UCSF Helen Diller Family Comprehensive Cancer Center

Antibody Drug Conjugates : A Revolution in Breast Cancer Treatment for Advanced HER2 Negative Breast CAncer

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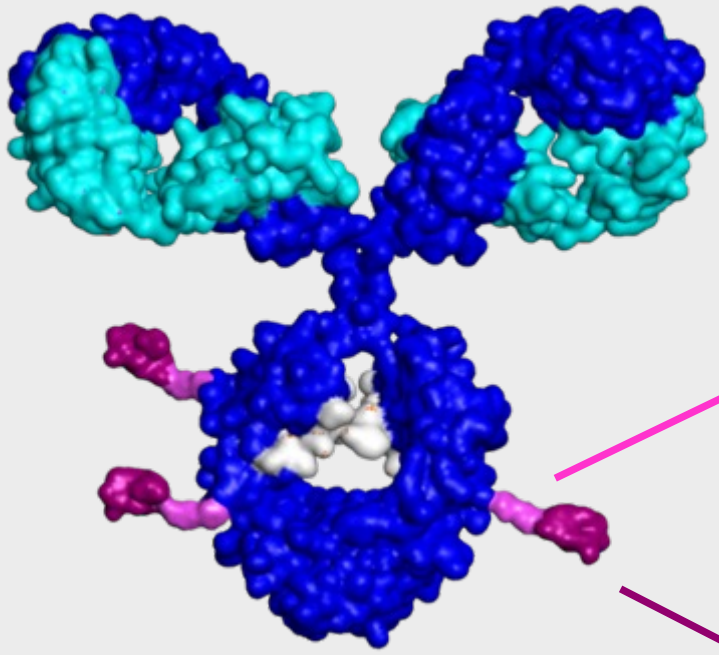
ADCs have different antibodies, linkers and payloads



Antibody Drug Conjugate

	ADC Attributes	Trastuzumab emtansine (T-DM1)	Trastuzumab deruxtecan (T-DXd)	Sacituzumab govitecan (SG)	Datopotamab deruxtecan (Dato-DXd)	MK2870 Sacituzumab Tirumotecan (Sac-TMT)	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.

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]

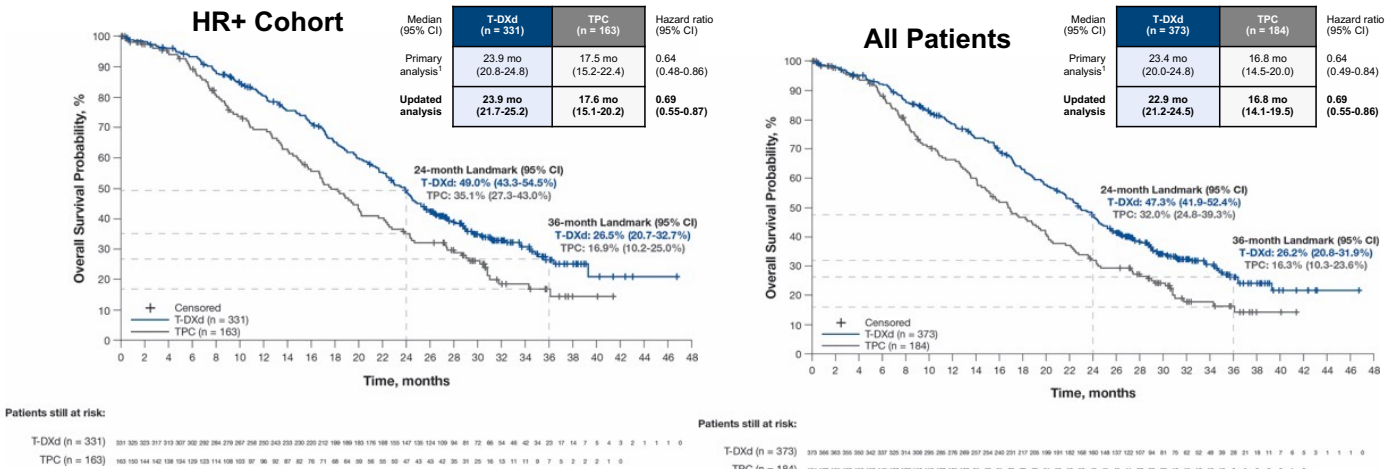
Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

