UCSF Helen Diller Family Comprehensive Cancer Center

Antibody Drug Conjugates : New Directions, New Agents!

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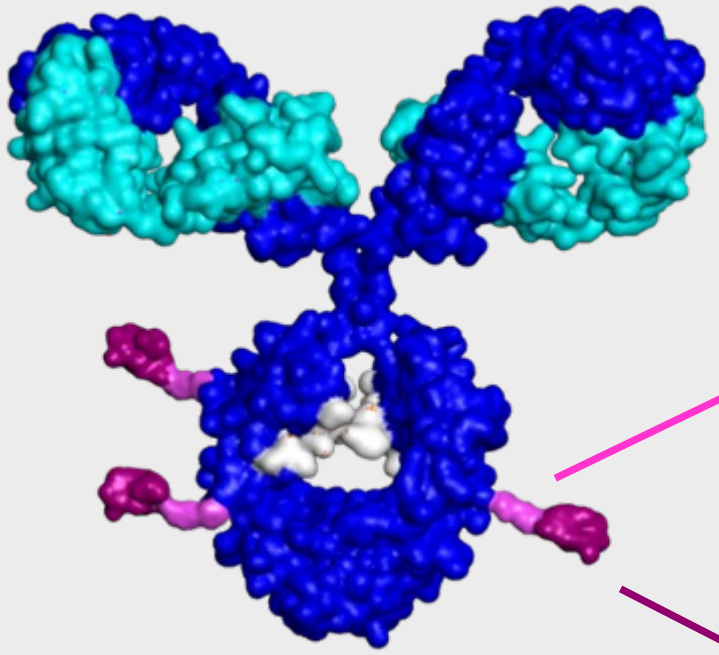
ADCs have different antibodies, linkers and payloads

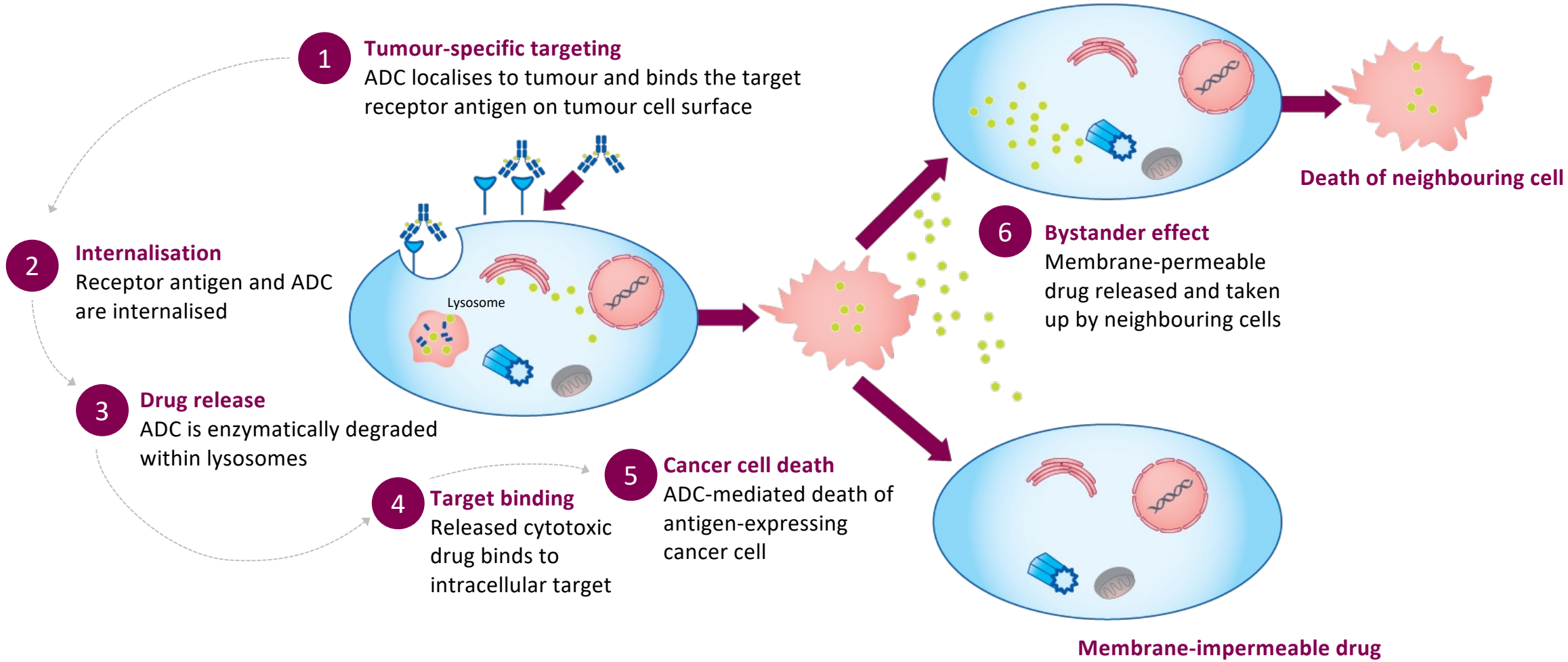


Antibody Drug Conjugate

	ADC Attributes	Trastuzumab emtansine (T-DM1)	Trastuzumab deruxtecan (T-DXd)	Sacituzumab govitecan (SG)	Datopotamab deruxtecan (Dato-DXd)	SKB264	Patritumab deruxtecan (HER3-DXd)	Disitamab vedotin (RC-48)	ARX788
Antibody	Target	HER2	HER2	TROP2	TROP2	TROP2	HER3	HER2	HER2
	Antibody	Trastuzumab	Trastuzumab	hRS7 IgG1k	Datopotamab	hRS7 IgG1	Patritumab	Hertuzumab	Trastuzumab
Linker	DAR	~3.5:1	7–8:1	~7.6:1	~4:1	~7.4:1	~8:1	4:1	2:1
	Linker	Thioether	Tetrapeptide-based	Hydrolysable	Tetrapeptide-based	2-methylsulfonyl pyrimidine	Tetrapeptide-based	Valine-citrulline	Hydroxyl-amine-PEG4
	Cleavable linker?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Payload	Payload	Emtansine	DXd	SN-38	DXd	KL610023 (T030)	DXd	Monomethyl Auristatin E (MMAE)	Amberstatin (MMAF)
	Payload MoA	Anti-microtubule	Topo1 inhibitor	Topo1 inhibitor	Topo1 inhibitor	Topo1 inhibitor	Topo1 inhibitor	Anti-microtubule	Anti-microtubule
	Membrane permeable?	Low	Yes	Yes	Yes	Yes	Yes	Yes	No

ADC=antibody-drug conjugate; DAR=drug to antibody ratio; Dato-DXd=datopotamab deruxtecan; HER2/3=human epidermal growth factor receptor 2/3; IgG-immunoglobulin; MMAE-Monomethyl Auristatin E; MoA=mechanism of action; SG=sacituzumab govitecan; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan; TROP=trophoblast cell surface antigen.

ADC technology enables tumour-specific targeting



ADC=antibody-drug conjugate

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

Trastuzumab deruxtecan in HER2+ MBC

Destiny Breast-03

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

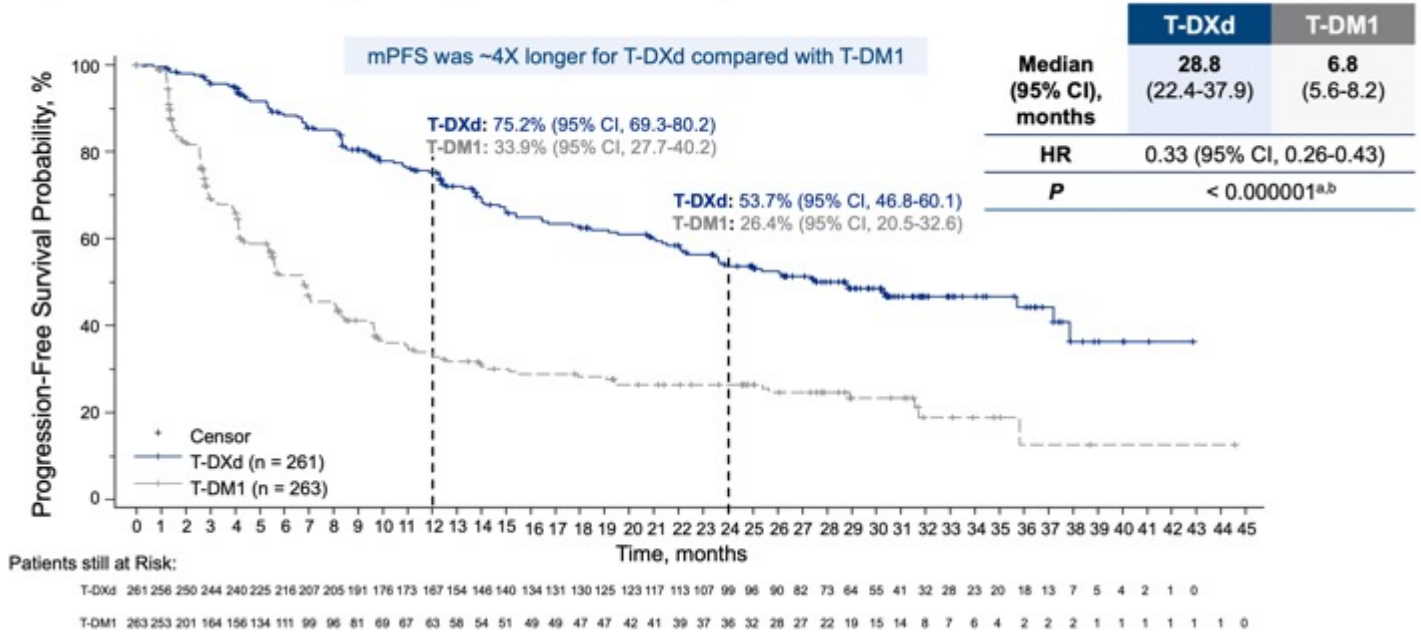
- ILD: 15.2%, no grade 4 or 5

All grade AE

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

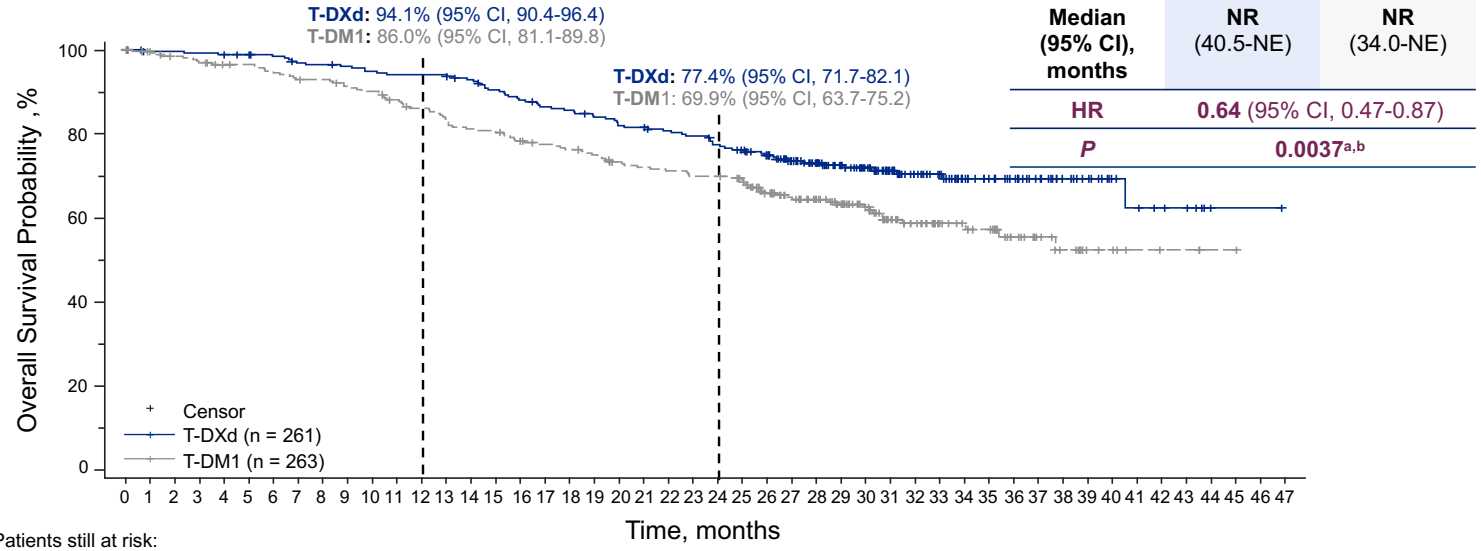
Hurvitz S et al. SABCS 2022; Lancet Oncology 2023

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]	

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]**

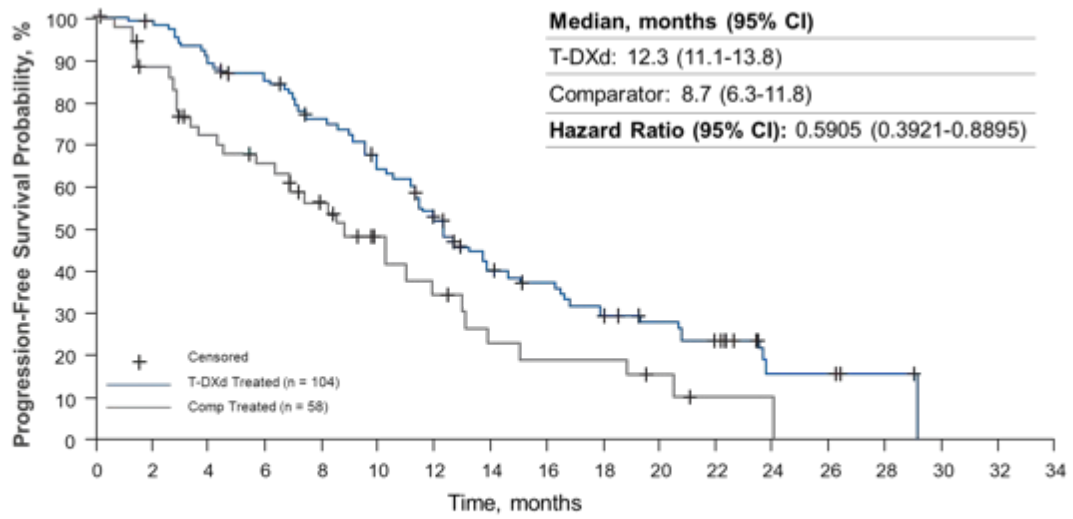
Toxicity
- ILD 10.4% (0.5% gr 5)
- Nausea 72.5%
- Alopecia 37.1%

Krop et al, SABCS 2022; Andre et al, Lancet 2023

Pooled Analysis of T-DXd in HER2+ Brain Metastases: DB01, 02, 03

Exploratory CNS-PFS per BICR

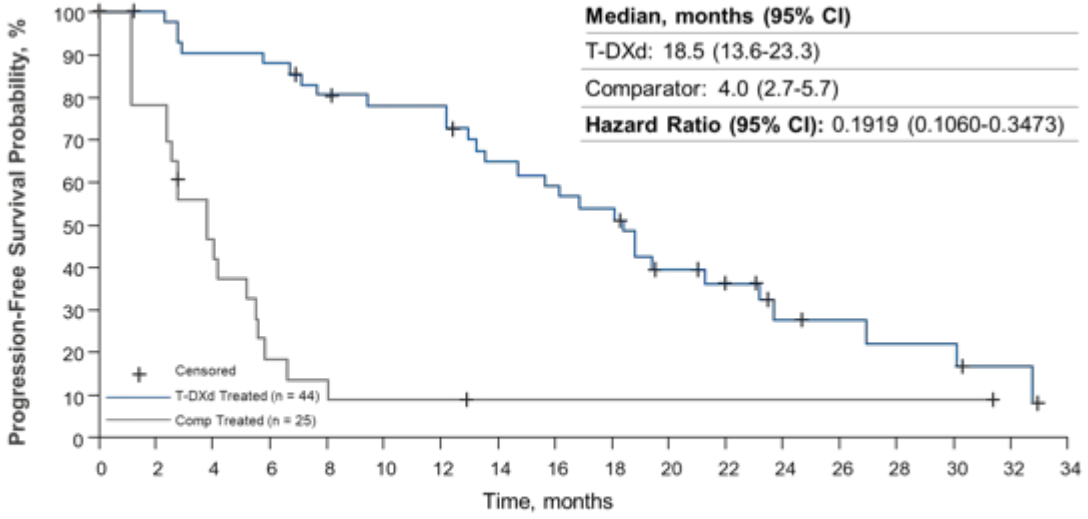
Treated/Stable BMs



Patients still at risk

T-DXd Treated (n = 104)	104	100	89	83	72	58	46	32	28	21	18	12	4	4	2	0	0	0
Comparator Treated (n = 58)	58	44	33	29	22	14	10	6	5	5	3	1	0	0	0	0	0	0

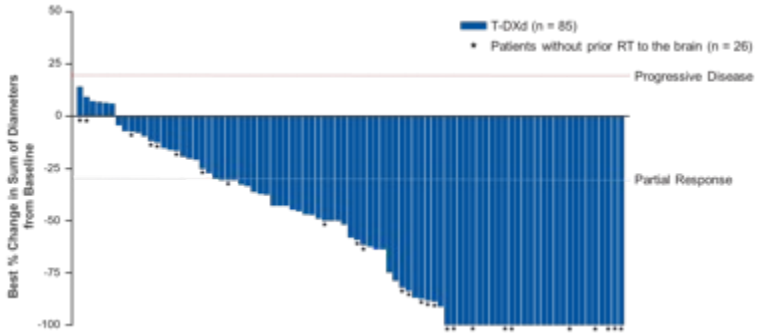
Untreated/Active BMs

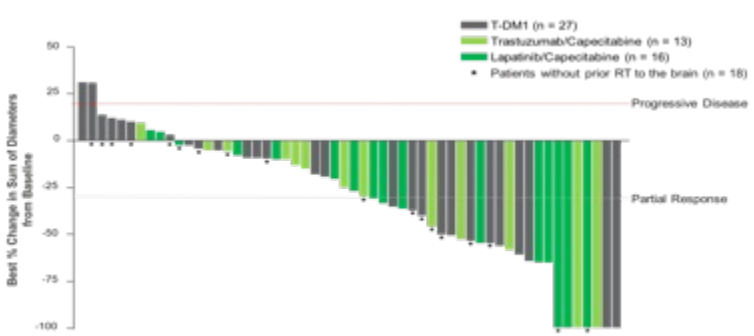


Patients still at risk

T-DXd Treated (n = 44)	44	41	37	36	32	30	30	24	22	20	13	11	6	5	4	4	2	0
Comparator Treated (n = 25)	25	18	11	5	3	2	2	1	1	1	1	1	1	1	1	1	0	0

