

BICR Analysis		SG (n=272)	TPC (n=271)
ORR, n (%)		57 (21)	38 (14)
Odds ratio; nominal *P* value[a]		1.63; 0.03	
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[b], n (%)		92 (34)	59 (22)
Odds ratio; nominal *P* value		1.84; 0.002	
Median DOR, months (95% CI)		7.4 (6.5-8.6)	5.6 (3.8-7.9)

TEAEs, n (%)	SG (n=268)	TPC (n=249)
Grade ≥3	198 (74)	149 (60)
Leading to treatment discontinuation	17 (6)	11 (4)
Leading to dose delay	178 (66)	109 (44)
Leading to dose reductions	89 (33)	82 (33)
Serious	74 (28)	47 (19)
Leading to death[c]	6 (2)	0
Treatment-related	1 (<1)	0

- 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

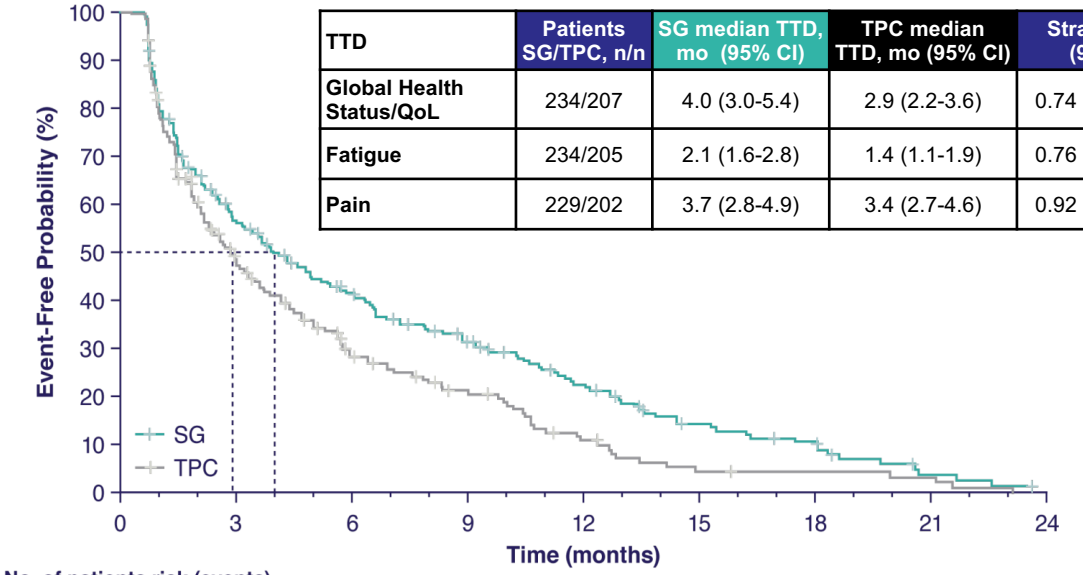
[a]Not formally tested because OS at interim analysis was not statistically significant. [b]CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR and SD ≥6 months. [c]Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment-related (septic 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.

Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: QoL and Summary

Time to Deterioration in Global Health Status/QoL Scale

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	4.0 (3.0-5.4)	2.9 (2.2-3.6)	0.74 (0.59-0.91)	0.005
Fatigue	234/205	2.1 (1.6-2.8)	1.4 (1.1-1.9)	0.76 (0.62-0.93)	0.007
Pain	229/202	3.7 (2.8-4.9)	3.4 (2.7-4.6)	0.92 (0.74-1.14)	0.45



No. of patients risk (events)

SG	234 (0)	125 (100)	84 (132)	59 (151)	36 (167)	19 (179)	13 (184)	3 (191)	0 (193)
TPC	207 (0)	87 (102)	43 (135)	28 (146)	13 (159)	5 (166)	4 (166)	3 (167)	0 (170)