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

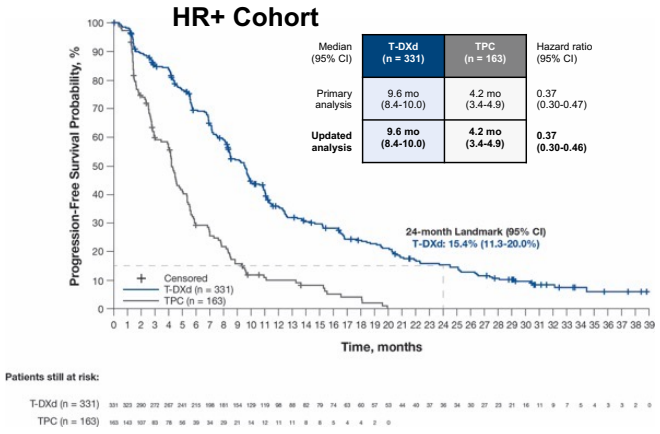
DB04: Updated Overall Survival in HER2 low MBC

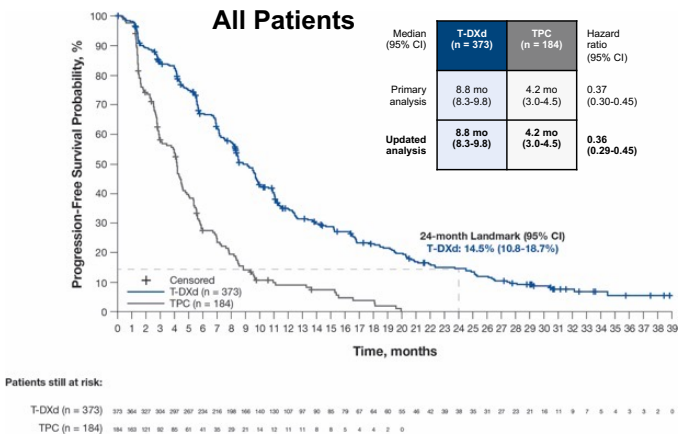


Primary Analysis (BICR)

OS	HR+		HR-		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=40)	TPC (n=18)	T-DXd (n=373)	TPC (n=184)
Median OS, months	23.9	17.5	18.2	8.3	23.4	16.8
HR (95% CI); *P* value	HR 0.64 (0.48-0.86); 0.0028		0.48 (0.24-0.95)		HR 0.64 (0.49-0.84); 0.0010	

DB04: Updated PFS (Investigator Assessed)

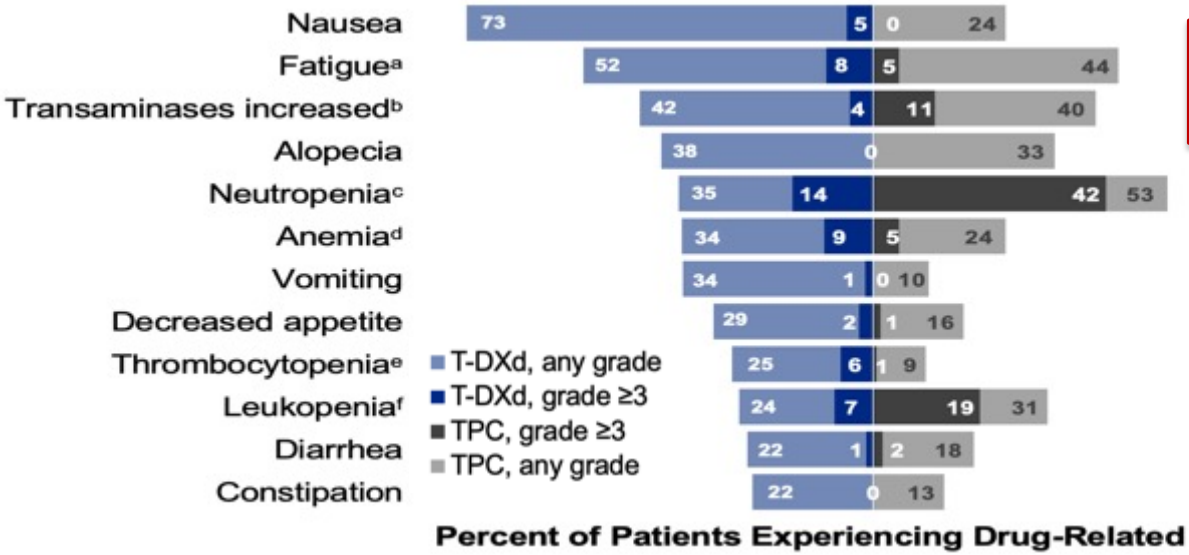




PFS	HR+		HR-		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=40)	TPC (n=18)	T-DXd (n=373)	TPC (n=184)
Median PFS, months	10.1	5.4	8.5	2.9	9.9	5.1
HR (95% CI); *P* value	0.51 (0.40-0.64); <0.0001		0.46 (0.24-0.89)		HR 0.50 (0.40-0.63); <0.0001	