Best percentage change from baseline in sum of diameters of brain tumors



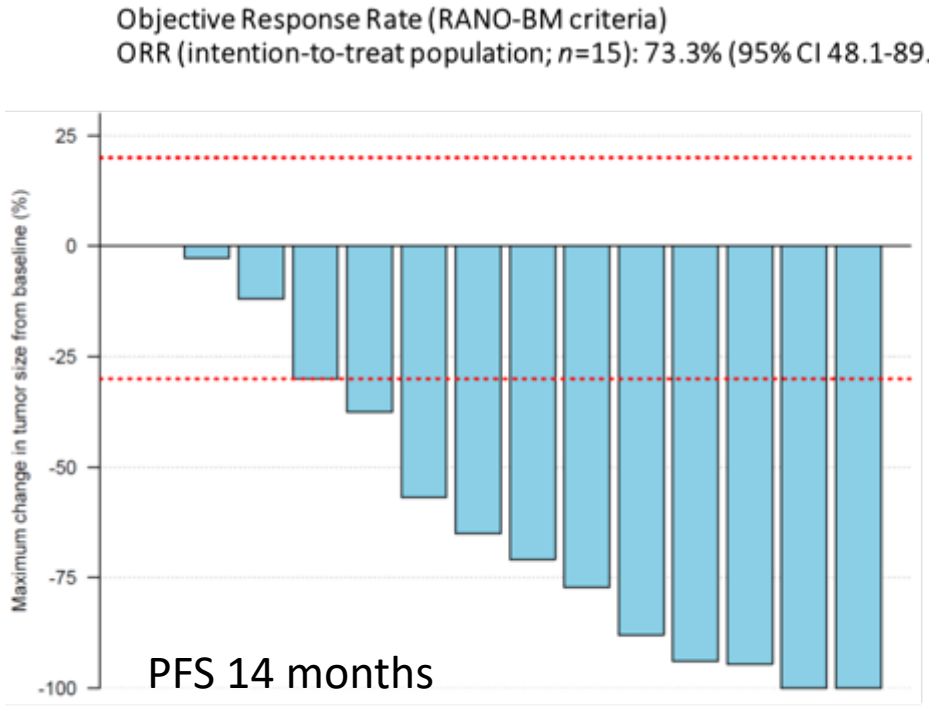


Hurvitz et al, ESMO 2023

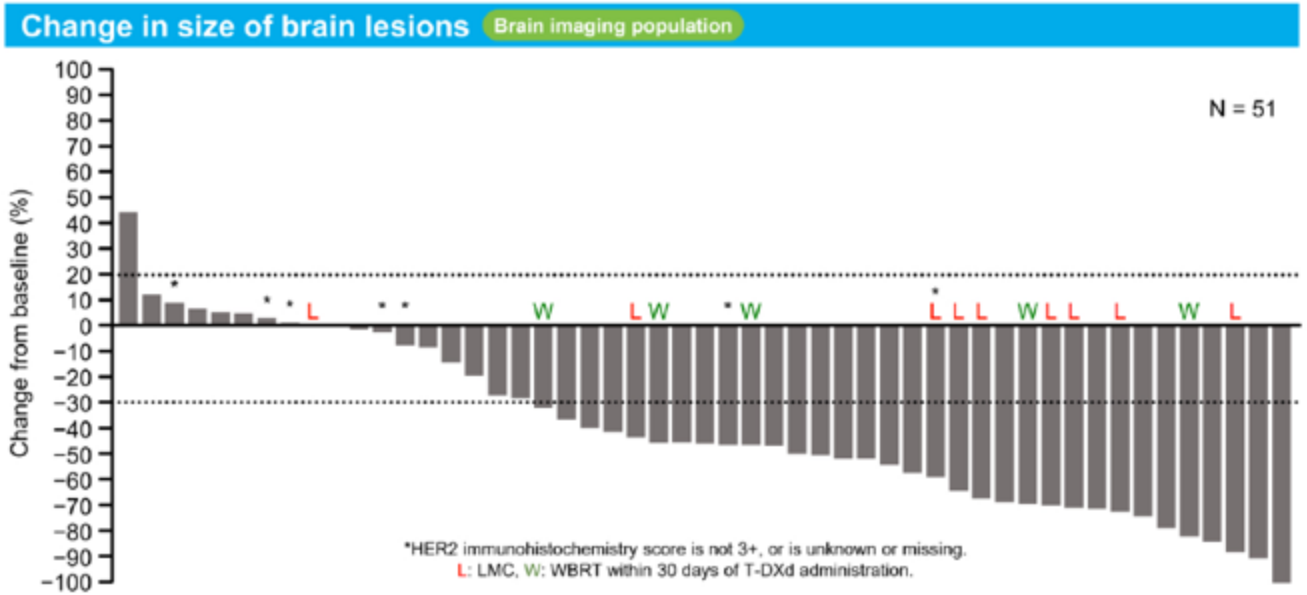
BICR, blinded independent central review; BM, brain metastasis; CNS, central-nervous system; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
CNS-PFS was defined by BICR as only radiological progression.

T-DXd in HER2+ Brain Metastases or LMD

TUXEDO-1 Study: Newly diagnosed BMs or PD after prior Rx; prior HP for all, T-DM1 allowed



ROSET-BM: Retrospective Review of Pts with HER2+ MBC and BM or LMD; N=89, independent review of imaging



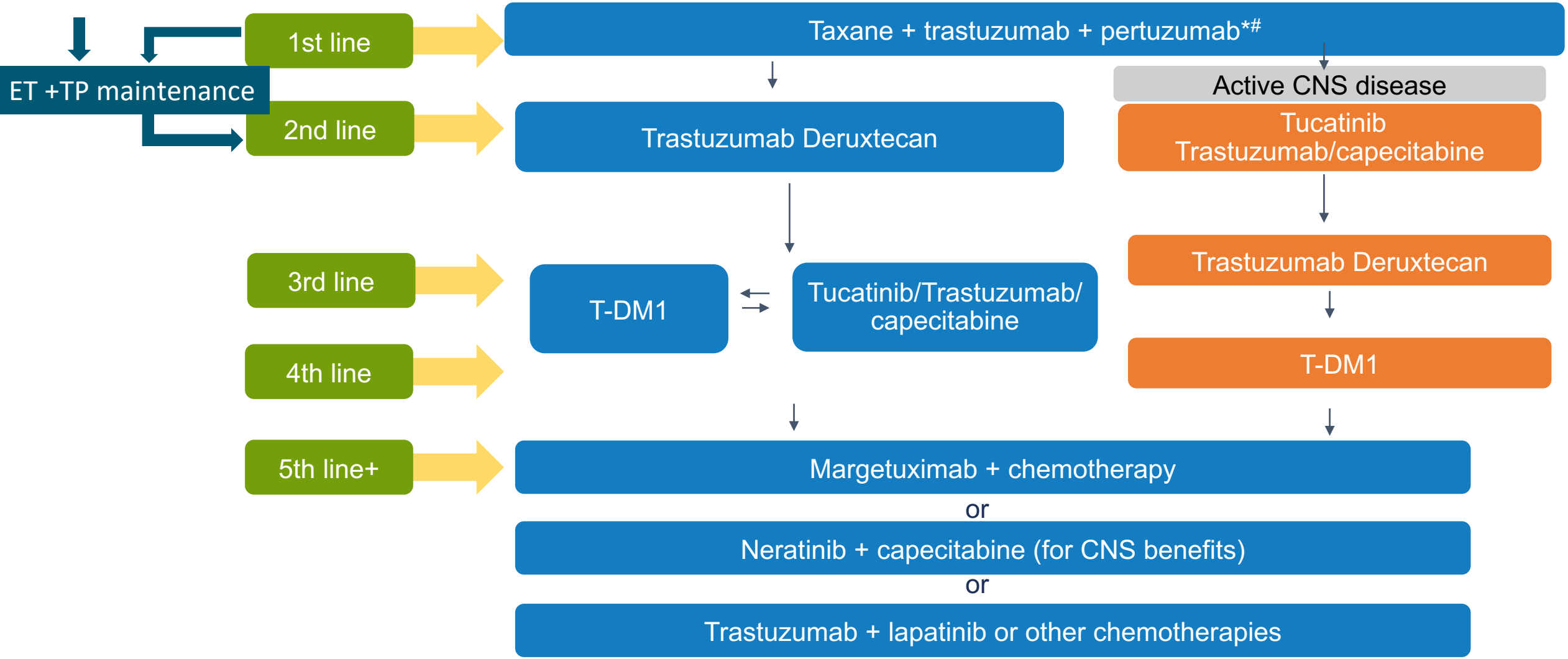
51 pts with BM by ICR
- ORR: 62.7%, PFS: 16.1 months

19 pts with LMD
- 12 mo PFS: 60.7%, 12 mo OS: 81.1%

Bartsch R, et al. Nature Med, 2022

Yamanaka et al, SABCS 2022 PD7-01; Nikura et al, NPJ Breast Cancer.

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)

Destiny-Breast04: Updated Survival Results of T-DXd in HER2-low Metastatic Breast Cancer

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]
- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

N=557

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]
- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

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

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

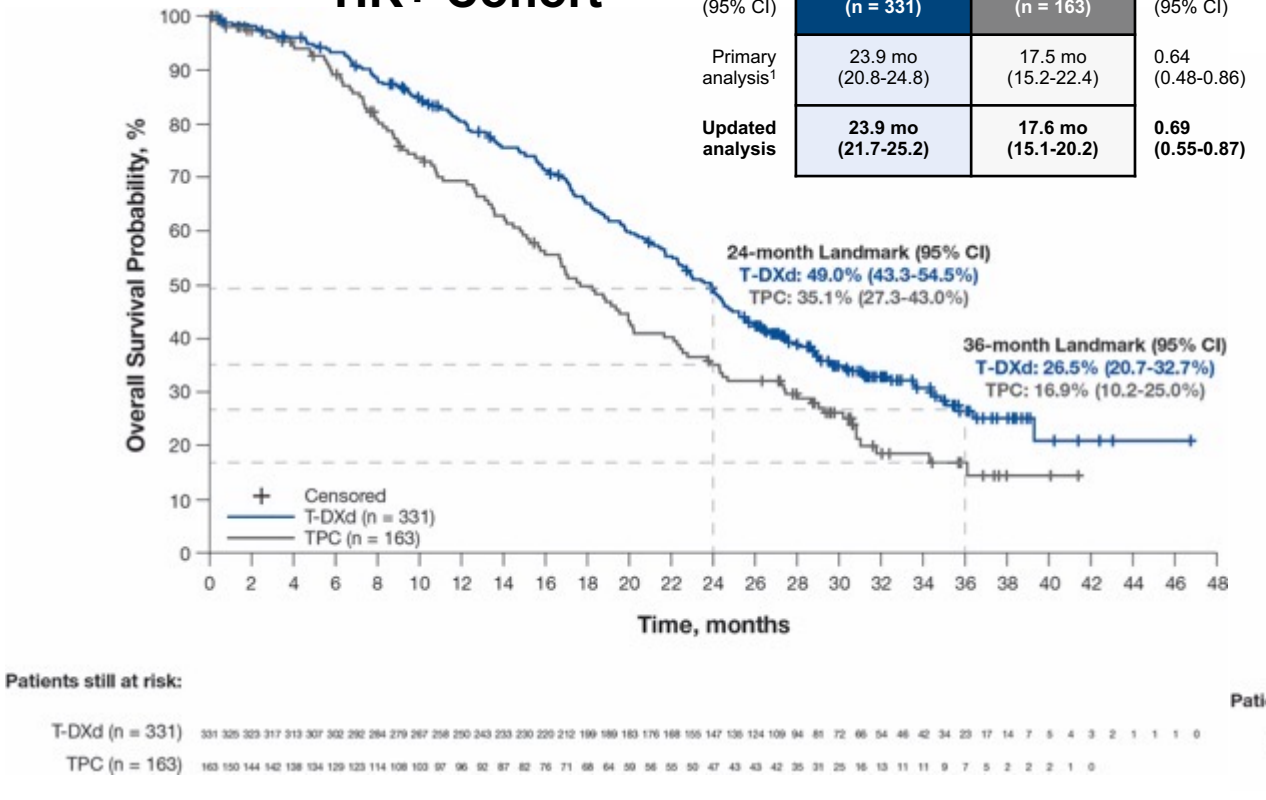
- At the primary analysis (data cutoff, January 11, 2022), median follow-up was 18.4 months
- The primary analysis of PFS was by BICR; this is comparing investigator assessment
- Patient population: Median one line of chemotherapy for MBC, 65-70% prior CDKi, 70% liver mets

Modi et al, NEJM 2022; ESMO 2023

Updated Overall Survival

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



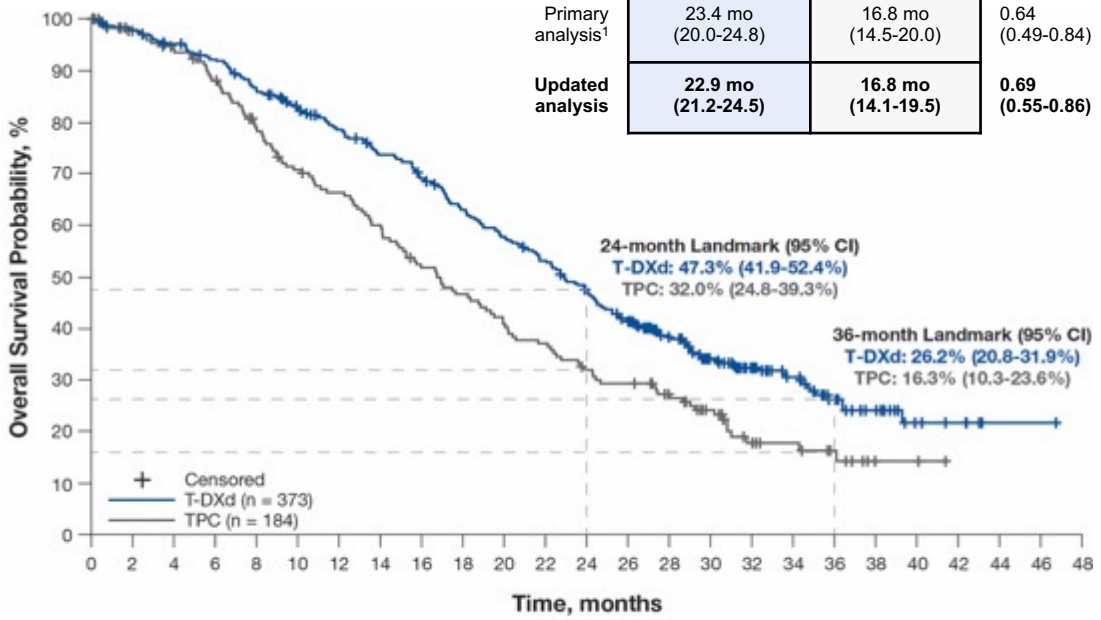
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 256 250 243 233 230 220 212 199 189 183 176 168 155 147 136 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 309 295 286 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

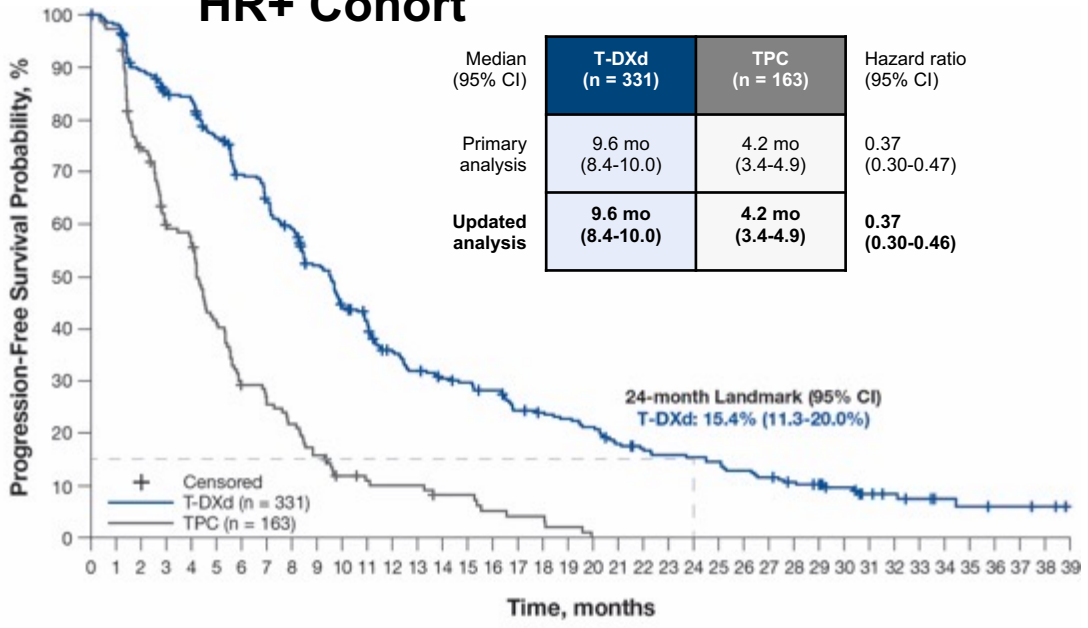
Primary Analysis (BICR)