Conclusions

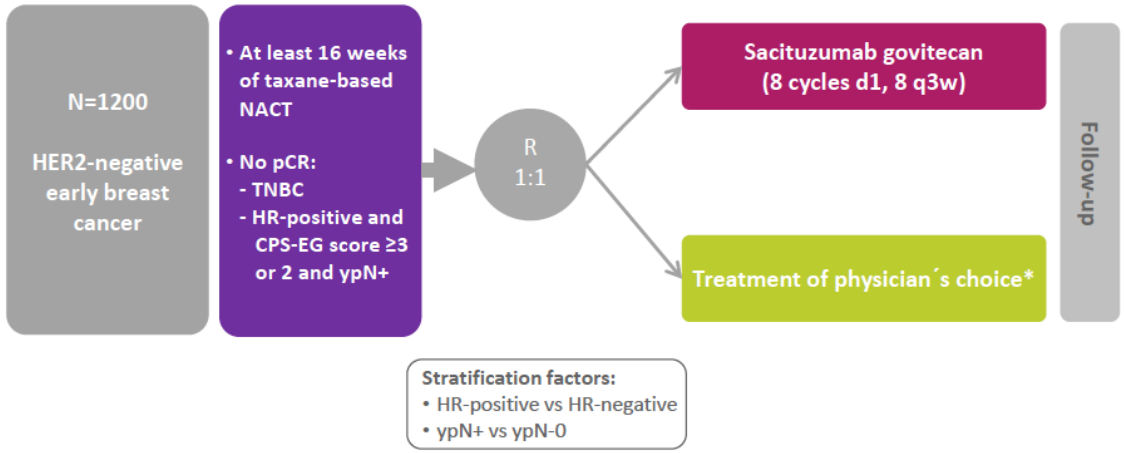
- SG demonstrated PFS benefit over TPC in patients with HR+/HER2- advanced BC who received prior
  - Endocrine-based therapy
  - Prior CDK4/6i
  - ≥2 prior lines of chemotherapy
- OS results were not mature and further follow-up is ongoing
- SG demonstrated a benefit in HRQoL over TPC
- The safety profile with SG was consistent with that observed in previous studies[1-3]

[a]Not formally tested because OS at interim analysis was not statistically significant.

1. Bardia A., et al. *Ann Oncol*. 2021;32:746-756. 2. Kalinsky K, et al. *Ann Oncol*. 2020;31(12):1709-1718.
3. Bardia A, et al. *New Engl J Med*. 2021;384:1529-1541.
Rugo H, et al. ASCO 2022. Abstract LBA1001.

GBG: SASCIA Post-Neoadjuvant Trial

NCT04595565

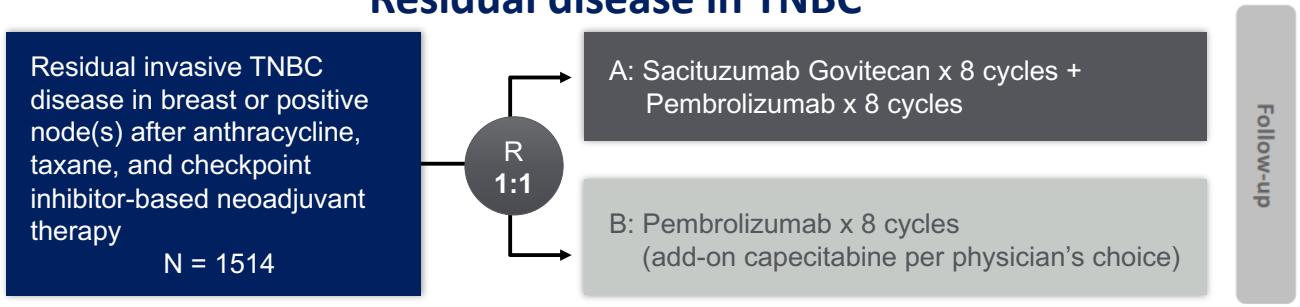


Challenge combining ER+ and TNBC pts

*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.