Modi et al, ESMO 2023

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

	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

1 5-HT$_3$ receptor antagonists

- **Palonosetron:** 0.25 mg IV; 0.5 mg oral
- **Granisetron:** 1 mg IV; 2 mg oral
- **Dolasetron:** 100 mg oral
- **Tropisetron:** 5mg IV; 5mg oral
- **Ondansetron:** 8 mg IV; 16 mg oral

2 NK-1 receptor antagonists

- **Aprepitant:** 125 mg (acute); 80 mg daily for 2 days (delayed)
- **Fosaprepirant:** 150 mg IV
- **Netupitant:** 300 mg

3 Corticosteroids

Dexamethasone:

- Acute emesis: 8 mg once
- Delayed emesis: 8 mg daily / 4 mg twice a day for 2–3 days

Modi et al, NEJM 2022; ESMO 2023; Rugo et al, ESMO Breast 2023; NCCN 2023

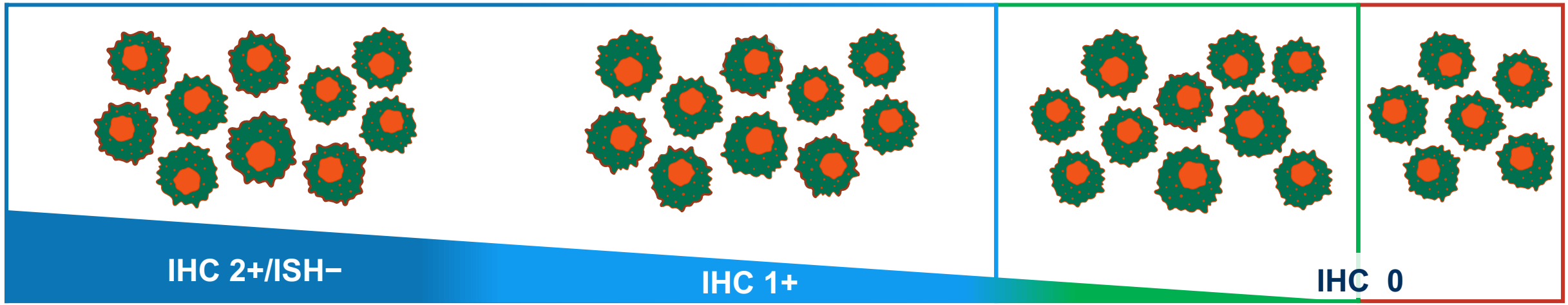
Targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC

HER2 IHC categories within HR+, HER2− mBC (per ASCO/CAP guidelines[1])

DESTINY-Breast06 patient population: ~85% of HR+, HER2− mBC

HER2-low ~60–65%[2,3]

HER2-ultralow ~20–25%[2,3]



IHC 2+/ISH−	IHC 1+	IHC 0	
Weak-to-moderate complete membrane staining in >10% tumor cells	Faint, incomplete membrane staining in >10% tumor cells	**Faint, incomplete membrane staining in ≤10% tumor cells**	Absent / no observable membrane staining

ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022;9:834651. CC BY 4.0; 1. Wolff A, et al. *J Clin Oncol.* 2023;41:3867–3872; 2. Denkert C, et al. *Lancet Oncol.* 2021;22:1151–1161; 3. Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

At DCO, 119 patients (14.0%) remained on treatment: 89 (20.5%) T-DXd and 30 (7.2%) TPC
Median duration of follow up: 18.2 mo (ITT)

TPC	n (%)
Capecitabine	257 (59.8)
Nab-paclitaxel	105 (24.4)
Paclitaxel	68 (15.8)