OS	HR+ T-DXd (n=331)	HR+ TPC (n=163)	HR- T-DXd (n=40)	HR- TPC (n=18)	All Patients T-DXd (n=373)	All Patients 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	

Modi et al, NEJM 2022; ESMO 2023

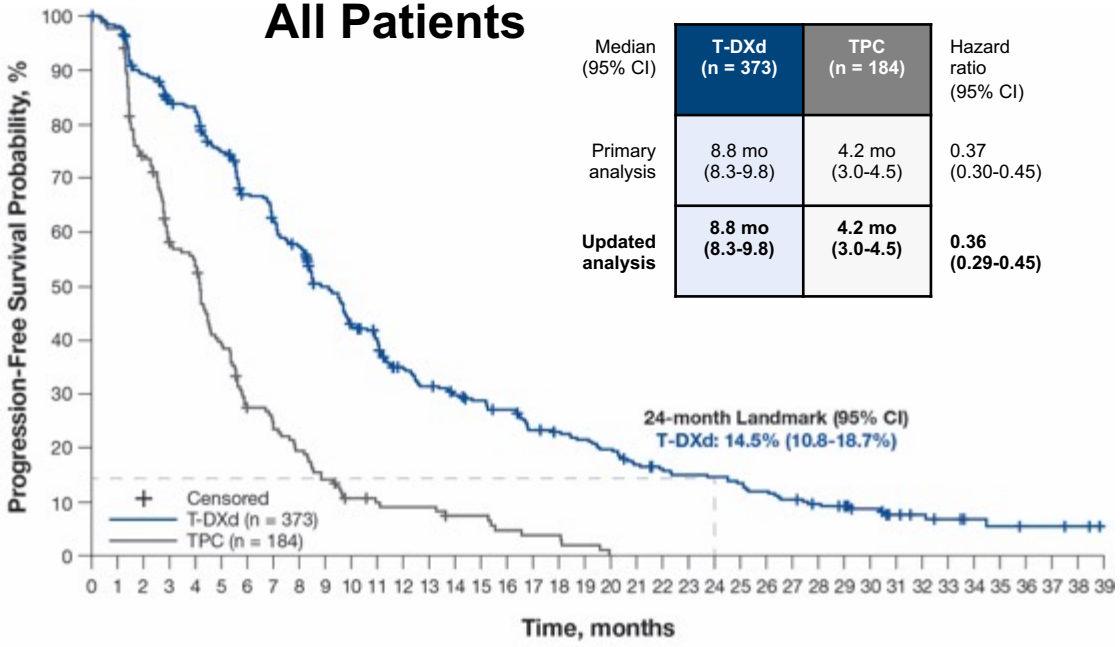
Updated Progression Free Survival (Investigator Assessed)

HR+ Cohort



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

All Patients



Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**

Primary Analysis (BICR)

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	

Modi et al, NEJM 2022; ESMO 2023

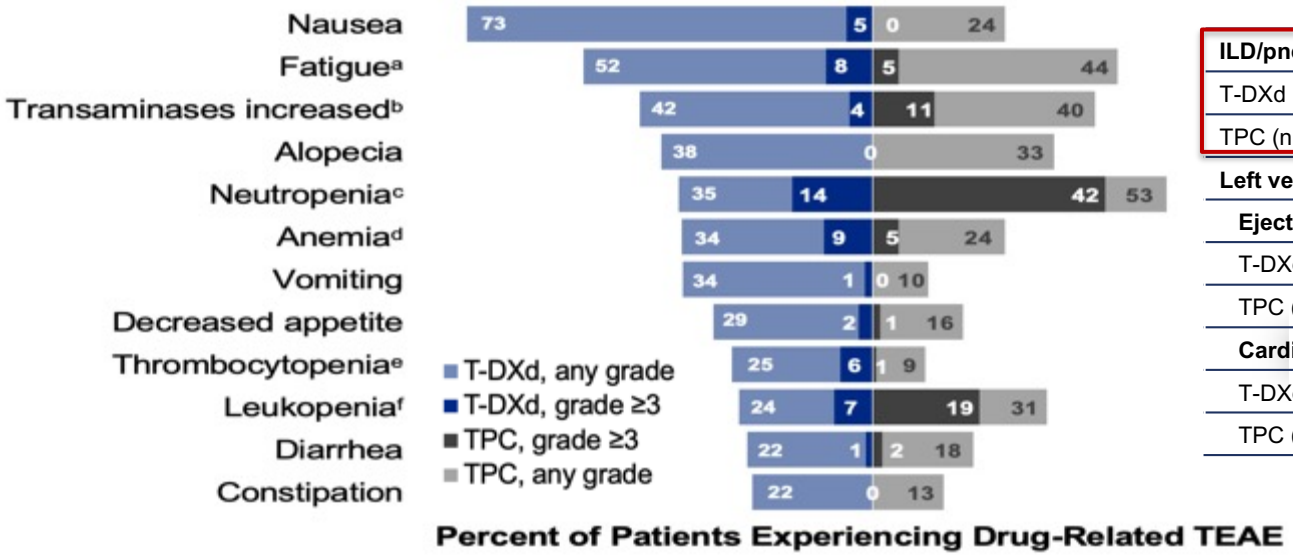
Subgroup analyses: OS in the HR+ Cohort

	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	156/233	78/115	22.3 (19.8-24.3)	16.8 (13.6-19.5)	0.71 (0.54-0.94)
No	53/96	31/47	30.3 (23.0-35.1)	22.4 (15.6-27.2)	0.63 (0.41-0.99)
IHC status					
IHC 1+	121/192	67/96	22.9 (20.8-25.2)	16.9 (13.5-22.4)	0.67 (0.50-0.91)
IHC 2+/ISH−	90/139	43/67	24.2 (20.8-26.5)	19.1 (15.1-22.3)	0.73 (0.51-1.05)
Prior lines of chemotherapy					
1	118/203	63/93	25.5 (23.9-28.8)	19.4 (16.7-23.9)	0.66 (0.48-0.89)
≥2	93/127	47/69	19.0 (16.7-22.7)	14.0 (10.8-20.0)	0.76 (0.53-1.08)
Age					
<65 years	164/260	81/120	23.0 (20.8-24.8)	17.6 (14.8-20.0)	0.67 (0.52-0.88)
≥65 years	47/71	29/43	25.5 (21.0-28.8)	19.5 (9.2-30.6)	0.72 (0.45-1.15)
Race					
White	104/156	51/78	23.9 (19.8-24.8)	15.1 (12.3-19.9)	0.65 (0.47-0.91)
Asian	80/131	46/66	23.9 (21.7-28.7)	19.9 (16.7-27.2)	0.75 (0.52-1.07)
Other	25/37	12/16	21.5 (15.0-30.4)	15.2 (6.2-23.9)	0.56 (0.28-1.12)
Region					
Asia	80/128	42/60	23.4 (21.0-27.4)	19.9 (16.7-27.2)	0.76 (0.53-1.11)
Europe and Israel	102/149	49/73	23.9 (20.8-25.7)	17.6 (12.3-20.2)	0.66 (0.47-0.93)
North America	29/54	19/30	24.5 (15.8-28.9)	16.0 (8.8-22.3)	0.59 (0.33-1.06)
ECOG performance status					
0	109/187	59/95	26.0 (23.0-29.6)	20.2 (16.7-24.4)	0.68 (0.49-0.93)
1	102/44	51/68	21.4 (17.9-23.9)	14.9 (12.6-18.4)	0.70 (0.50-0.99)
Visceral disease at baseline					
Yes	201/298	99/146	22.9 (21.4-24.5)	17.5 (14.8-20.2)	0.73 (0.57-0.93)
No	10/33	11/17	NE (20.4-NE)	18.4 (13.5-NE)	0.34 (0.14-0.81)

OS in all Patients

	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	158/235	81/118	22.3 (19.7-24.2)	16.7 (14.0-19.4)	0.71 (0.54-0.92)
No	55/98	32/48	29.6 (22.9-35.1)	22.4 (15.6-27.2)	0.64 (0.41-0.99)
IHC status					
IHC 1+	137/214	77/107	22.7 (20.3-24.7)	15.7 (13.5-19.9)	0.65 (0.49-0.86)
IHC 2+/ISH−	105/159	51/77	23.6 (20.0-26.0)	17.1 (13.1-21.7)	0.72 (0.51-1.01)
Prior lines of chemotherapy					
1	129/221	69/100	25.5 (23.4-28.9)	18.2 (15.6-22.5)	0.62 (0.46-0.83)
≥2	113/151	59/83	18.1 (16.1-21.5)	14.0 (10.8-19.1)	0.78 (0.57-1.07)
Age					
<65 years	185/290	95/136	22.7 (20.3-24.4)	16.7 (14.0-19.1)	0.64 (0.50-0.82)
≥65 years	57/83	33/48	24.4 (18.4-28.0)	19.5 (11.1-30.2)	0.77 (0.50-1.19)
Race					
White	123/176	62/91	22.0 (18.2-24.2)	14.5 (10.7-19.4)	0.68 (0.50-0.93)
Asian	90/151	51/72	25.2 (21.7-29.6)	19.1 (15.7-24.3)	0.68 (0.48-0.96)
Other	26/38	13/17	21.2 (17.0-28.9)	15.2 (6.2-23.9)	0.55 (0.28-1.07)
Region					
Asia	90/147	47/66	24.0 (21.7-29.3)	19.1 (15.7-24.3)	0.69 (0.49-0.98)
Europe and Israel	118/166	59/85	22.3 (19.0-24.2)	14.8 (10.7-19.9)	0.67 (0.49-0.91)
North America	34/60	22/33	20.6 (13.6-25.9)	14.9 (10.5-19.5)	0.66 (0.38-1.13)
ECOG performance status					
0	117/200	68/105	25.9 (23.0-29.3)	19.4 (15.1-22.8)	0.62 (0.46-0.83)
1	125/173	60/79	20.6 (17.2-22.7)	14.5 (12.3-18.4)	0.74 (0.54-1.01)
Visceral disease at baseline					
Yes	227/332	109/157	22.4 (20.0-24.0)	16.9 (14.0-20.0)	0.71 (0.57-0.90)
No	15/41	19/27	NE (28.0-NE)	15.7 (12.9-20.6)	0.35 (0.18-0.70)

Adverse Events



	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure, n (%)						
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

For T-DXd: 8.2% discontinued for ILD/pneumonitis; 4.6% dose reduced for N/V

Modi et al, NEJM 2022; ESMO 2023

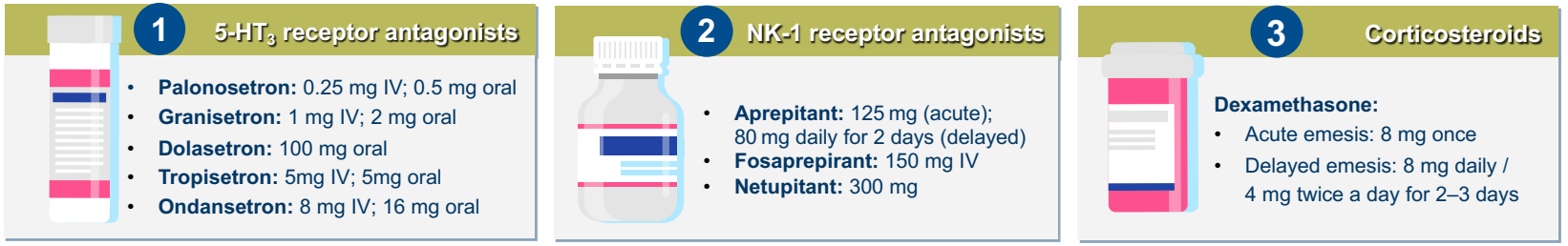
DB04: Nausea and Vomiting

- 189/371 patients (50.9%) in the T-DXd arm and 64/172 patients (37.2%) in the TPC arm received antiemetic prophylaxis[a]
- Prophylaxis was not mandatory per study protocol, but was recommended

	Nausea		Vomiting	
n (%)	T-DXd n = 371	TPC n = 172	T-DXd n = 371	TPC n = 172
Dose reduction associated with N/V	17 (4.6)	4 (2.3)	3 (0.8)	1 (0.6)
Drug interruption associated with N/V	5 (1.3)	4 (2.3)	0	0
Drug discontinuation associated with N/V	1 (0.3)	0	1 (0.3)	0

Three Classes of Anti-Emetic Premedication is Recommended

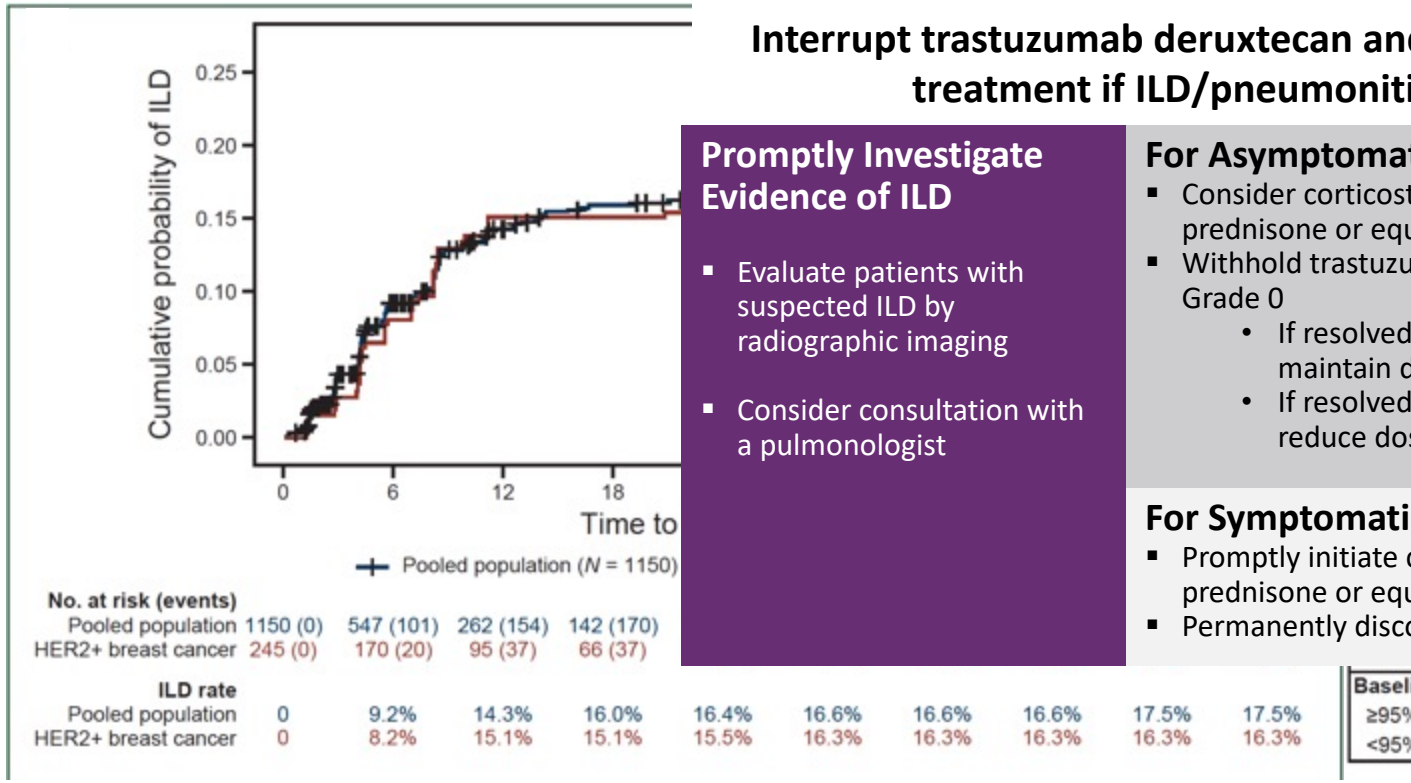
This can be individualized to patient symptoms



N/V, nausea or vomiting; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Prophylaxis included antiemetics and antinauseants, corticosteroids for systemic use, drugs for functional gastrointestinal disorders, or other.