Proposed Phase III Trial: Optimice-RD

Residual disease in TNBC



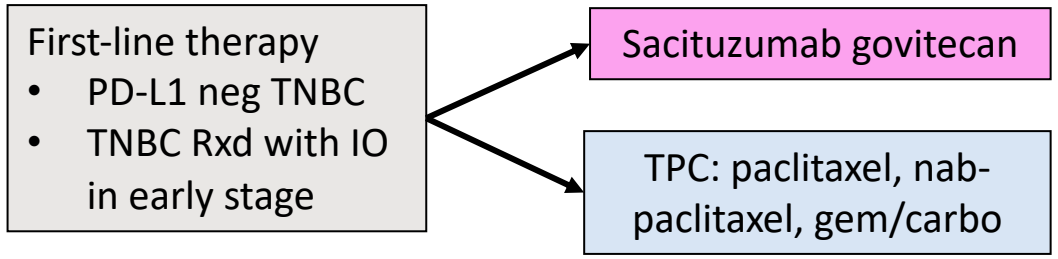
Courtesy of Sara Tolaney; Alliance for Clinical Trials in Oncology

ASPRIA Trial: +ctDNA post NAC/RT with RD
Sacituzumab and atezolizumab (n=40)
Primary endpoint: clearance of ctDNA
PIs: Mittendorf, DeMichele
SU2C funded consortium

STAND UP TO CANCER
standup2cancer.org

ASCENT-03 (NCT05382299)

N=540



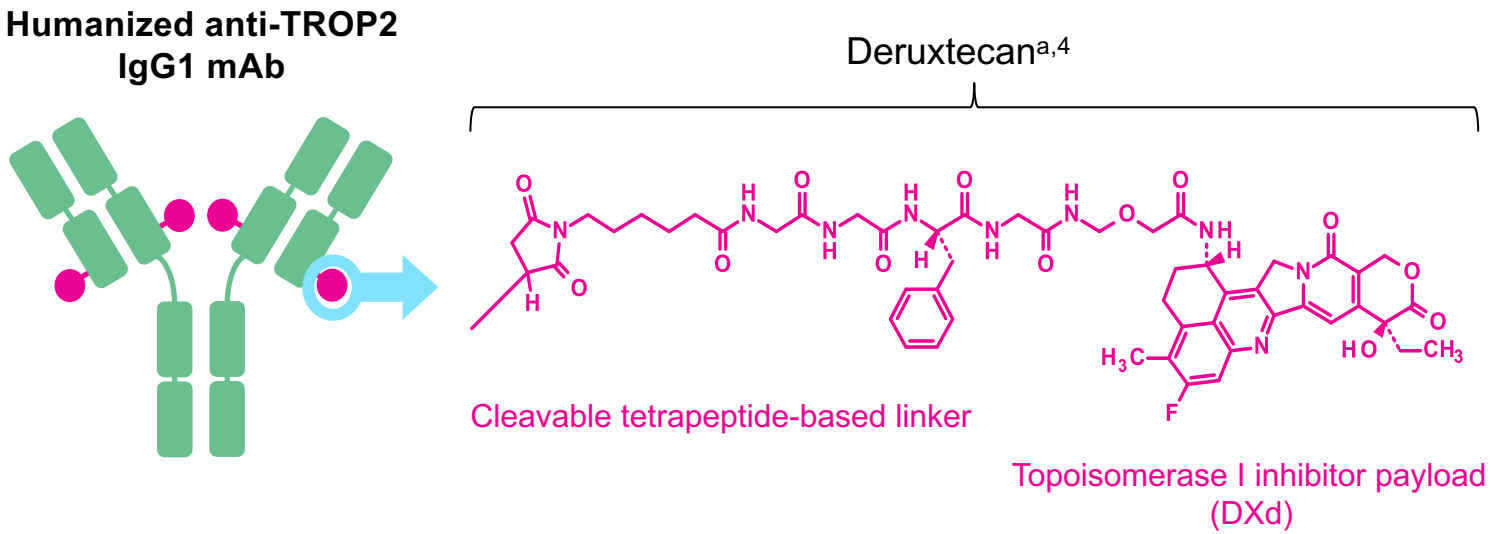
NeoSTAR: neoadjuvant SG x 4 for TNBC (n=50)
- pCR 30% (Spring et al, ASCO 2022)

Ongoing study in combination with pembrolizumab

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.