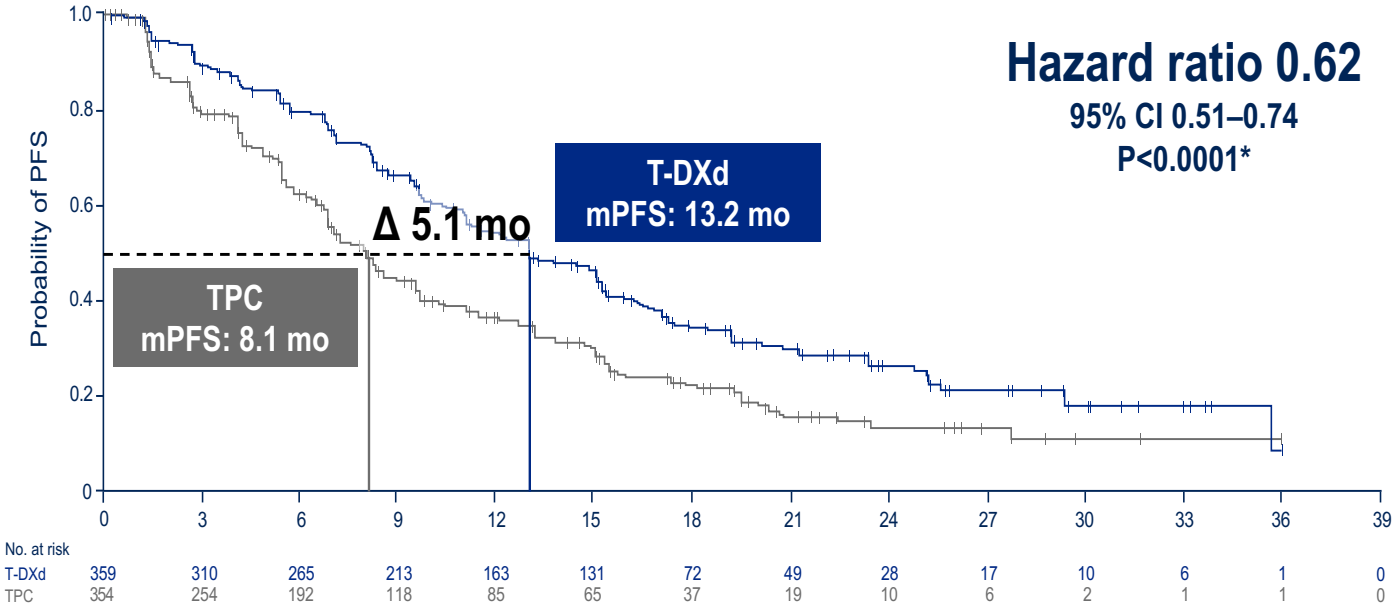
Patient population

- ~30% primary endocrine resistance
- ~30% de novo metastatic disease
- 3% bone only disease
- ~66% liver metastases
- HER2 ultra-low similar to HER2 low population
- Median 2 prior lines of ET
- 89% prior CDKi (9%<6 mo), ~30% other targeted agents
- ~54% chemotherapy for early-stage disease

Curigliano et al, ASCO 2024 LBA

Destiny Breast-06: PFS and OS in HER2-Low

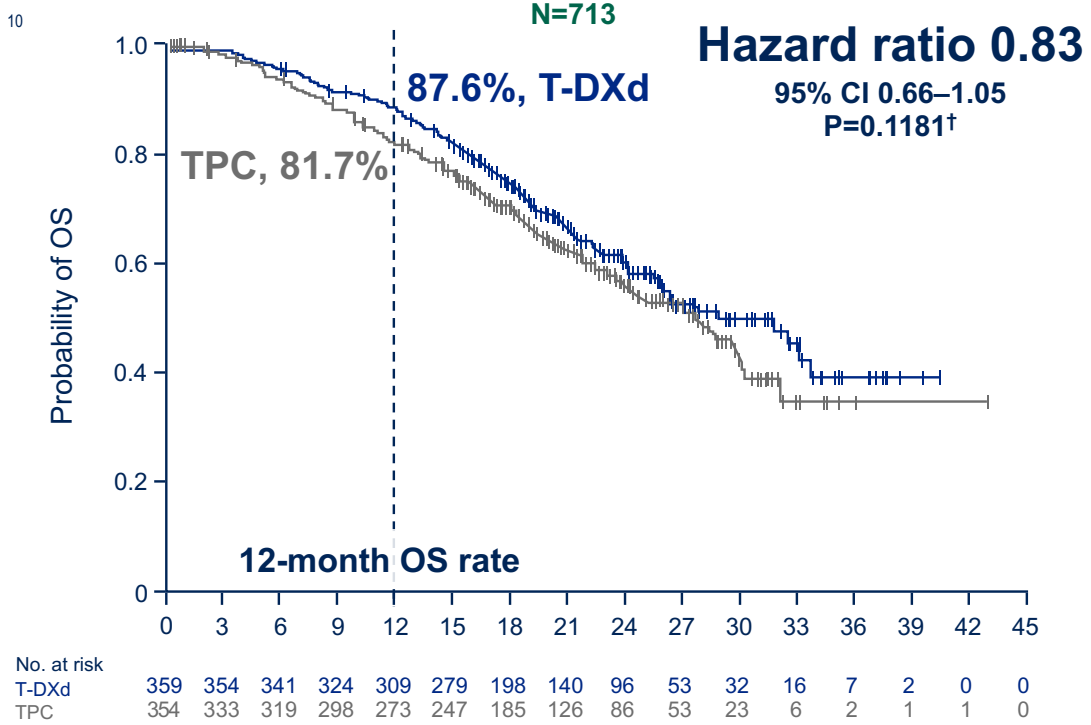
PFS (BICR) in HER2-low: primary endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