Rugo et al, ESMO Breast 2023; NCCN 2023

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

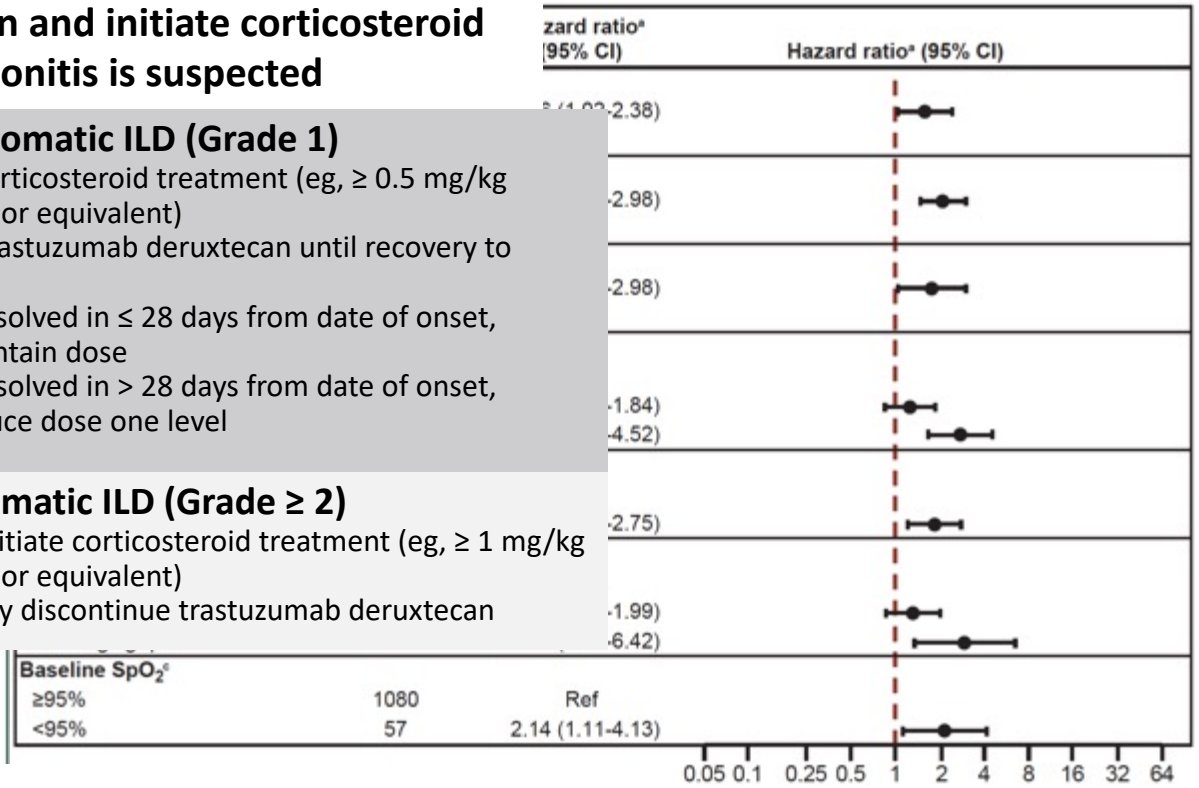
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

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)

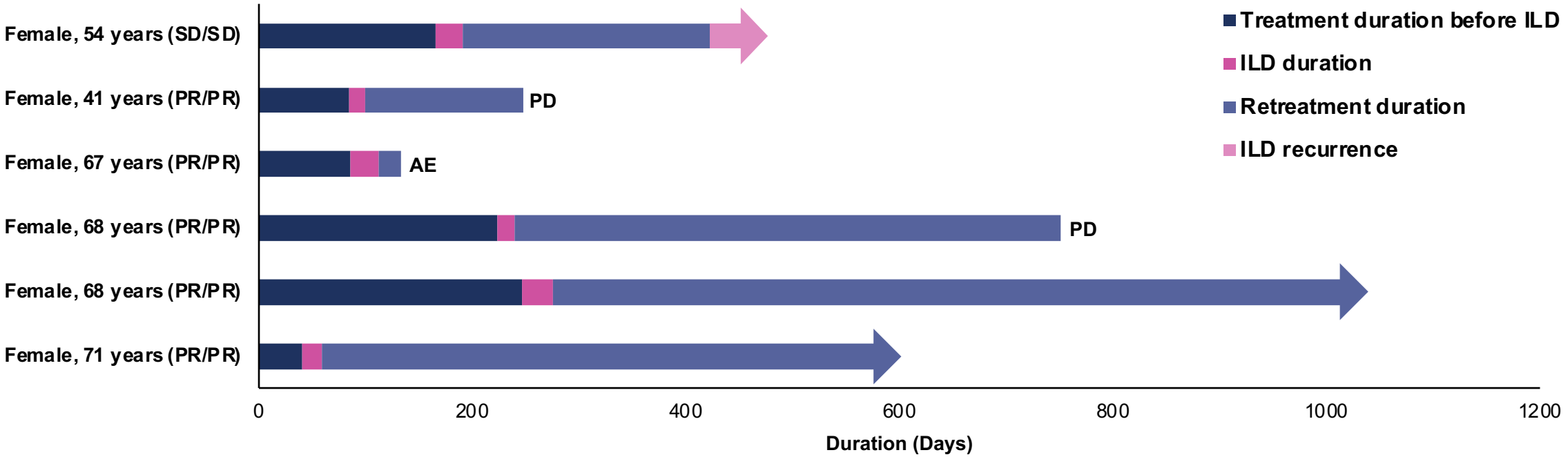
- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan



- 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

Re-Treatment in Patients After Occurrence of Grade 1 ILD

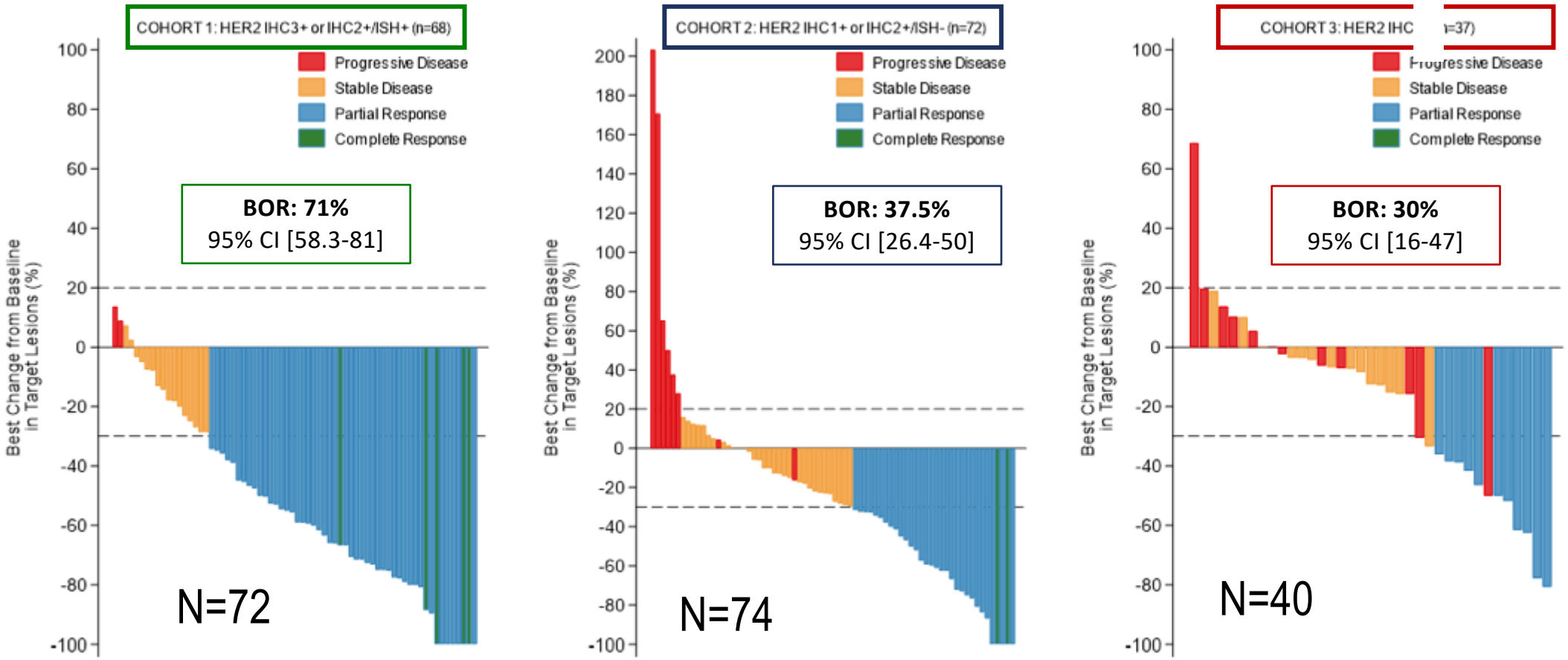


- 6 patients with grade 1 ILD (as assessed by investigator) were re-treated after resolution; 1 of these patients had a second ILD event that was adjudicated as grade 2 by the adjudication committee at re-occurrence
  - At DCO, 1 patient discontinued due to an AE; 2 patients discontinued due to PD; 3 patients remained on T-DXd

AE, adverse event; DCO, data cutoff; ILD, interstitial lung disease; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

Rugo et al, ESMO Breast 2023

DAISY: BOR rate according to HER2 expression



THE BOR RATE IS DEFFERENT BETWEEN THE THREE COHORTS *p* <0.0001

Data cut-off: Oct 19, 2021

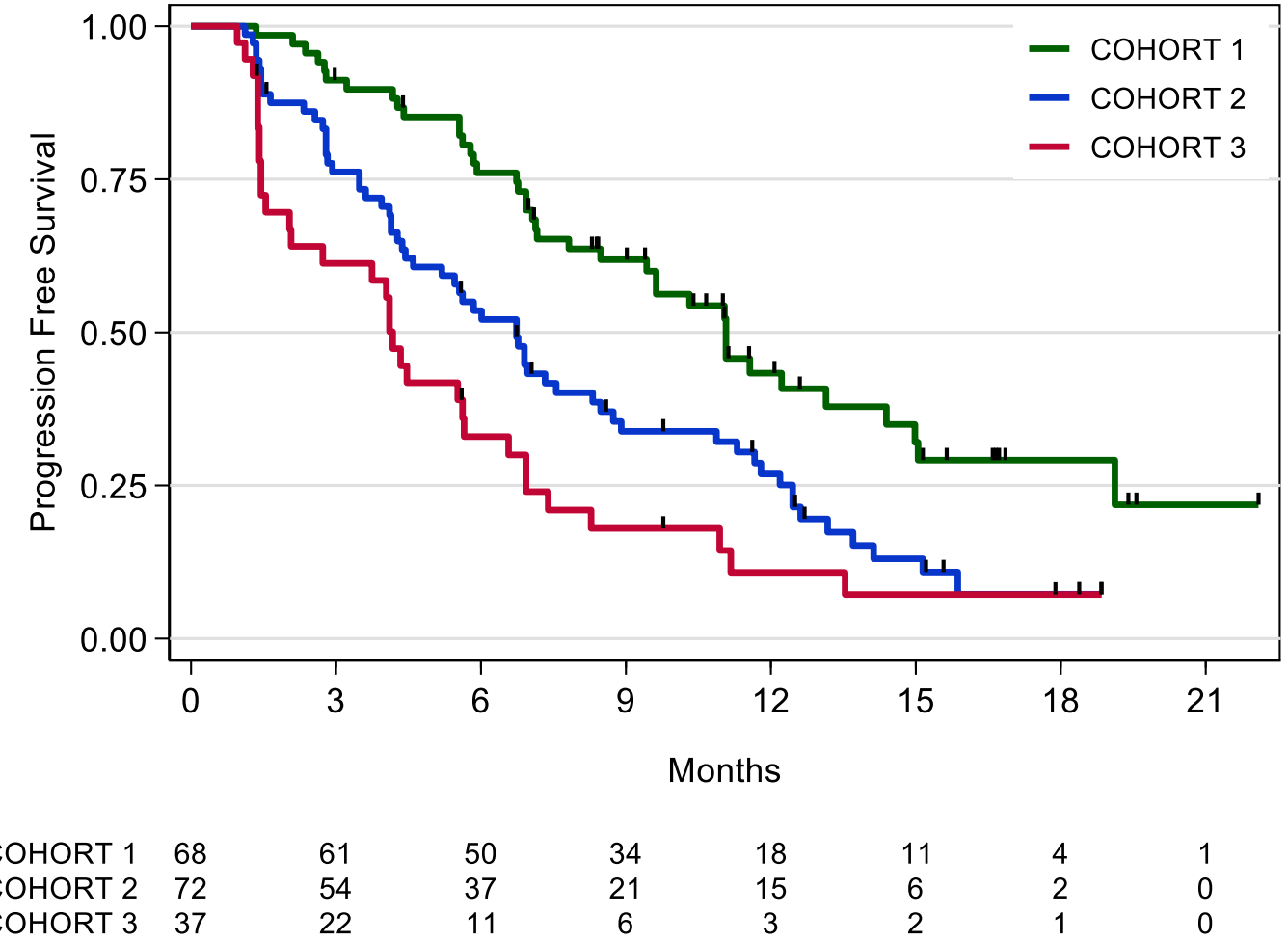
Mosele et al, Nature Medicine 2023

NCT04132960

DAISY: PFS according to HER2 expression

Data cut-off: Oct 19, 2021	Cohort 1 HER2 IHC 3+ or IHC 2+/ISH+ (n=68)	Cohort 2 HER2 IHC 2+/ISH- or IHC 1+ (n=72)	Cohort 3 HER2 IHC 0 (n=37)
Median PFS (mths) (95% CI)	11.1 (8.5–14.4)	6.7 (4.4-8.3)	4.2 (2-5.7)
HR (95% CI)	0.53 (0.34-0.84)	1.00	1.96 (1.21-3.15)
***p*-value**	***p* <0.0001**		

	Median PFS	Median OS
(HR+)	4.5 months	11.6 months
(HR-)	2.1 months	10.3 months



THE PFS IS DEFFERENT BETWEEN THE THREE COHORTS *p* <0.0001

Median follow up: 15.6 months

NCT04132960

Testing Trastuzumab Deruxtecan in HER2 'Ultralow' DESTINY-Breast06

Key differences with DB-04:

- Includes IHC0 (ultralow, n=150))
- Larger (n=850)
- Restricted to HR+ disease
- Chemo-naïve patients

Status: Completed accrual

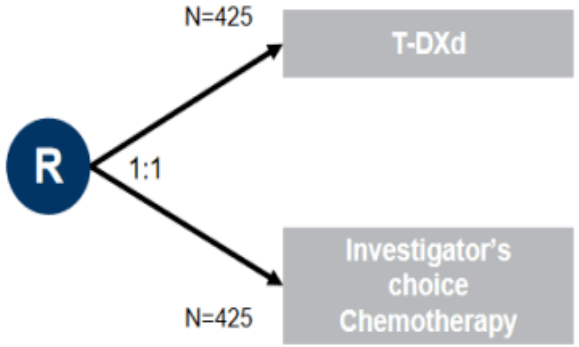
POPULATION

- 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

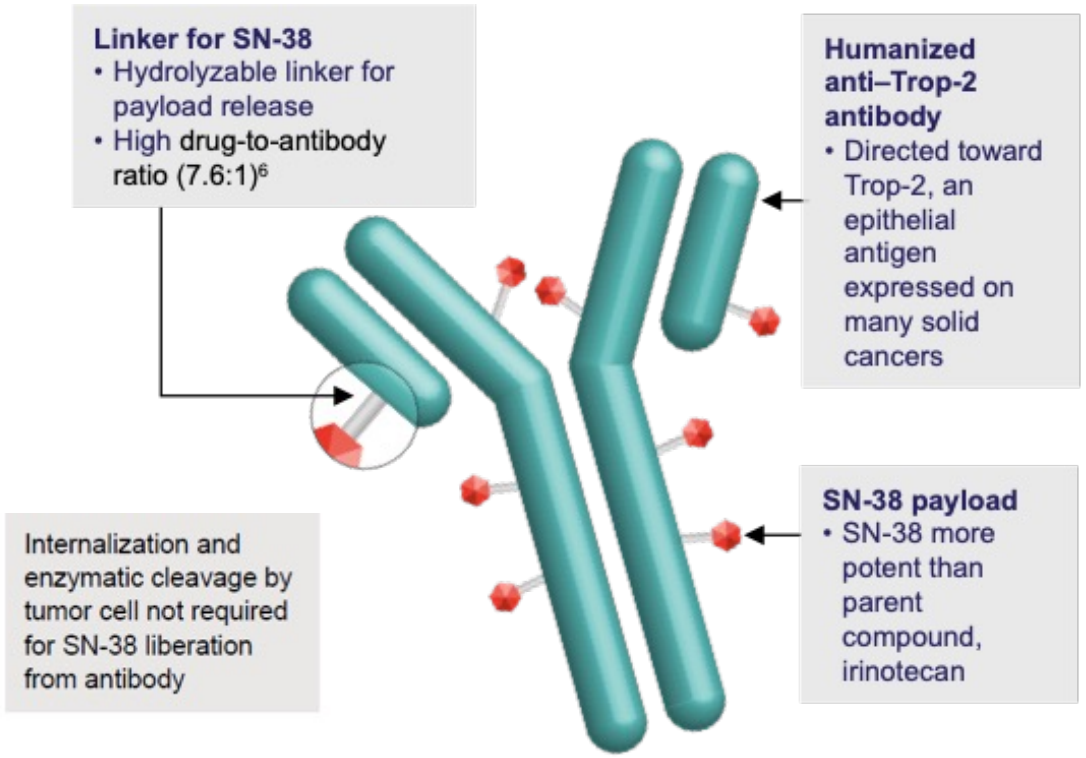
Secondary:

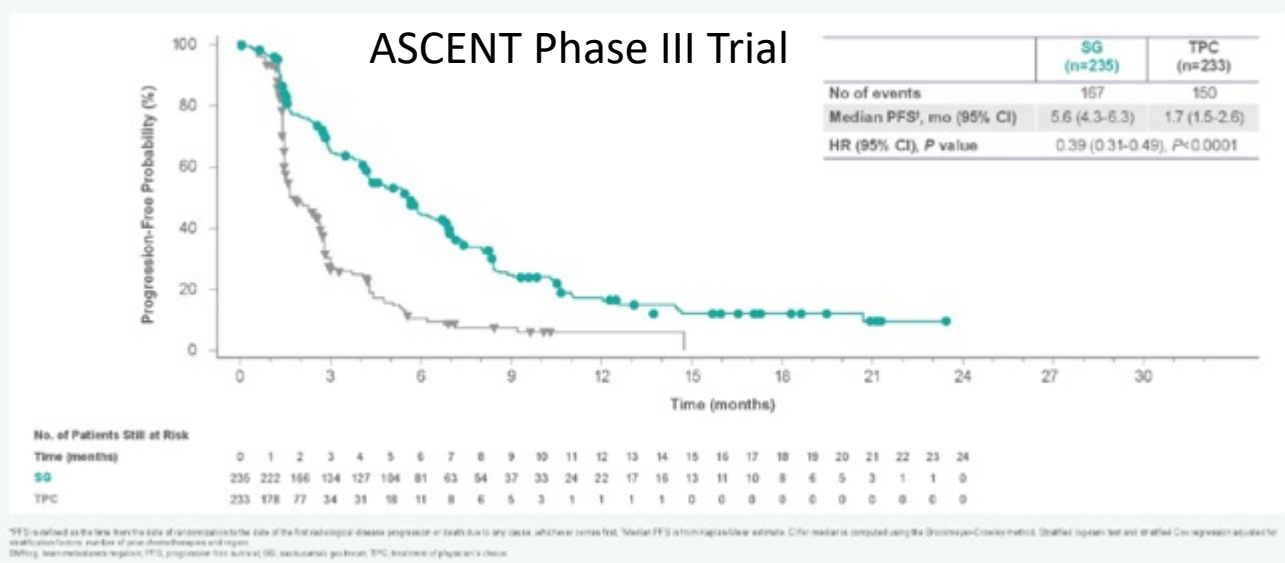
- PFS (investigator assessed) in HER2 IHC 1+/2+
- ORR and DOR of HER2 IHC 1+/2+ and ITT populations
- Safety and tolerability
- Symptoms, functioning and HRQoL