Krop et al, SABCS 2021

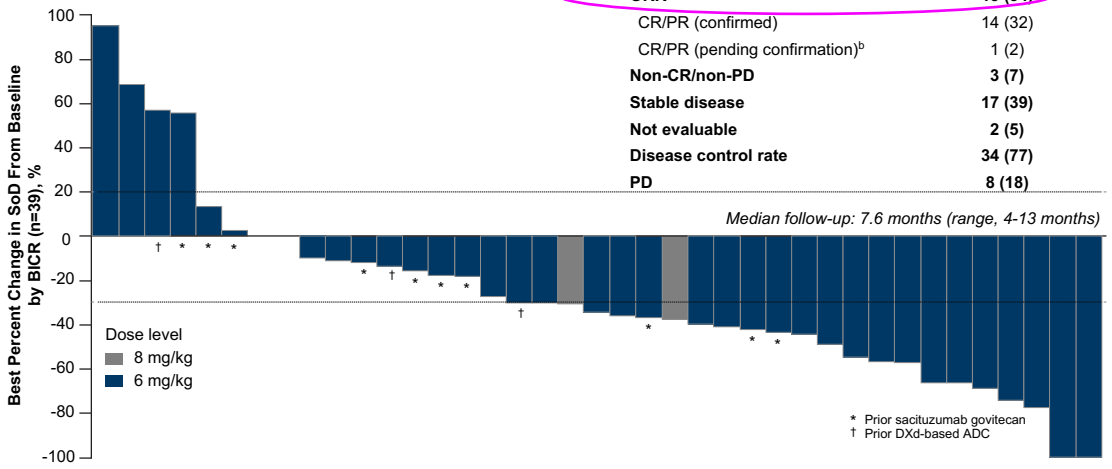
TROPION-PanTumor01 Dato-DXd TNBC Cohort: Results

- Two breast cancer cohorts; HR+ and TNBC. TNBC presented at SABCS
- 13/44 (30%) with prior Trop-1 inhibitor-based ADC treatment

Antitumor Responses by BICR

All patients with TNBC

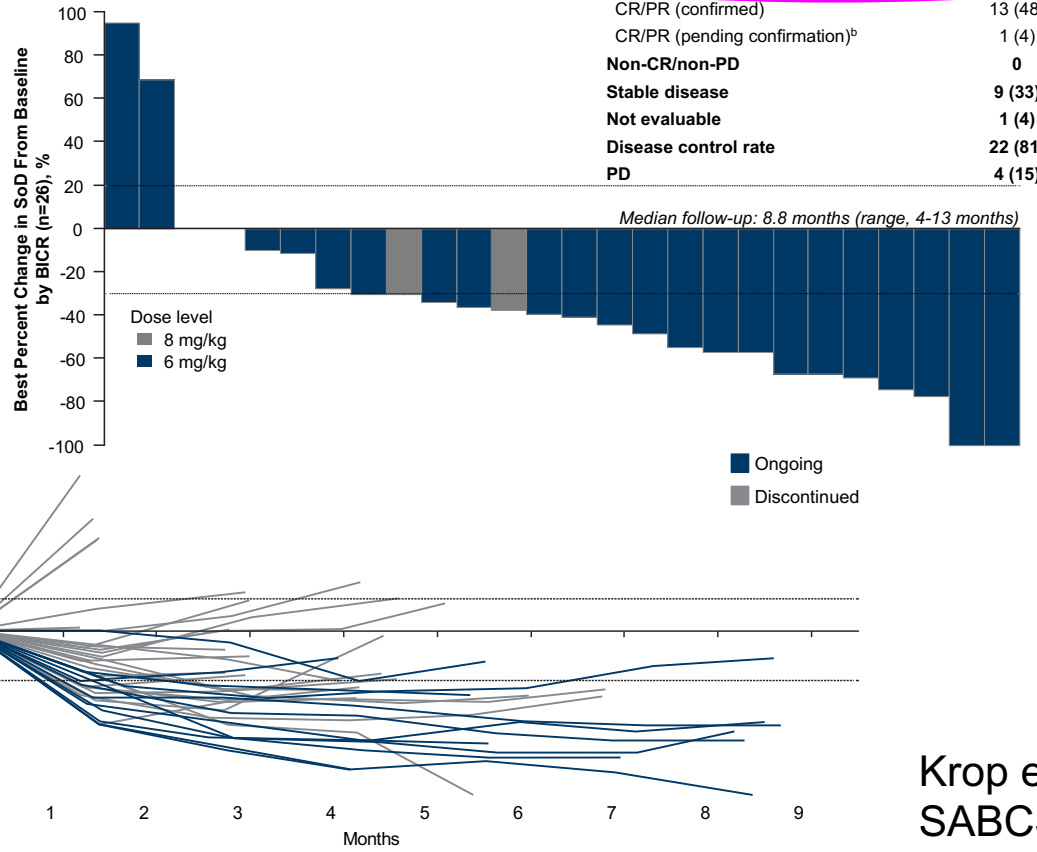
Patients, n (%)[a]	All Patients (n=44)
ORR	**15 (34)**
CR/PR (confirmed)	14 (32)
CR/PR (pending confirmation)[b]	1 (2)
Non-CR/non-PD	**3 (7)**
Stable disease	**17 (39)**
Not evaluable	**2 (5)**
Disease control rate	**34 (77)**
PD	**8 (18)**