HER2-low*

N=713

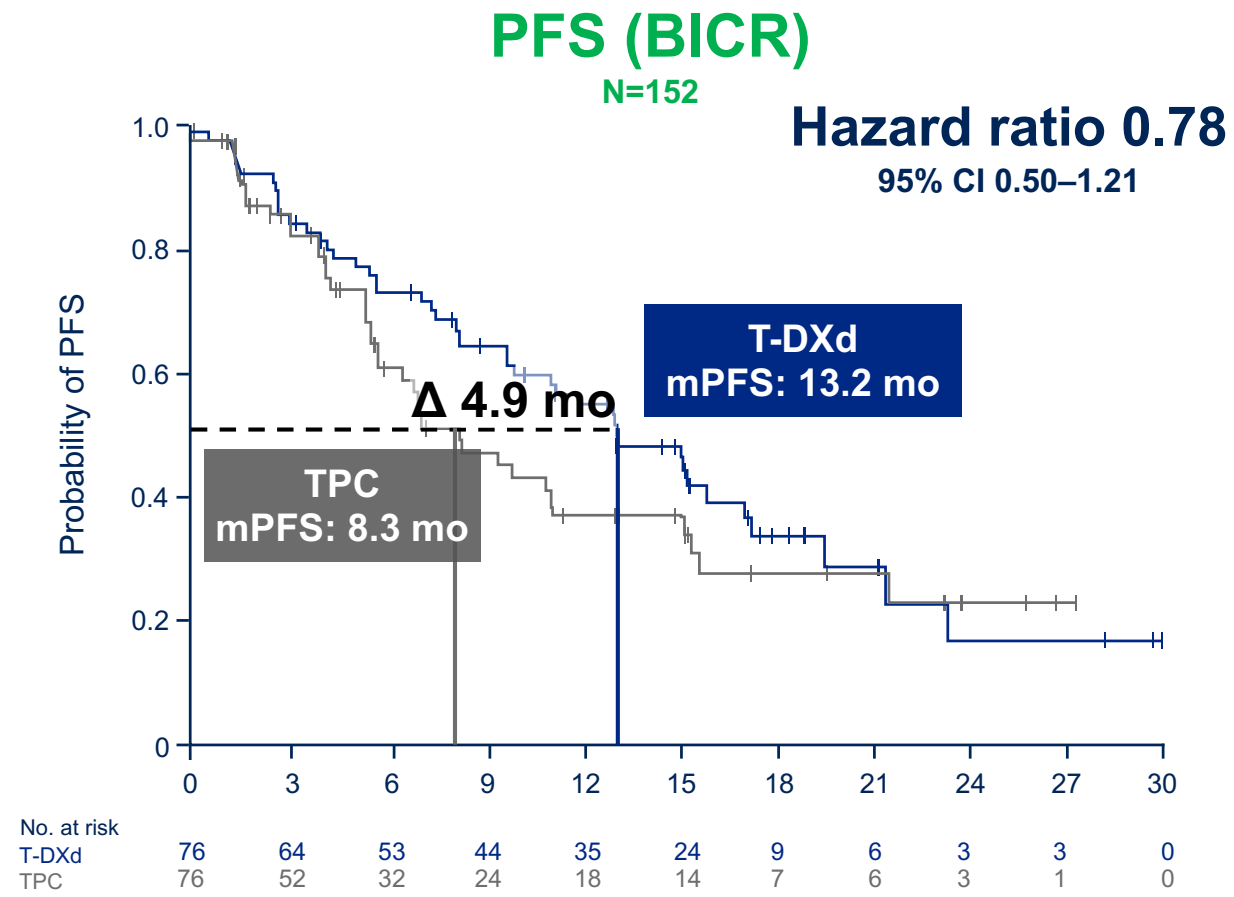