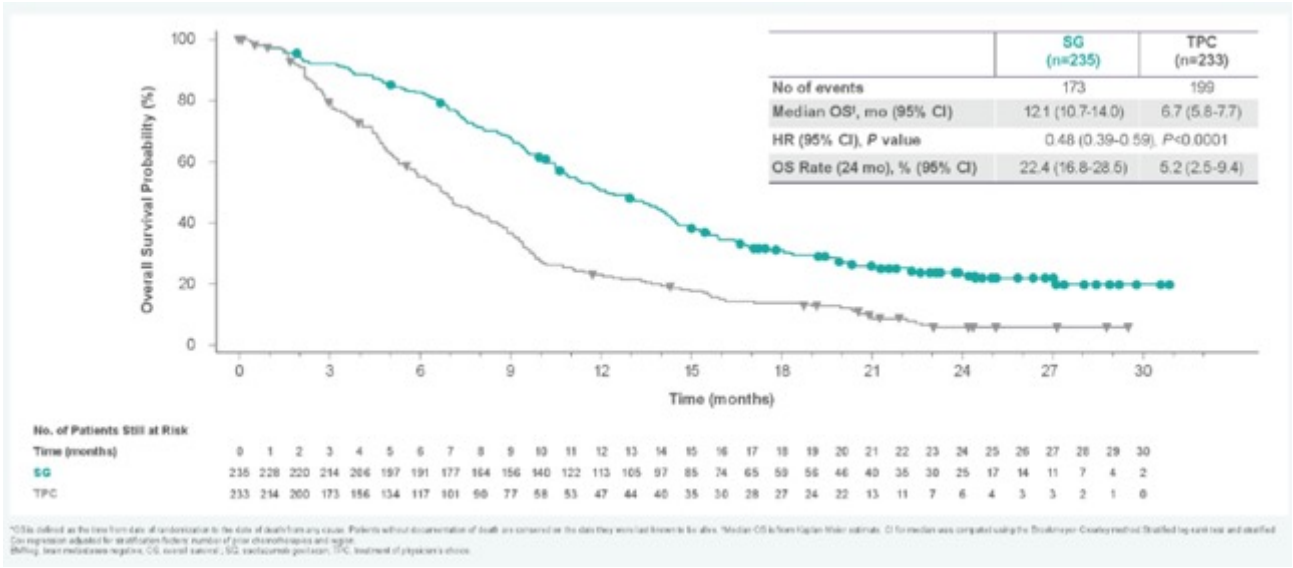
Exploratory:

- PRO
- Pharmacodynamic biomarkers

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







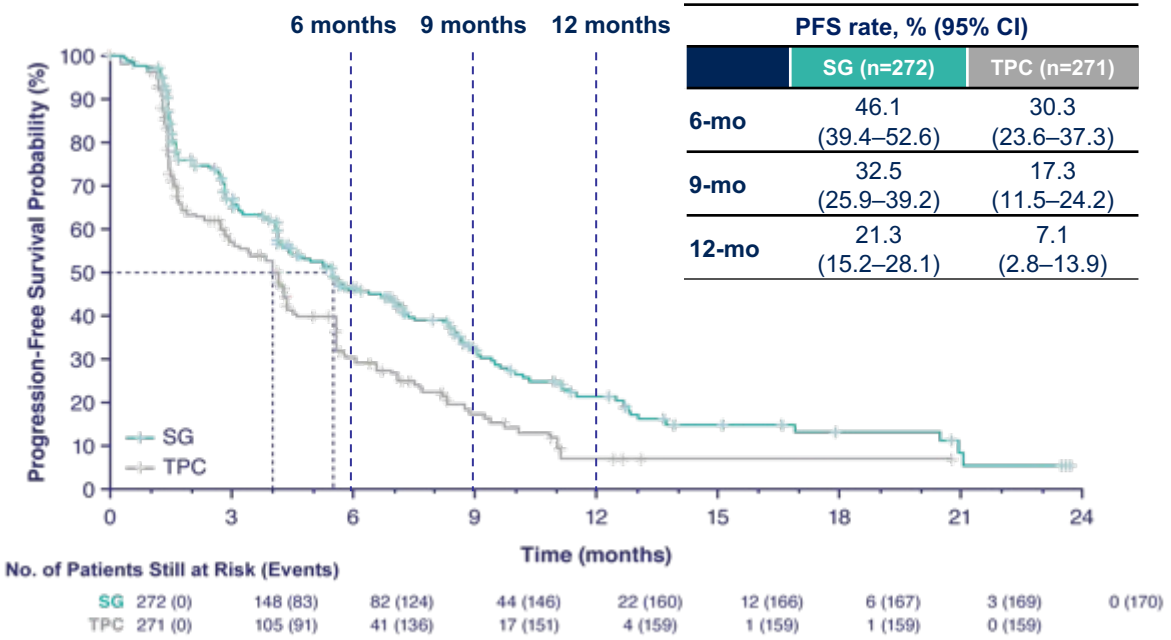
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- **Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), FN (6% vs 2%)**
  - G-CSF: 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due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

Bardia et al. *NEJM*, 2021.

TROPICS 02 for HR+/HER2- Disease: PFS & OS in the ITT Population

PFS[1]

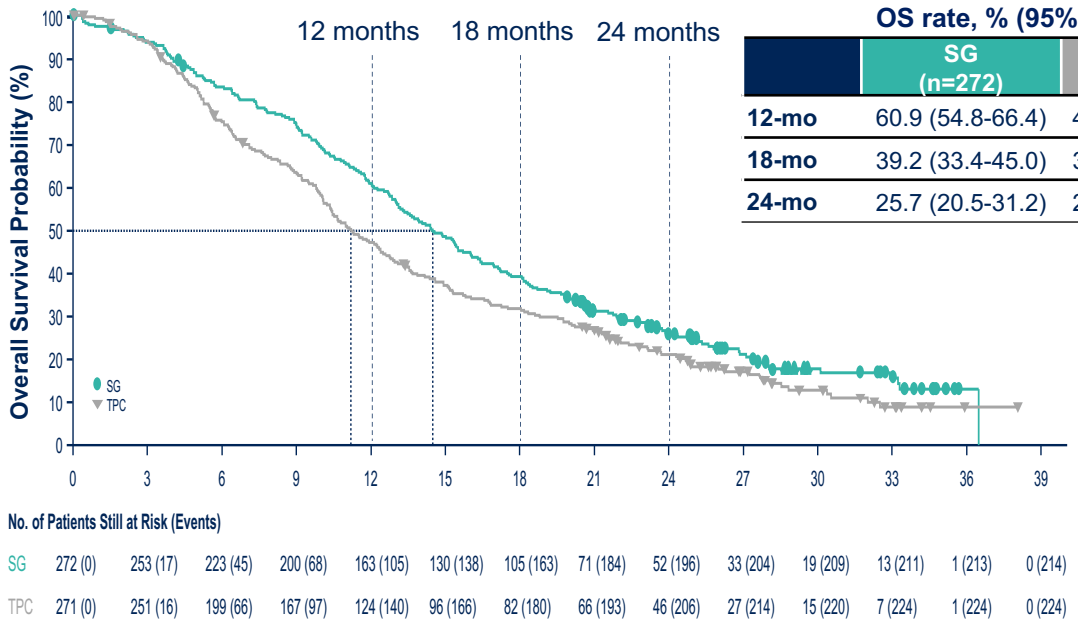
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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; Rugo et al, Lancet 2023

No new toxicity signals compared to ASCENT

TROPiCS-02: PFS and OS by Trop-2 Expression Level and HER2 IHC Status

PFS

	Status	Median PFS, months (95% CI)		HR (95% CI)
		SG	TPC	
Trop-2	H-score <100	5.0 (4.1, 6.0) n=96	4.0 (2.7, 5.6) n=96	**0.79** (0.56, 1.12)
	H-score ≥100	5.8 (4.0, 8.3) n=142	4.1 (2.3, 4.5) n=128	**0.61** (0.45, 0.83)
HER2	IHC1+, IHC2+/ISH−	5.8 (4.1, 8.4) n=149	4.2 (2.8, 5.5) n=134	**0.60** (0.44, 0.62)
	IHC0	5.0 (3.9, 7.2) n=101	3.4 (1.8, 4.2) n=116	**0.70** (0.51, 0.98)

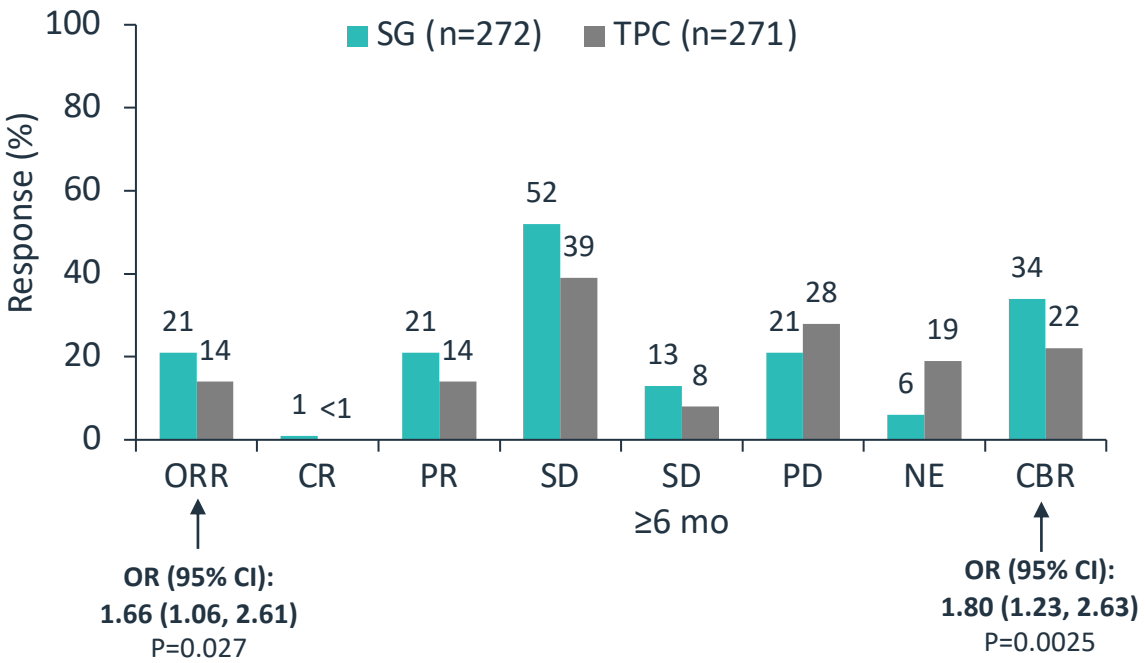
OS

	Status	Median OS, months (95% CI)		HR (95% CI)
		SG	TPC	
Trop-2	H-score <100	14.9 (12.7, 18.1) n=96	11.3 (10.0, 13.3) n=96	**0.78** (0.57, 1.06)
	H-score ≥100	14.4 (12.7, 17.0) n=142	11.2 (9.9, 12.7) n=128	**0.82** (0.63, 1.08)
HER2	IHC1+, IHC2+/ISH−	15.4 (13.5, 19.1) n=149	11.5 (10.1, 12.9) n=134	**0.75** (0.57, 0.97)
	IHC0	13.6 (12.1, 16.0) n=101	10.8 (9.2, 14.2) n=116	**0.85** (0.63, 1.14)

Tolaney et al. ASCO 2023. Abstract 1003; updated from Rugo et al, ESMO 2022 and Rugo et al, SABCS 2022; Rugo et al, Lancet 2023

TROPiCS-02: Responses and Safety Summary

Tumor response



Median DoR, months (95% CI): 8.1 (6.7, 8.9) vs **5.6** (3.8, 7.9)

Safety summary

n (%)		SG (n=268)		TPC (n=249)	
AE Grade ≥3		199 (74)		149 (60)	
AEs → discontinuation		17 (6)		11 (4)	
AEs → dose delay		178 (66)		109 (44)	
AEs → dose reductions		91 (34)		82 (33)	
SAEs		74 (28)		48 (19)	
AEs → death[a]		6 (2)		0	
		Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic	Neutropenia	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia	17 (6)	1 (<1)	41 (16)	9 (4)
GI	Diarrhea	166 (62)	27 (10)	57 (23)	3 (1)
	Nausea	157 (59)	3 (1)	87 (35)	7 (3)
	Constipation	93 (35)	1 (<1)	61 (24)	0
	Vomiting	64 (24)	3 (1)	39 (16)	4 (2)
	Abdominal pain	53 (20)	10 (4)	34 (14)	2 (1)
Other	Alopecia	128 (48)	0	46 (18)	0
	Fatigue	105 (39)	16 (6)	82 (33)	9 (4)
	Asthenia	62 (23)	6 (2)	50 (20)	5 (2)
	Decreased appetite	57 (21)	4 (1)	52 (21)	2 (1)
	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)

[a]Of 6 AEs leading to death, 1 (septic shock due to neutropenic colitis) was considered treatment related by investigator

Rugo et al, JCO 2022; Rugo et al, ESMO 2022; Rugo et al, SABCS 2022; Tolaney et al. ASCO 2023. Abstract 1003; Rugo et al, Lancet 2023

ASCENT and TROPiCS-02: Safety Outcomes by UGT1A1 Status

UTG1A1

- ✓ Variants affect enzymatic function, causing reduced metabolic capacity
- ✓ Over 50% of individuals may harbor an UTG1A1 polymorphism, dependent on genetic ancestry

	ASCENT		TROPiCS-02	
SG patients (n=250)	UTG1A1 Status n(%)	Dose Intensity (%)	UTG1A1 Status n(%)	Dose Intensity (%)
***1/*1 (wt)**	113 (44)	99.8	104 (38)	99
***1/*28**	96 (37)	99.5	119 (44)	98
***28/*28**	34 (13)	99.8	25 (9)	94

Grade ≥3 TEAEs Overall (%)	SG (n=268)
Neutropenia	52
Diarrhea	10
Anemia	8
Febrile neutropenia	6

	ASCENT			TROPiCS-02		
Grade ≥3 TEAEs By UTG1A1 Status (%)	*1/*1 (wt)	*1/*28	*28/*28	*1/*1 (wt)	*1/*28	*28/*28
Neutropenia	53	47	59	45	57	64
Diarrhea	10	9	15	6	13	24
Anemia	4	6	15	6	8	8
Febrile neutropenia	3	5	18	6	7	4
Growth factor for neutropenia (initiated on/after first dose) overall 54%						
				33	49	11

ASCENT: Treatment discontinuation due to TRAEs more common in *28 homozygous genotype

Nelson, RS, et al. *Cancers.* 2021;13:1566.
Rugo, HS, et al. *npj Breast Cancer.* 2022;8:98.
Marmé, F, et al. *Annals of Oncol.* 2023;8(1suppl_4):101223-101223.
Rugo et al, Lancet 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 → Sacituzumab govitecan 10 mg/kg IV d1, 8 q21 days + pembrolizumab 200 mg/kg d1 q21 days

N=110 → 1:1 → Sacituzumab govitecan 10 mg/kg d1,8 q21 days

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

Endpoints
Primary
- PFS

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

Ascent-07:
First-line Chemotherapy in HR+

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

N = 654
2:1 randomization

→ Sacituzumab govitecan 10 mg/kg IV Days 1 and 8, every 21 days

→ Treatment of physician's choice (capecitabine, paclitaxel, nab-paclitaxel)

Stratification:
- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint
- PFS by BICR

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

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

GBG: SASCIA Post-Neoadjuvant Trial
NCT04595565

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)

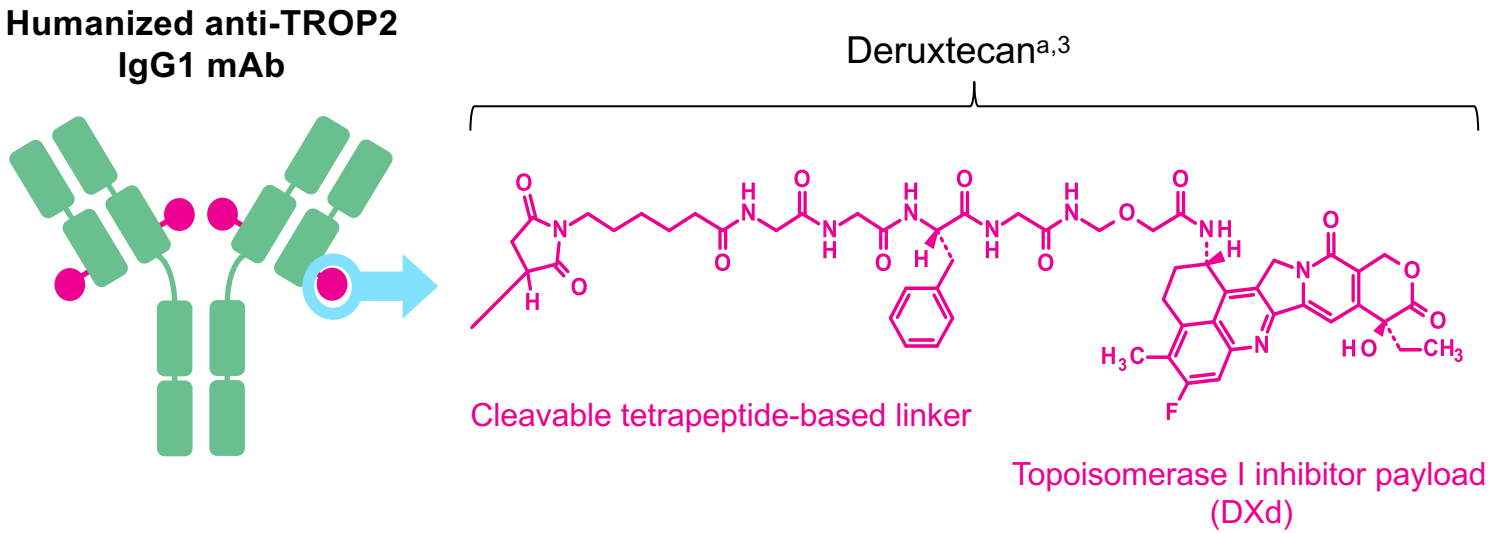
Follow-up

PI: Sara Tolaney; Alliance Foundation Trial

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.