Antitumor Responses by BICR

Patients with TNBC without prior Topo I inhibitor-based ADC

Patients, n (%)[a]	SG/DXd Naïve Patients with Measurable Disease at BL (n=27)
ORR	**14 (52)**
CR/PR (confirmed)	13 (48)
CR/PR (pending confirmation)[b]	1 (4)
Non-CR/non-PD	**0**
Stable disease	**9 (33)**
Not evaluable	**1 (4)**
Disease control rate	**22 (81)**
PD	**4 (15)**



Median DOR not reached (range, 2.7-7.4+ mos)
Majority of responses ongoing at the data cutoff

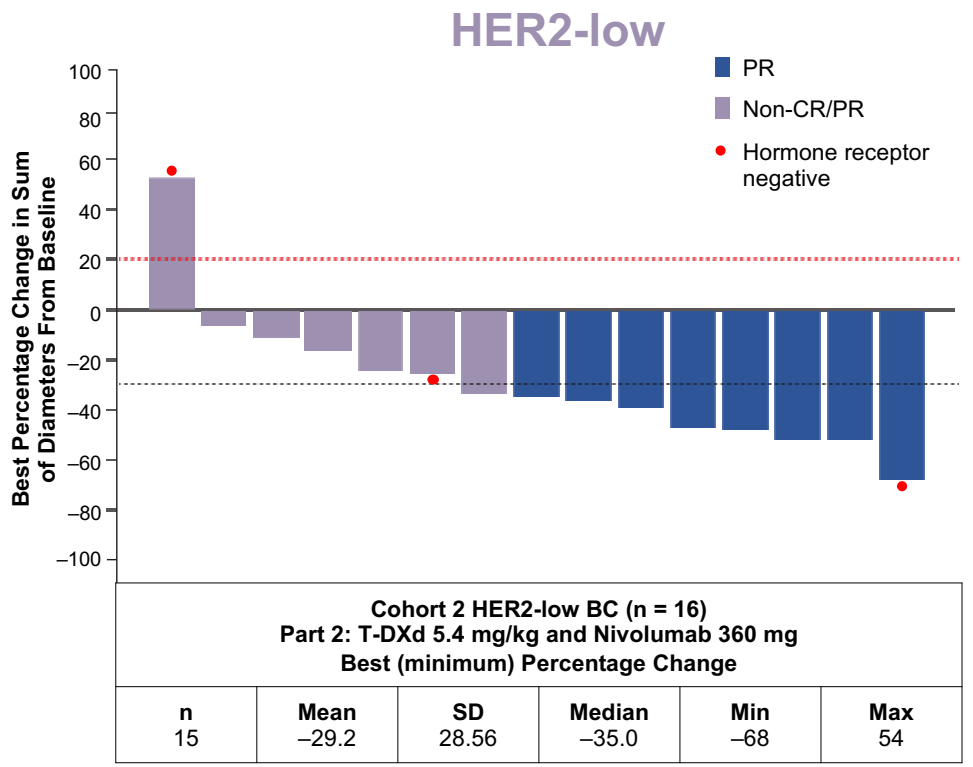