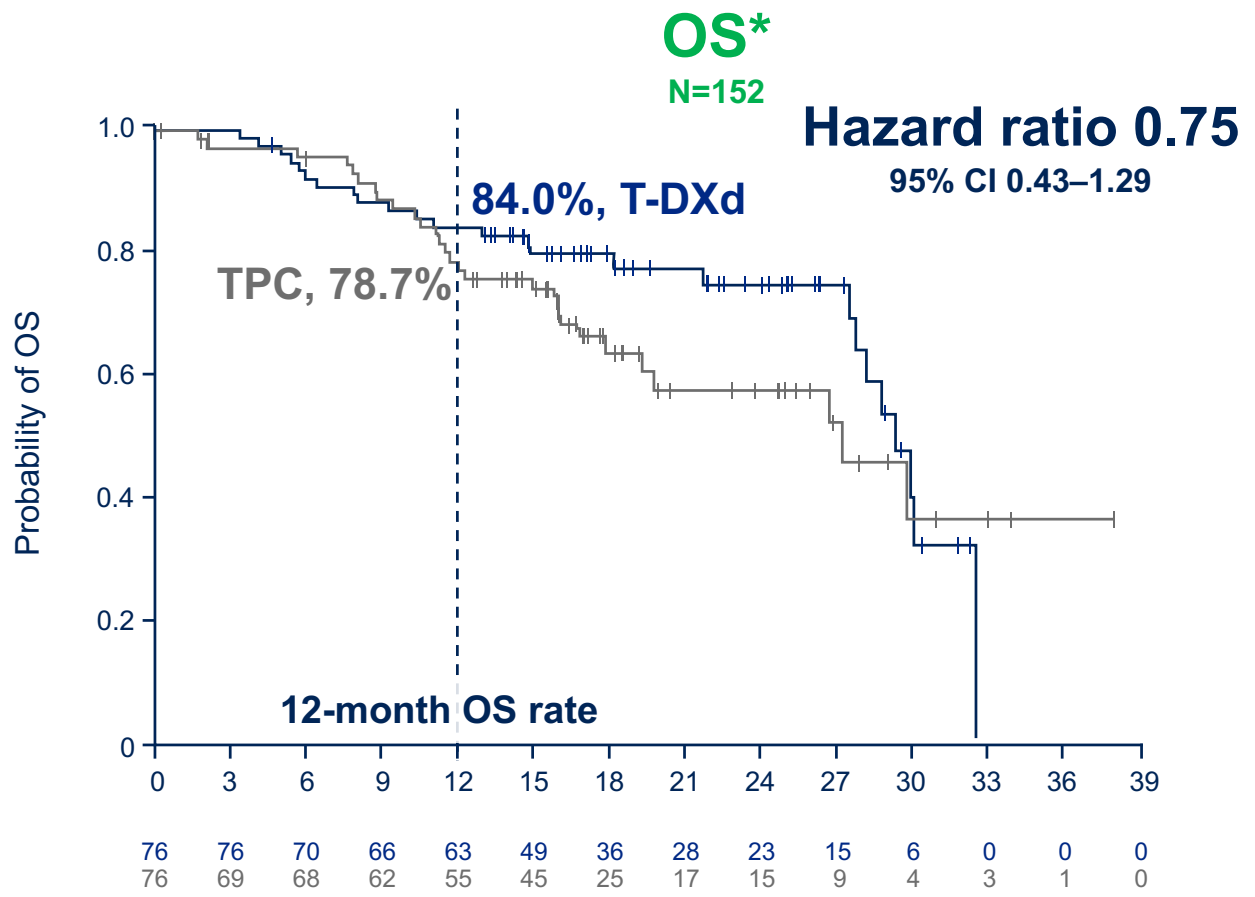
20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