TROPION-Breast01 (Phase 3): Datopotamab deruxtecan vs chemo for unresectable/inoperable or metastatic HR+, HER2– breast cancer

Key eligibility

- HR+/HER2–[a] breast cancer
- Previously treated with 1–2 lines of chemo (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0/1

R 1:1

Dato-DXd 6 mg/kg IV Day 1 Q3W (n=365)

TPC[b] (n=367)

Continue until PD, unacceptable toxicity / other discontinuation criteria

Dual primary endpoints[c]:

- PFS by BICR
- OS

Key secondary endpoint:

- ORR
- PFS (investigator assessed)
- Safety

Stratification factors

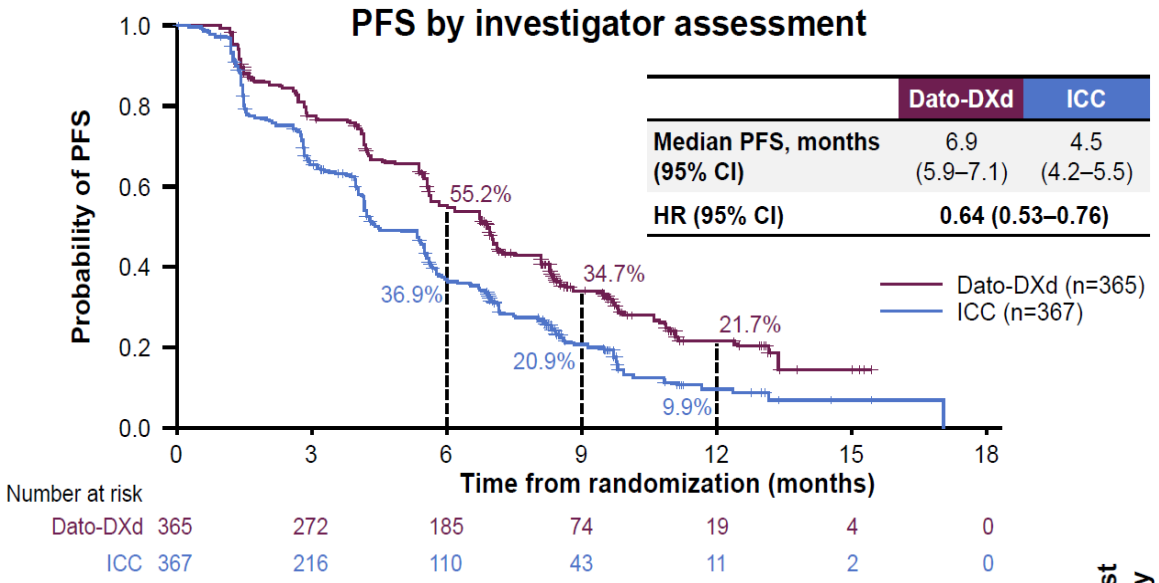
- Lines of chemo in unresectable/ metastatic setting (1 vs 2)
- Geographical location (US/Canada/ Europe vs ROW)
- Previous CDK4/6 inhibitor (yes vs no)

- At data cutoff (July 17, 2023), patients remaining on treatment:
  - Data-DXd, n=93
  - TPC, n=39
- Median follow-up: 10.8 months
- Meidan one line of prior therapy

aIHC 0/1+/2+; ISH−; bInvestigator's choice of chemotherapy; cBy BICR per RECIST v1.1.
Dato-DXd, datopotamab deruxtecan; TPC, treatment of physician's choice.
Bardia A, et al. SABCS 2023. Abstract GS02-01

TROPION-Breast01: PFS and time to subsequent therapy

PFS by investigator assessment

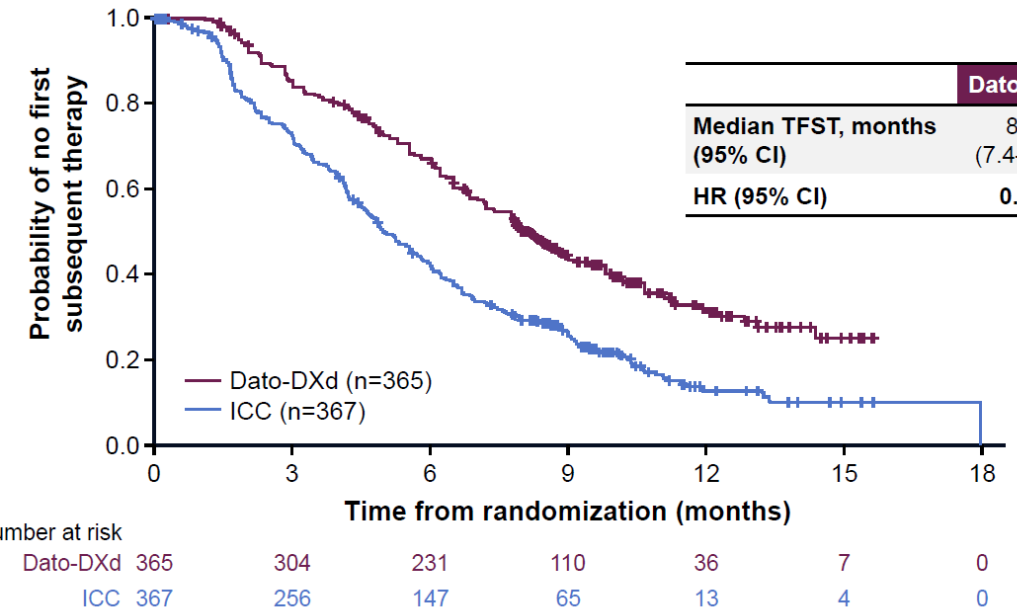


	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	**0.64 (0.53–0.76)**	

PFS by BICR (primary endpoint)

- Median 6.9 vs 4.9 months
- HR 0.63 (95% CI: 0.52, 0)

Time to subsequent therapy

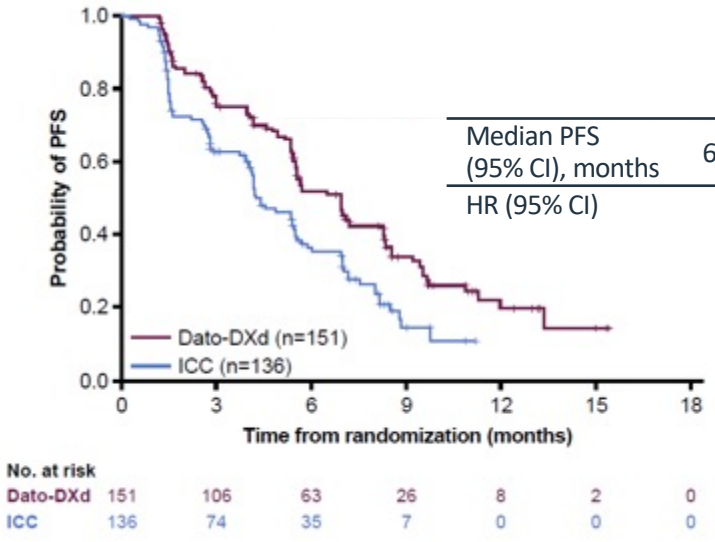


	Dato-DXd	ICC
Median TFST, months (95% CI)	8.2 (7.4–8.9)	5.0 (4.6–5.7)
HR (95% CI)	**0.53 (0.45–0.64)**	

Bardia A, et al. SABCS 2023. Abstract GS02-01

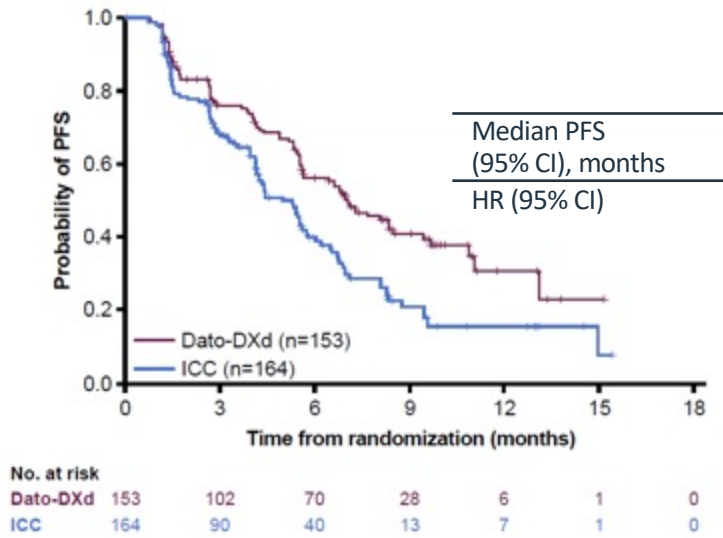
TROPION-Breast01: PFS by BICR in subgroups

Prior duration of CDK4/6i, ≤12 months



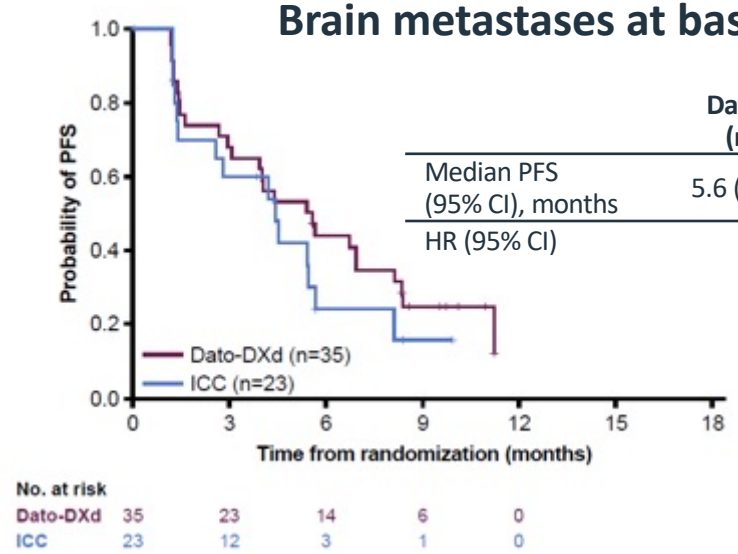
	Dato-DXd (n=151)	ICC (n=136)
Median PFS (95% CI), months	6.9 (5.5, 8.1)	4.2 (4.0, 5.5)
HR (95% CI)	0.61 (0.45, 0.81)	

Prior duration of CDK4/6i, >12 months



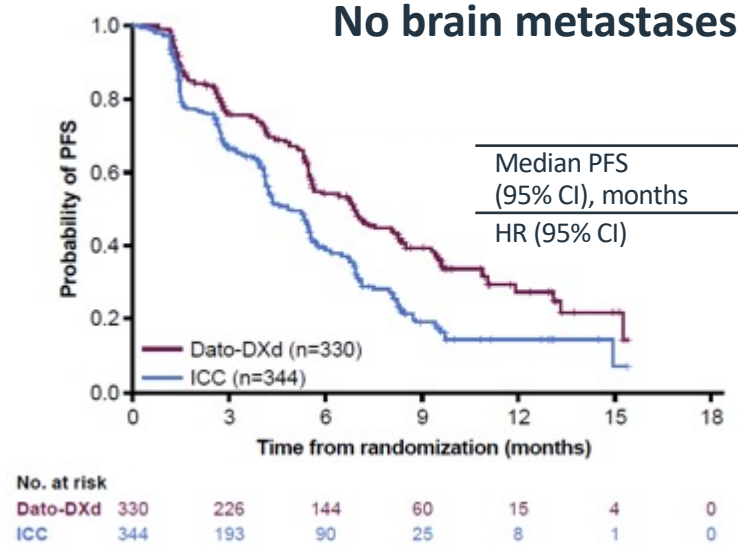
	Dato-DXd (n=153)	ICC (n=164)
Median PFS (95% CI), months	7.1 (5.8, 8.5)	5.0 (4.1, 5.7)
HR (95% CI)	0.61 (0.45, 0.82)	

Brain metastases at baseline



	Dato-DXd (n=35)	ICC (n=23)
Median PFS (95% CI), months	5.6 (3.0, 8.1)	4.4 (1.4, 5.7)
HR (95% CI)	0.73 (0.39, 1.42)	

No brain metastases at baseline



	Dato-DXd (n=330)	ICC (n=344)
Median PFS (95% CI), months	7.0 (5.7, 8.1)	4.9 (4.2, 5.5)
HR (95% CI)	0.62 (0.51, 0.75)	

Bardia A, et al. SABCS 2023. Abstract GS02-01

TROPION-Breast01: Safety

Overall safety summary

TRAEs, n (%)[1]	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

AE of clinical interest

Neutropenia*	Dato-DXd (n=360)	ICC (n=351)
Treatment-related neutropenia*, n (%)		
Any grade	39 (11)	149 (42)
Grade ≥3	4 (1)	108 (31)
Leading to dose interruption	0	60 (17)
Leading to dose reduction	1 (0.3)	45 (13)
Leading to dose discontinuation	0	1 (0.3)
G-CSF usage, n (%)		
On treatment	10 (3)	81 (22)
Post-treatment†	1 (0.3)	30 (8)

Stomatitis‡	Dato-DXd (n=360)	ICC (n=351)
Treatment-related stomatitis‡, n (%)		
Any grade	180 (50)	46 (13)
Grade 3	23 (6)	9 (3)
Leading to dose interruption	5 (1)	3 (1)
Leading to dose reduction	44 (12)	5 (1)
Leading to dose discontinuation	1 (0.3)	0

TTD global health status/quality of life, physical functioning and pain

TTD	Median TTD, months (1st instance)		HR (95% CI)	Median TTD, months (confirmed)		HR (95% CI)
	Dato-DXd	ICC		Data DXd	ICC	
GHS/QOL	3.4	2.1	0.85 (0.68, 1.06)	9.0	4.8	0.76 (0.58, 0.98)
Physical functioning	5.6	3.5	0.77 (0.61, 0.99)	12.5	6.2	0.77 (0.59, 1.01)
Pain	3.5	2.8	0.85 (0.68, 1.07)	9.0	5.5	0.72 (0.55, 0.94)

GHS/QOL, global health status/quality of life; TTD, time to deterioration.

Bardia A, et al. SABCS 2023. Abstract GS02-01

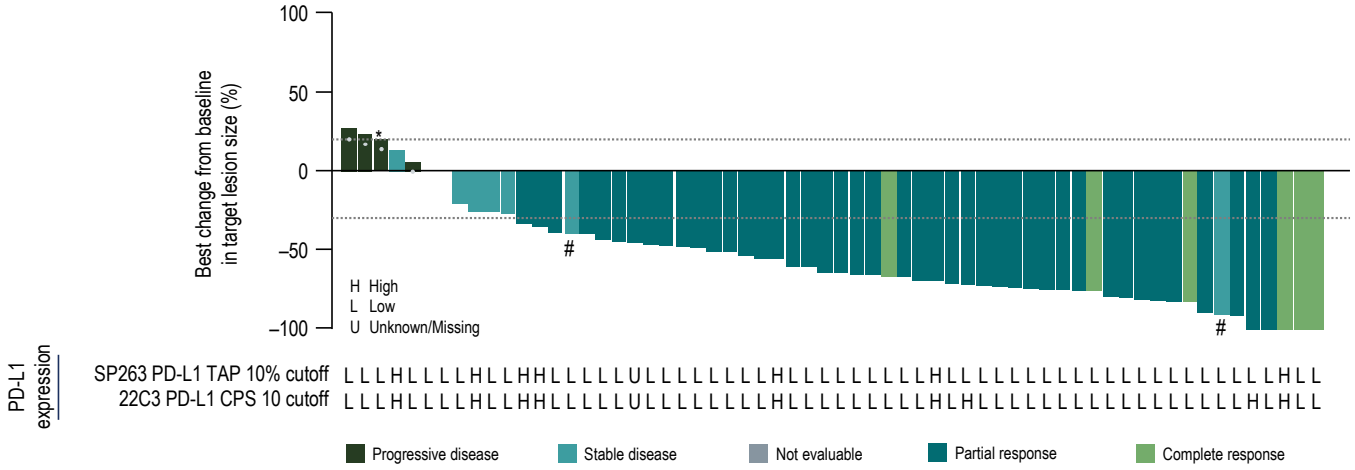
- Clear efficacy as second line chemotherapy for HR+ MBC
- Primary toxicity stomatitis can likely be managed in most with steroid MW, low heme toxicity
- Await OS data