Toxicity

>50% stomatitis, ~10% grade 3
~70% nausea

Krop et al, SABCS 2021

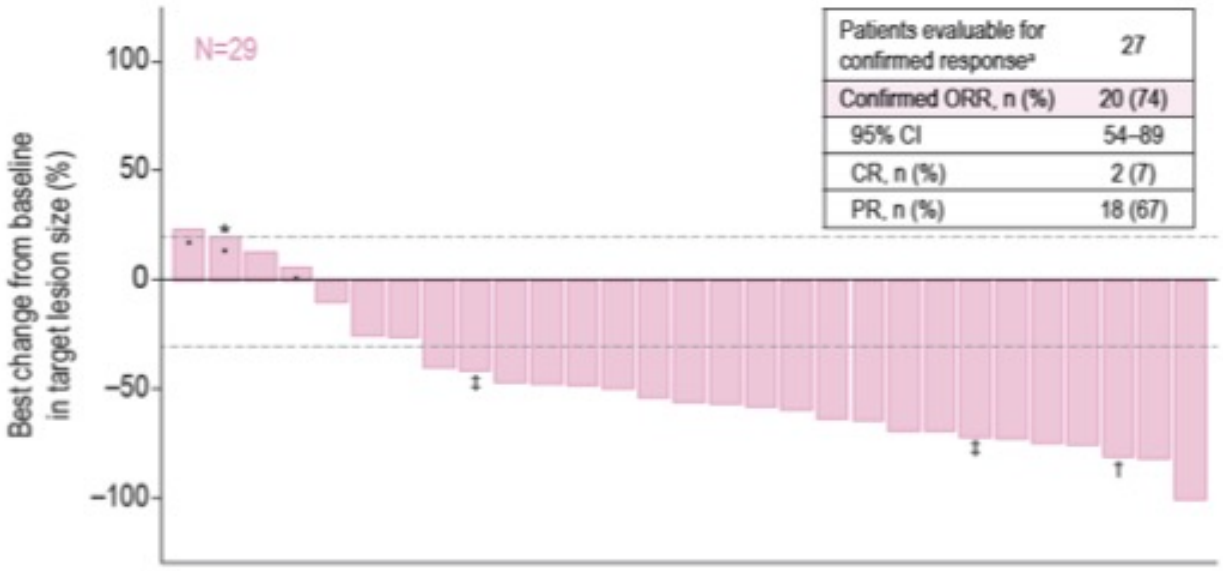
Additional Combinations in HER2 Low MBC

- Dato-DXd+durvalumab
  - N=16; 13 HR+, 3 TN
  - ORR 50%, all PR (24.7-75.3), mPFS 7mo (2.3-10.8)
  - ILD: 14.6%; 1 death
- Dato-DXd+durvalumab as 1st line Rx
  - N=27 evaluable (Begonia Trial)
  - ORR 74% (18/27 PR); durable responses
  - 69% stomatitis, 14% grade 3
  - 21% grade 2 alopecia, 66% gr1-2 nausea