Curigliano et al, ASCO 2024 LBA

Destiny Breast-06: PFS and OS in HER2-ultralow

Prespecified Exploratory Analyses

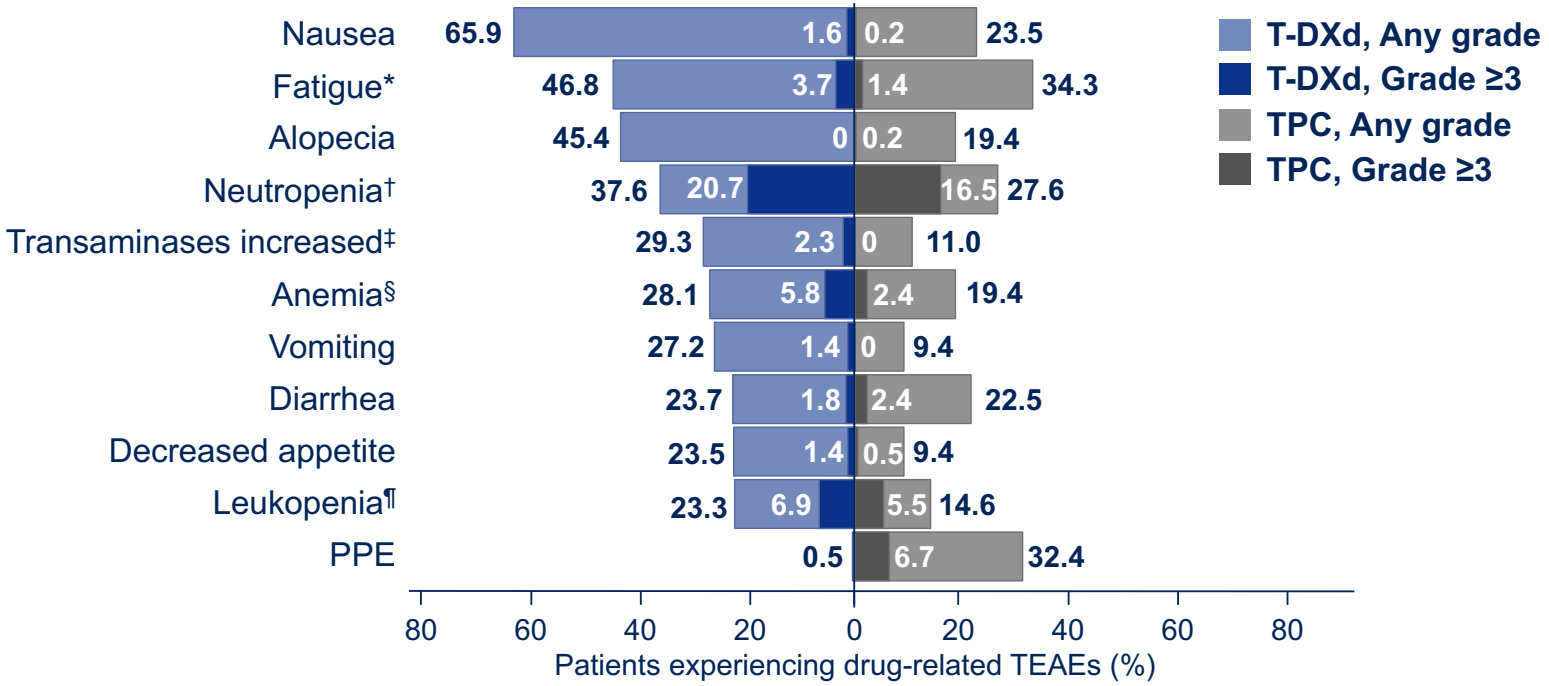




PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

Curigliano et al, ASCO 2024 LBA

Safety



TEAEs leading to death

- 11(2.4%) vs 6 (1.4%)
- Treatment related: 5 (1.2%) vs 0

Most common TEAE associated with treatment discontinuation

- T-DXd: 5.3%, pneumonitis*
- TPC: 1.4%, peripheral neuropathy

Left ventricular dysfunction

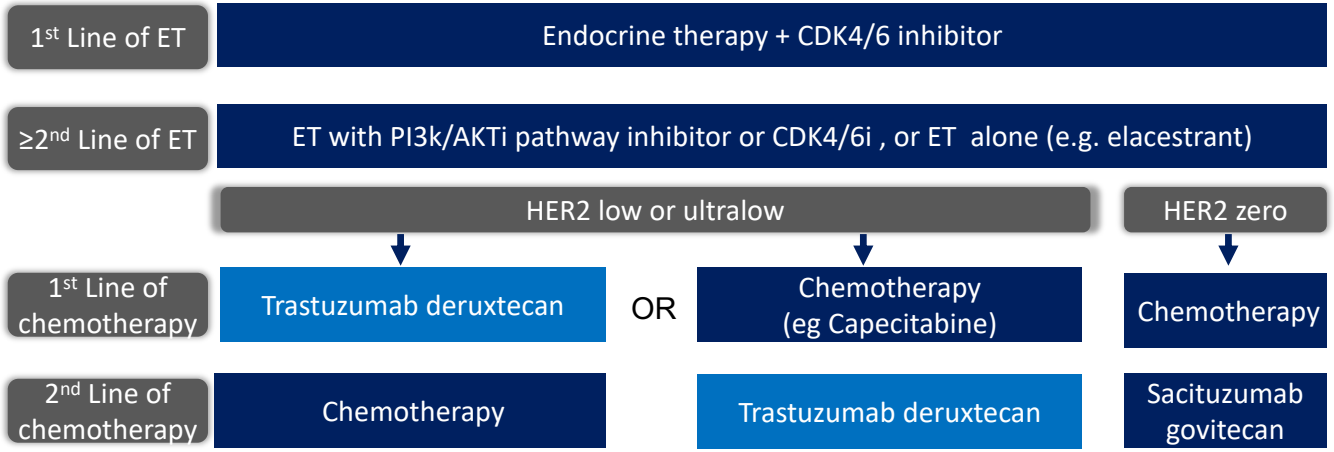
- 8.1% any grade
- 0.7% grade 3

Adjudicated as drug-related interstitial lung disease / pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n=434)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)	49 (11.3)
TPC (n=417)	0	1 (0.2)	0	0	0	1 (0.2)