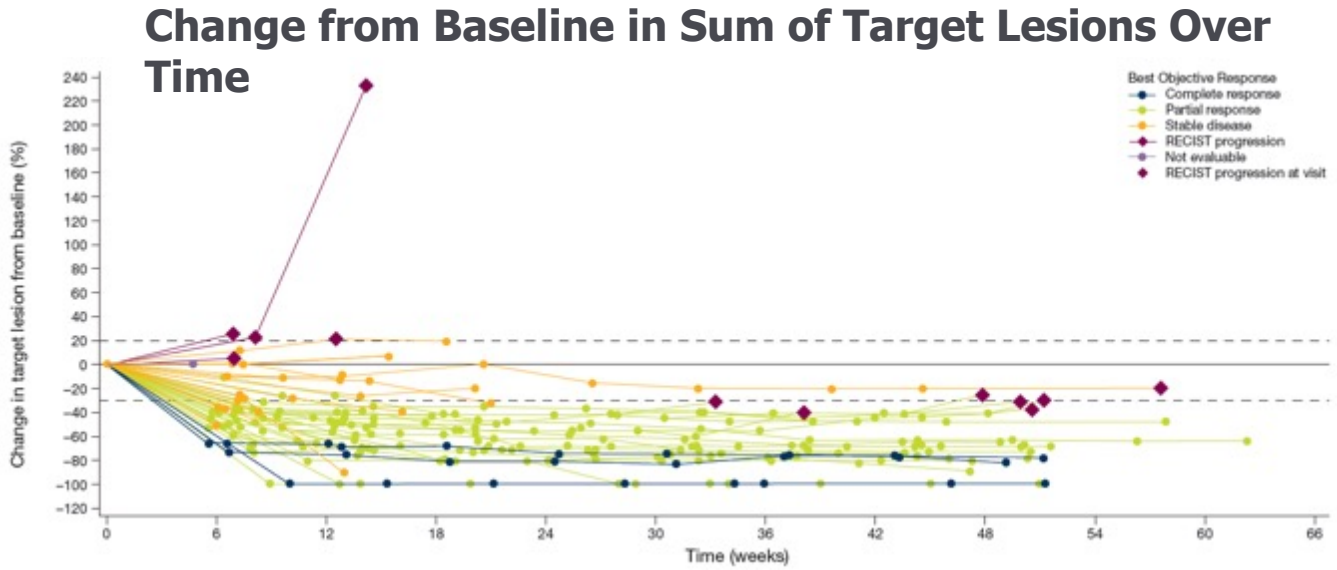
BEGONIA Trial: Dato-DXd + Durvalumab

- 1st line TNBC
  - N=62;
  - Median FU 11.7 mo
  - Durable responses
    - Median FU 13.8 mo, DOR 15.5 mo
  - Adverse events
    - 57% grade 3/4 AEs; 16% d/c due to AEs
    - Stomatitis (65%), rash (32%), dry eye (21%), hypothyroidism (14.5%), keratitis (14.5%)
      - 11% Gr3/4 stomatitis
    - **ILD/pneumonitis in 5% (3)**
      - **All grade 1-2**

Confirmed ORR was 79% (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods





Schmid et al, ESMO 2023; SABCS 2022; PD11-09

TROPION-Breast02 (n=625)

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

TROPION Breast05 (n=625)

NCT06103864

Key Eligibility Criteria

- Previously untreated locally recurrent inoperable or metastatic TNBC
- ECOG PS 0 or 1
- Measurable disease as defined by RECIST 1.1
- Adequate haematologic and end-organ function
- PD-L1 centrally confirmed
- PD-L1 positive by 22C3 assay CPS ≥ 10 IHC
- No systemic steroids
- No active autoimmune diseases
- No active brain metastases
- DFI ≥ 6 months since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

Stratification Factors

- DFI history (de novo versus prior DFI 6 to 12 months[a] versus prior DFI > 12 months)
- Geographic location (US/Canada/Europe versus Dato-DXd Monotherapy Enrolling Countries versus Rest of World)
- Prior PD-1/PD-L1 treatment for early stage TNBC (yes versus no)

N=625

1:1:1[c]

Arm 1
Dato-DXd
6.0 mg/kg IV Q3W
+
Durvalumab
1120 mg IV Q3W
(n=275)

Arm 2
Investigator's Choice Chemotherapy[b]
+
Pembrolizumab
200 mg IV Q3W
(n=275)

Arm 3
Dato-DXd
6.0 mg/kg IV Q3W
(n=75)[d]

Primary endpoint:
PFS (BICR)

Key secondary endpoint:
OS

Secondary endpoints including:
PFS (inv), ORR, DoR, CBR, TTD, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints including:
TROP2

[a] DFI 6 to 12 months capped at 20%.
[b] Chemotherapy options include paclitaxel (90 mg/m² IV on days 1, 8, and 15, Q4W), nab-paclitaxel (100 mg/m² IV days 1, 8, and 15, Q4W) or gemcitabine 1000 mg/m² IV + carboplatin AUC 2 IV days 1 and 8 Q3W.
[c] Once approximately 75 participants are randomised to Arm 3, this cohort will close, and all countries will continue with a 1:1 randomisation strategy for Arms 1 and 2.
[d] In selected countries only.

TROPION Breast03 (n=1075)

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

TROPION Breast04 (n=1728)

NCT06112379

Neoadjuvant therapy for TNBC

- Durvalumab + Dato-DXd x 8 cycles followed by surgery; durva x 9 cycles postop vs KN522

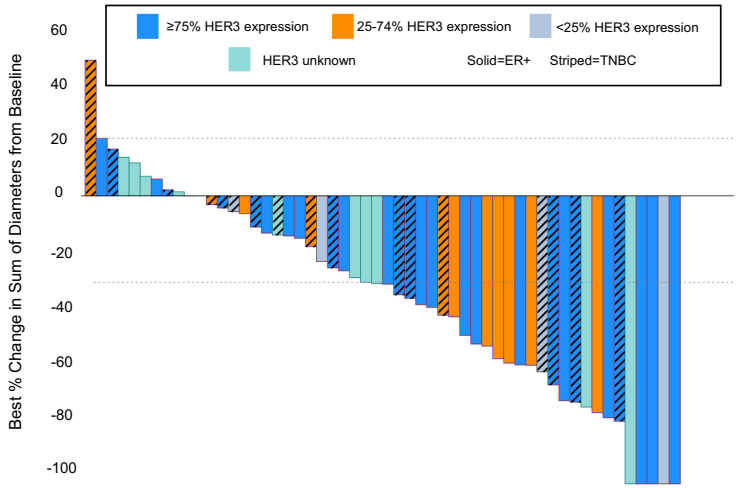
Patritumab Deruxtecan: Phase 2 Study of HER3-DXd in MBC

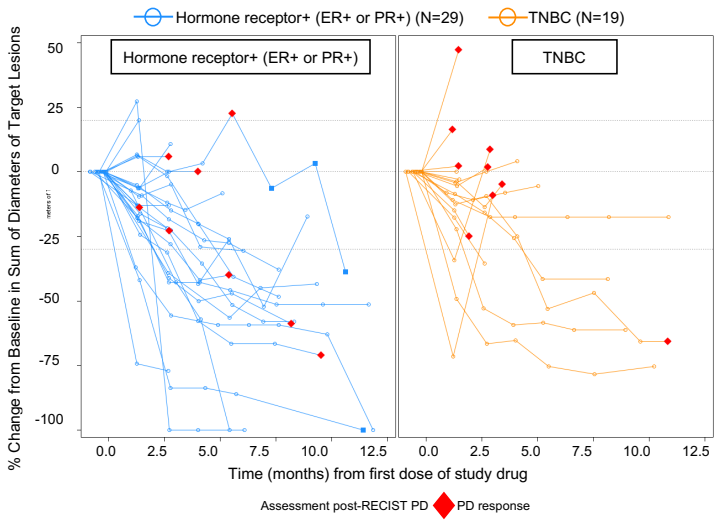
- 60 pts:
  - HR+: Prior CDKi, 0-2 chemo
  - TN: 1-3 chemo
  - 27 HR+/19 TN (n=48)
  - 64% HER3 ≥75%; 8% <25% (n=47)
- ORR 35%, CBR 43%,
  - No relationship to HER3 expression
- DOR ≥ 6mo: 47.6% in responders (n=10)
- Most common AE:
  - Nausea/diarrhea/fatigue
  - TEAE: 2 ILD, 1 low plt

	(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

Newer ADCs: SABCS 2023

- SKB264 (MK-2870)
  - TROP2 ADC with novel TOPO1 inhibitor (belotecan derivative); DAR 7.4
  - Efficacy in phase II TNBC (n=59): ORR 42.4%; PFS 5.7 mo
  - Toxicity (Gr ≥3): stomatitis (6.8%) , neutropenia (25.4%), N/V
- BL-B01D1 dose escalation/expansion study
  - EGFR/HER2 bispecific ADC with TOPO1 payload
  - Responses 31-45%, seen in all subtypes
  - Toxicity: stomatitis, neutropenia, N/V, elevated liver e

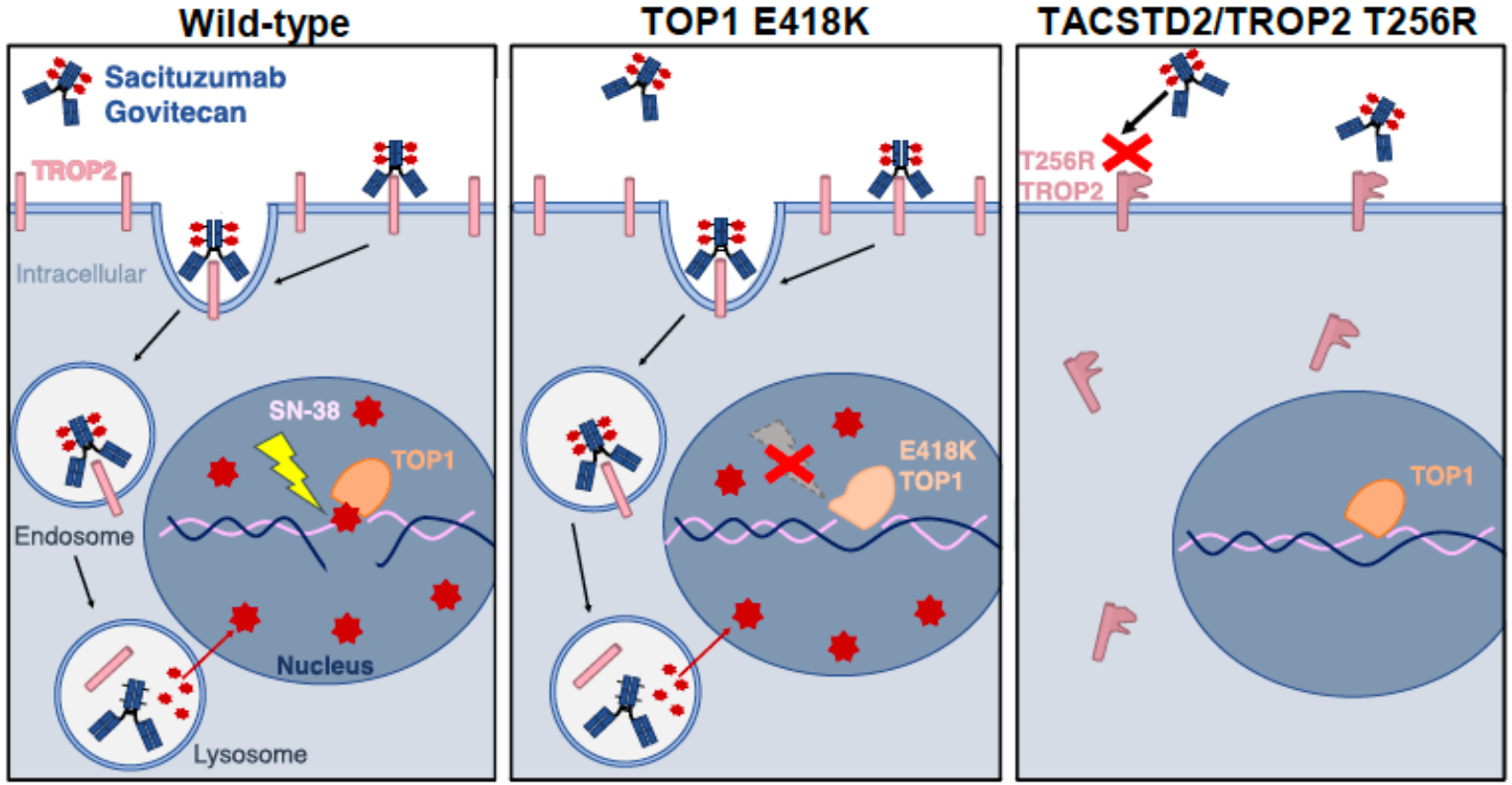
BOR, n	TNBC (n=35)	HR+ HER2- (n=38)	HER2+ (n=23)
Prior treatment line median (range)	3 (1-9)	4 (1-13)	4 (0-8)
ORR, % (95% CI)	31.4% (16.9-49.3)	44.7% (28.6-61.7)	39.1% (19.7-61.5)

- B7-H4 – TOPO1 ADC
  - Dose escalation
  - Toxicity:
    - bone marrow suppression

		0.7 mg/kg (N=2)	1.4 mg/kg (N=2)	4.8 mg/kg (N=12)	5.8 mg/kg (N=11)	7.2 mg/kg (N=1)	Total (N=28)
TNBC	ORR*, % (95% CI)	50.0 (1.3,98.7)	0	33.3 (9.9,65.1)	27.3# (6.0,61.0)	0	28.6 (13.2,48.7)
	DCR, % (95% CI)	50.0 (1.3,98.7)	100.0 (15.8,100.0)	66.7 (34.9,90.1)	81.8 (48.2,97.7)	100.0 (2.5,100.0)	75.0 (55.1,89.3)

Yin Y, et al. SABCS 2023. PS08-08; Wu et al SABCS 2023 PS08-07; Wu et al, ESMO 2023 381O

Mechanisms of Resistance to TROP2 ADC



- Analysis of tumor tissue from 3 patients pre- and post Sacituzumab treatment
- Two acquired resistance mechanisms identified
  - Mutations in TOP1 leading to decreased binding of SN38 with topoisomerase I
  - Mutation in TROP2 leading to decreased binding of SG and decreased cell surface expression

Failed SN38/TOP1 Binding → Resistance to payload

Altered TROP2 Localization and Binding → Resistance to antibody target

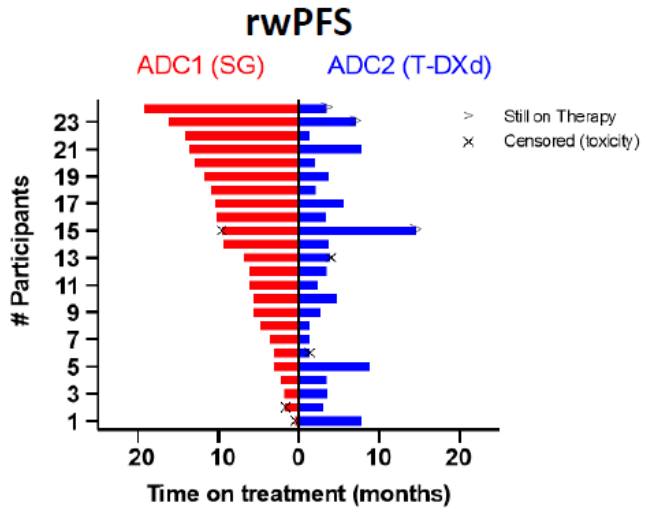
Coates et al. Cancer Discov 2021; courtesy of Elison

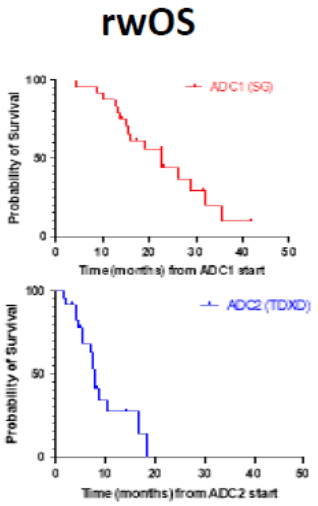
HR+/HER2-low efficacy data (n=56)

SG → T-DXd
(n=24, 42.9%)

- Median lines of therapy for MBC prior to SG:
  - Median lines chemotherapy: 2.0 (range 0-5)
  - Median total lines of therapy: 3.0 (range 0-9)
- Intervening therapies between ADCs: 47.8%

	ADC1 (SG)	ADC2 (T-DXd)
ORR (CR+PR) by investigator assessment, %	77.3%	34.8%
CBR (CR + PR + SD) by investigator assessment, %	86.4%	60.9%
Median rwPFS, months	8.0	3.7
Median rwOS from time of each ADC start, months	22.8	7.8

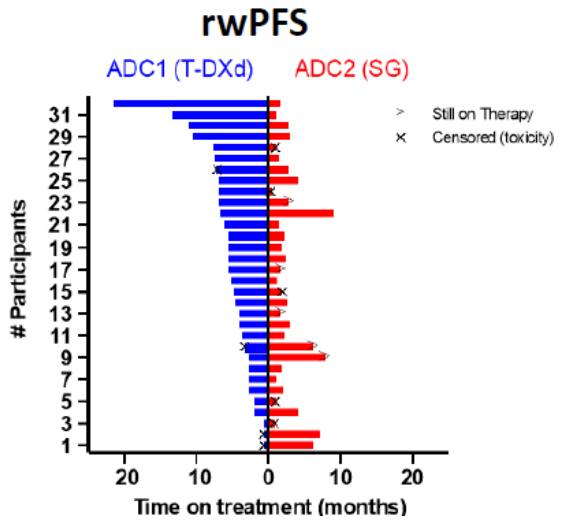


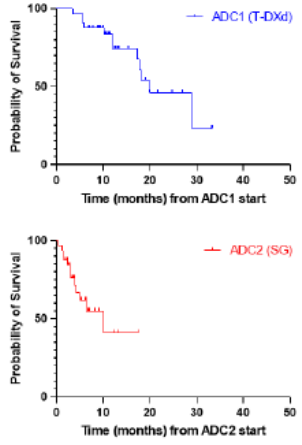


T-DXd → SG
(n=32, 57.1%)

- Median lines of therapy for MBC prior to T-DXd:
  - Median lines chemotherapy: 2.0 (range 0-5)
  - Median total lines of therapy: 4.5 (range 2-10)
- Intervening therapies between ADCs: 42.4%

	ADC1 (T-DXd)	ADC2 (SG)
ORR (CR+PR) by investigator assessment, %	46.9%	18.5%
CBR (CR + PR + SD) by investigator assessment, %	78.1%	37.0%
Median rwPFS, months	5.5	2.6
Median rwOS from time of each ADC start, months	19.8	10.1