Cohort 2 HER2-low BC (n = 16)
Part 2: T-DXd 5.4 mg/kg and Nivolumab 360 mg
Best (minimum) Percentage Change

n	Mean	SD	Median	Min	Max
15	–29.2	28.56	–35.0	–68	54



Hamilton et. al. ESMO Breast 2022; Schmid et al, ESMO Breast 2022

TROPION-Breast01
NCT05104866

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

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

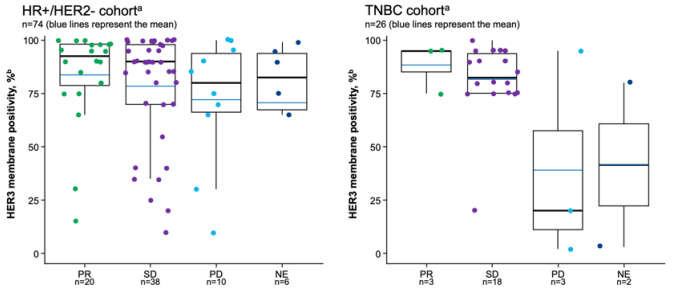
- Confirmed ORR for all patients (N=182): 28.6%
- (95% CI, 22.1-35.7)
- Median DOR: 7.0 months (95% CI, 5.5-8.5)
- In HER2+ disease, clinical activity was not associated with HER3 membrane expression

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

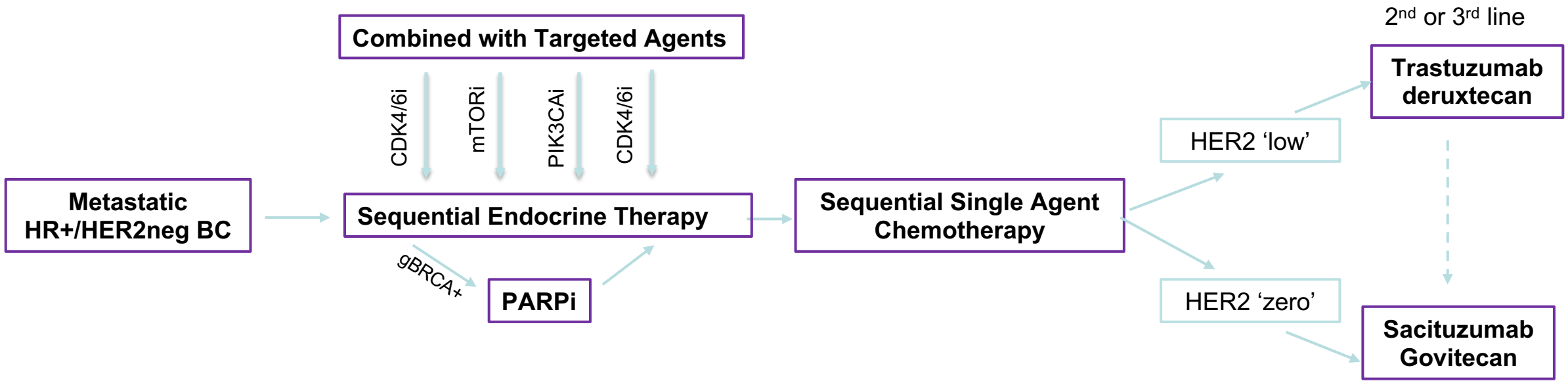
[a]HER3 status by IHC in archival tumor tissue; HER3-positive was defined as IHC 2+ and IHC 3+ for DE/DF cohorts and as ≥25% membrane positivity at 10x for DEXP cohorts. [b]Guided by mCRM with EWOC. [c]HER3-high = ≥75% membrane positivity at 10x; HER3-low = ≥25% and <75% membrane positivity at 10x. [d]HER2 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 TNBC**
  - SG is a new standard of care for mTNBC
    - Post-neoadjuvant SASCIA trial, expected Alliance trial
- **Established role in HER2+ disease**
  - T-DXd is a new standard of care for mHER2+ BC
- **Established role in HER2 low and HR+ disease**
  - T-DXd is a new standard of care of HER2 ‘low’ disease
    - Further definition of HER2 low is important
  - Sacituzumab a treatment option for heavily pre-treated HR+ disease
- **Ongoing trial in earlier lines, early stage disease, and new ADCs in phase III trials**
- **Toxicity management is critical**

Roadmap for HR+/HER2- Metastatic Breast Cancer – and New Directions



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

Thank you!

‘Our destiny is not written for us, it’s written by us.’

Barak Obama