Huppert L, et al. SABCS 2023. Abstract PS08-04

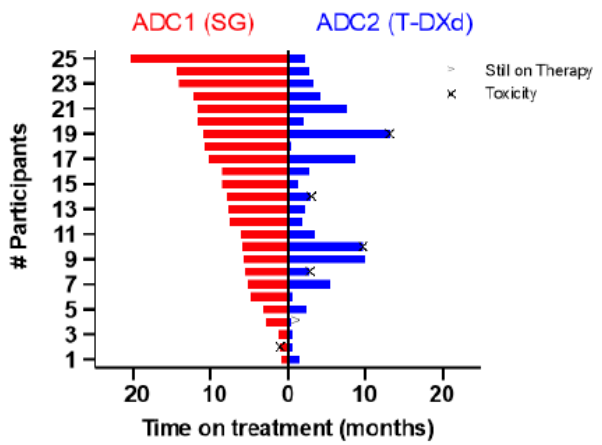
HR−/HER2-low efficacy data (n=28)

SG → T-DXd (n=25, 89.3%)

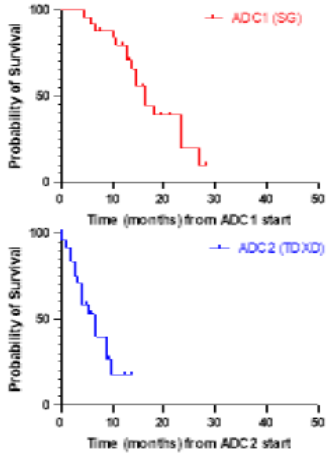
- Median lines of therapy for MBC prior to SG: 2.0 (range 0-5)
- Intervening therapies between ADCs: 40.0%

	ADC1 (SG)	ADC2 (T-DXd)
ORR (CR+PR) by investigator assessment, %	68.0%	35.0%
CBR (CR + PR + SD) by investigator assessment, %	80.0%	45.0%
Median rwPFS, months	7.8	2.8
Median rwOS from time of each ADC start, months	16.5	6.5

rwPFS



rwOS

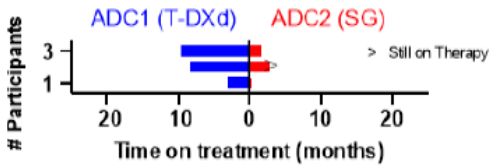


T-DXd → SG (n=3, 10.7%)

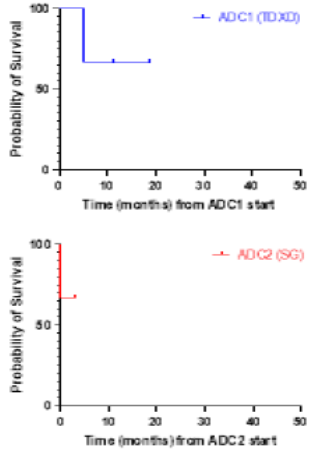
- Median lines of therapy for MBC prior to T-DXd: 3.0 (range 1-5)
- Intervening therapies between ADCs: 66.7%

	ADC1 (T-DXd)	ADC2 (SG)
ORR (CR+PR) by investigator assessment, %	33.3%	0.0%
CBR (CR + PR + SD) by investigator assessment, %	66.7%	50.0%
Median rwPFS, months	undetermined	
Median rwOS from time of each ADC start, months	undetermined	

rwPFS

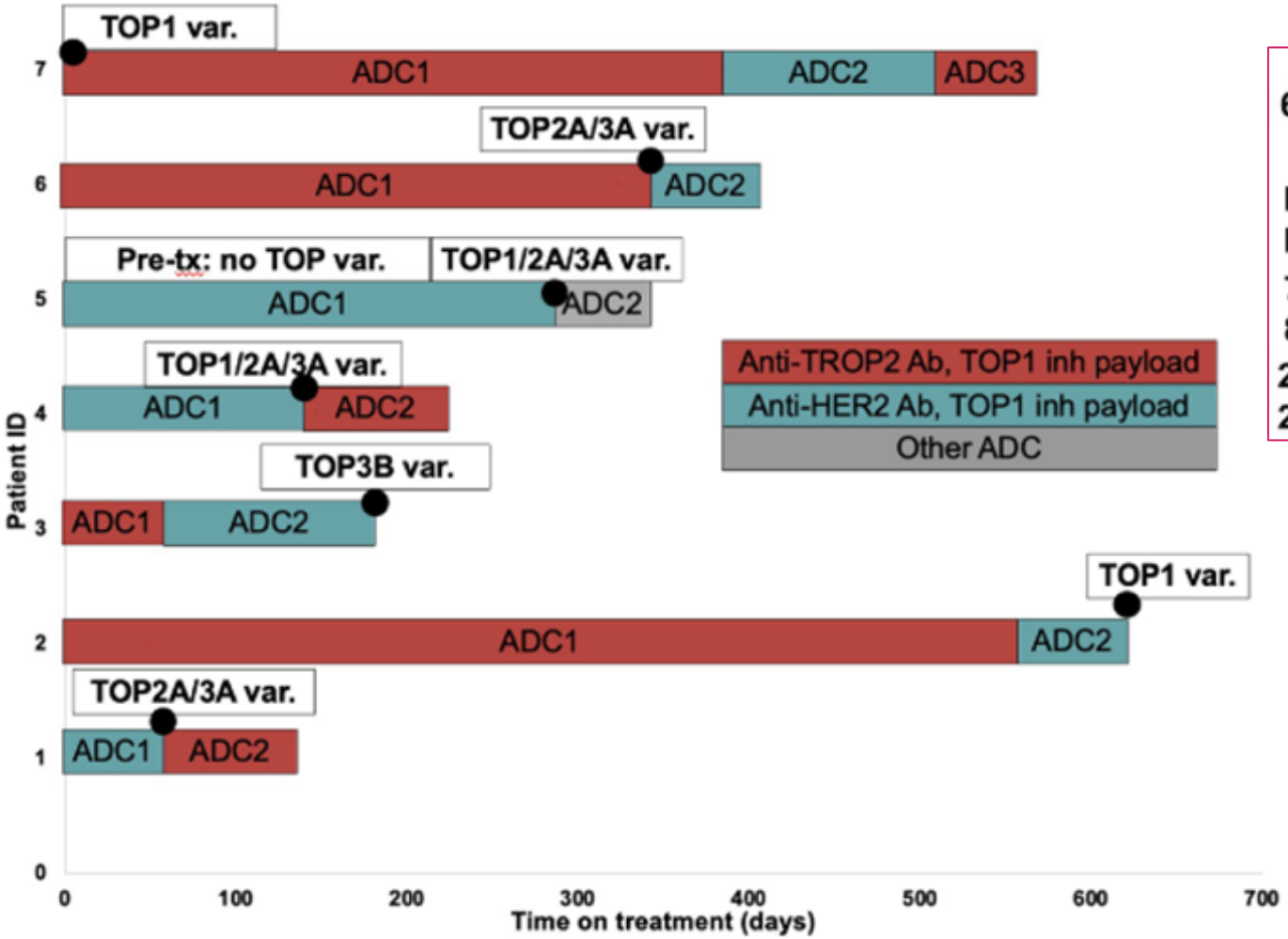


rwOS



Huppert L, et al. SABCS 2023. Abstract PS08-04

A3 study: Clinical course of patients with TOP variants



68 patients included
- 30 patients HR+/HER-2 (44.1%)
- 38 patients TNBC (55.9%)
- 50 patients HER2 low (73.5%)

Median age at ADC2: 59.6 years (range 29.9-88.6)
Median lines of treatment in metastatic setting before ADC2: 4
74 ADC-to-ADC transitions; 36 with cross-resistance (50%)
8 patients with 3 ADCs, 60 with 2 ADCs
20 patients with clinically available tissue sequencing
23 ADC:ADC transitions

- ADC sequencing data suggests PFS on ADC2 is shorter than on ADC1 for most patients, though there are some that benefit more from ADC2 than ADC1
- Genomic data revealing TOP1 variants suggestive of payload resistance can be an acquired resistance mechanism, but doesn't always clearly explain lack of benefit given one patient with prolonged benefit to a TROP2 ADC with a topo1 payload despite having a mutation

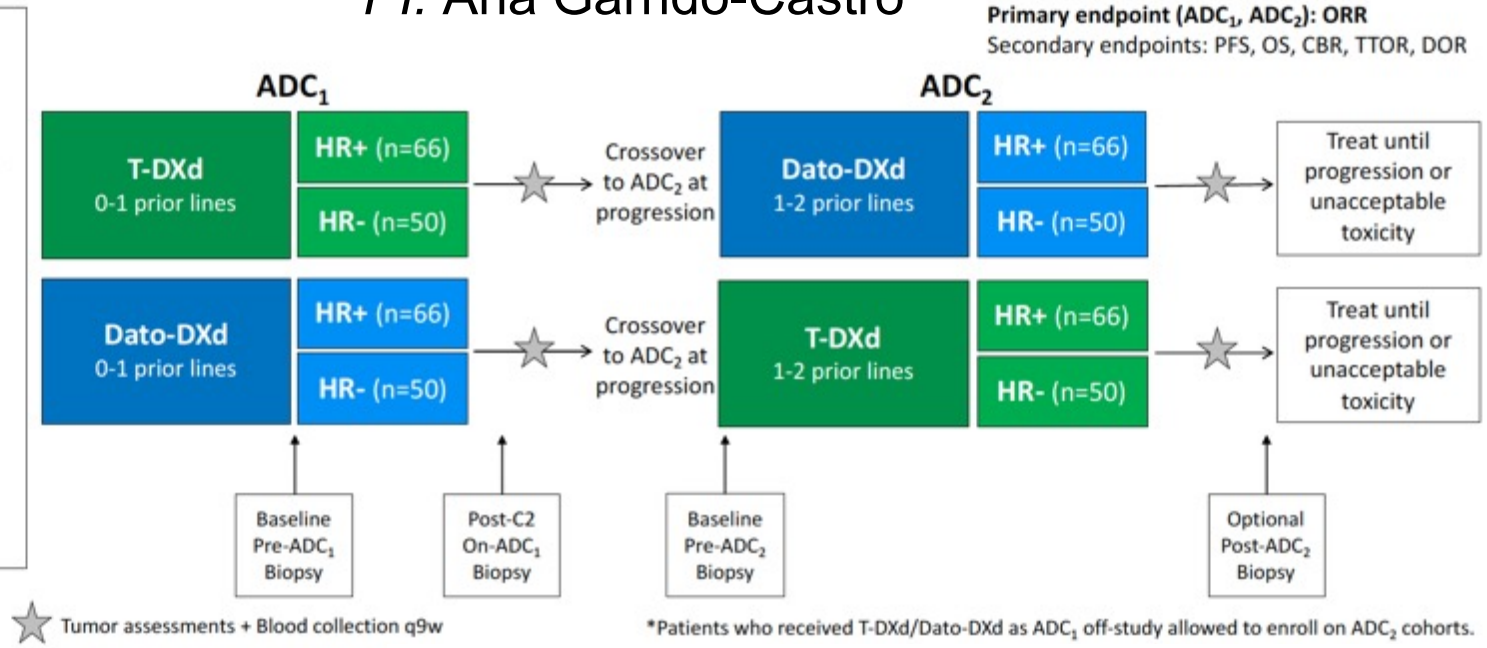
Occhiogrosso R, et al. SABCS 2023. Abstract PS08-03

TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE DXd).
PI: Ana Garrido-Castro

Eligibility:

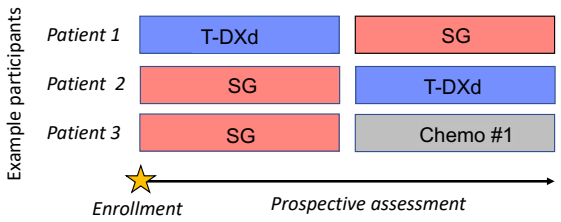
- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low BC: IHC 1+ or 2+/ISH- (any sample: primary or met)
- Measurable disease
- Prior endocrine therapy and CDK4/6 inhibitor for HR+ MBC
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

*Randomization 1:1 to T-DXd or Dato-DXd as ADC_1 for allocation purposes.



Registry Sequencing Study: Laura Huppert UCSF

Cohorts 1 & 2: Enrollment Prior to ADC #1



Cohort 1: HR+/HER2- HER2 low
~35 patients

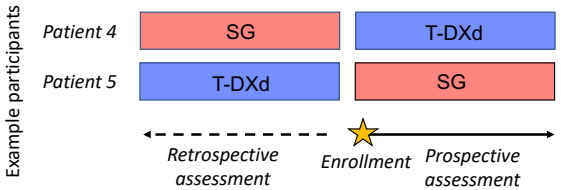
Cohort 2: TNBC, HER2 low
~25 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

Objectives/considerations:

- Allows for prospective assessment of ADC #1 and ADC #2 efficacy, including PRO data and collection of blood for translational endpoints
- Potential barrier: Patient not guaranteed to get ADC #2 (e.g., example patient #3 shown here)

Cohorts 3 & 4: Enrollment Prior to ADC #2



Cohort 3: HR+/HER2-
~25 patients

Cohort 4: TNBC
~15 patients

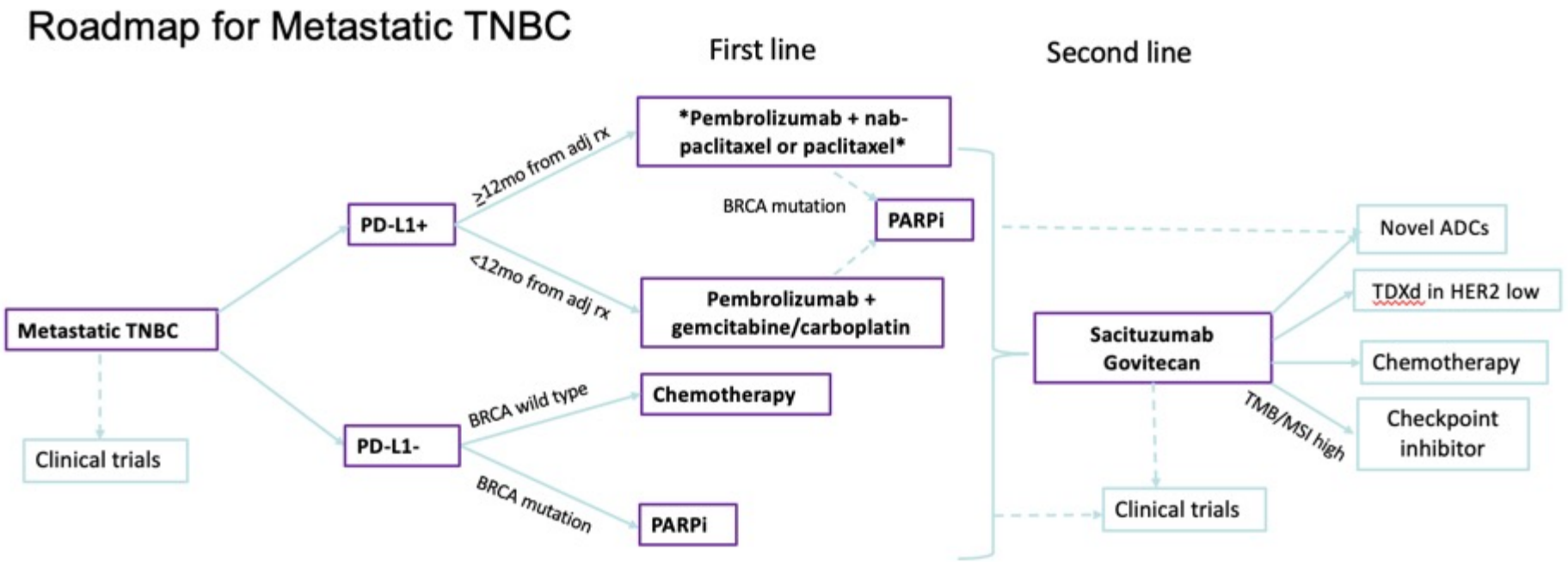
- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

Objectives/considerations:

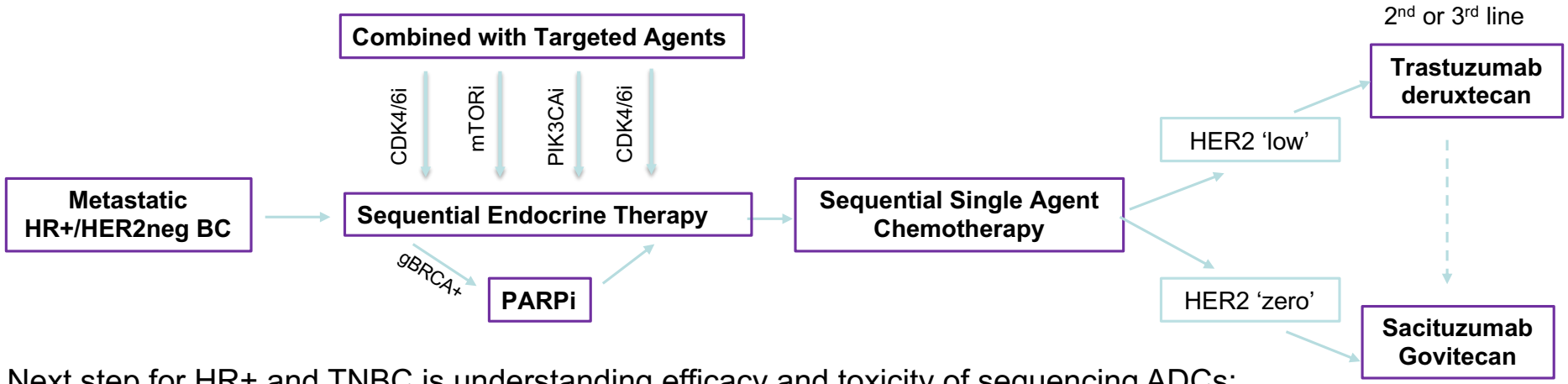
- Allows for prospective assessment of ADC #2 safety and efficacy, including PRO data and translational endpoints
- Allows for retrospective safety and efficacy of ADC #1

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
  - Understanding resistance.
- **Toxicity management is critical**
  - Combination data with radiation largely lacking



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!