Interpretation

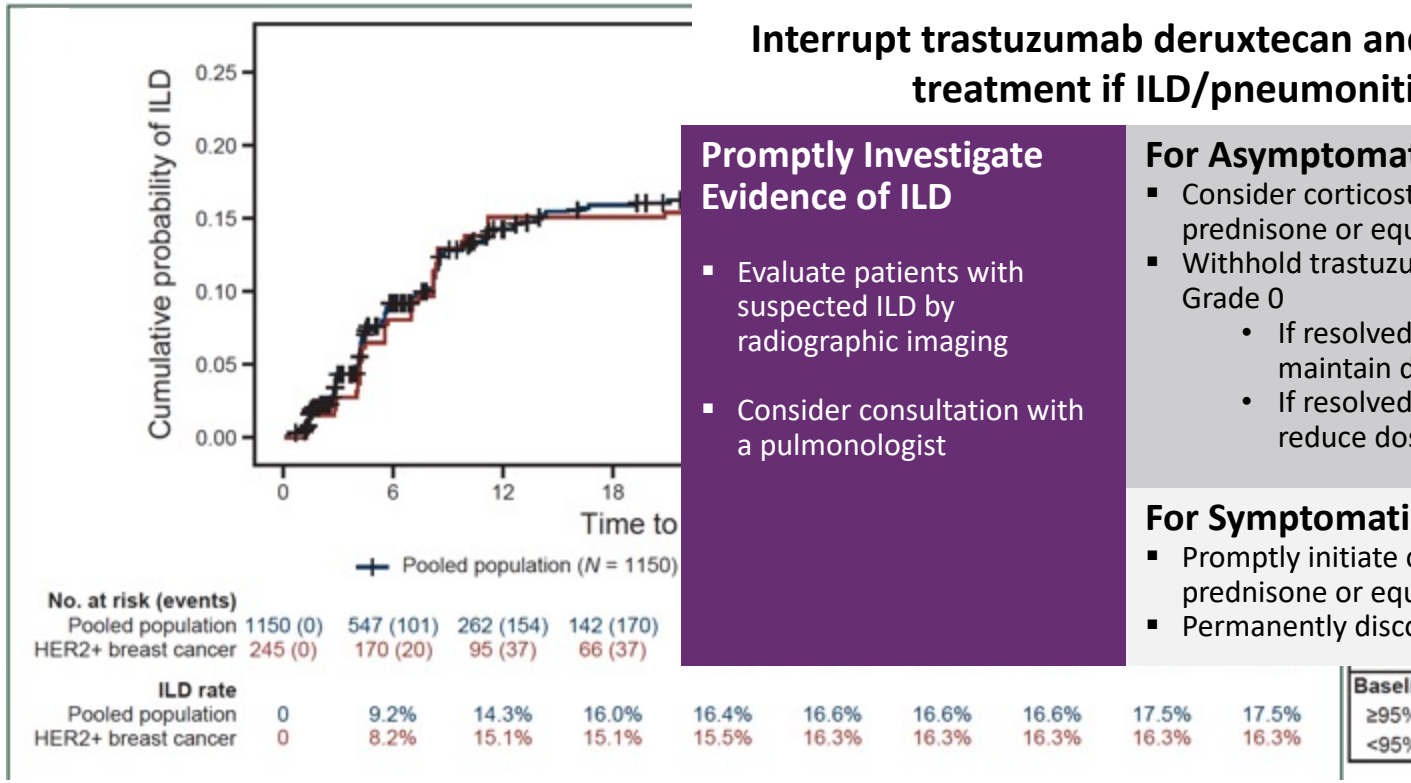
- T-DXd shows a clear efficacy advantage over TPC as first line chemotherapy
  - No OS benefit to date, cross-over may impact this endpoint
  - More toxicity (grade ≥3 AEs, fatal AEs)
- Although an exploratory endpoint, similarity of efficacy in ultra-low to HER2 low suggest this is a reasonable and effective option in this subset
- Definition of ultra-low: 0-1+? A challenge for our pathologists
  - Multiple new assays in development
  - Destiny Breast 15 evaluating clinically HER2 0 cancers



Krop, ASCO 2024

- Highly effective option after endocrine therapy, but appropriate sequence (1st or 2nd chemotherapy line) should be determined for individual patients
  - 2nd line: Bone/soft tissue dominant, less symptomatic, long DFI
  - 1st line: Visceral dominant, more symptomatic, short DFI

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

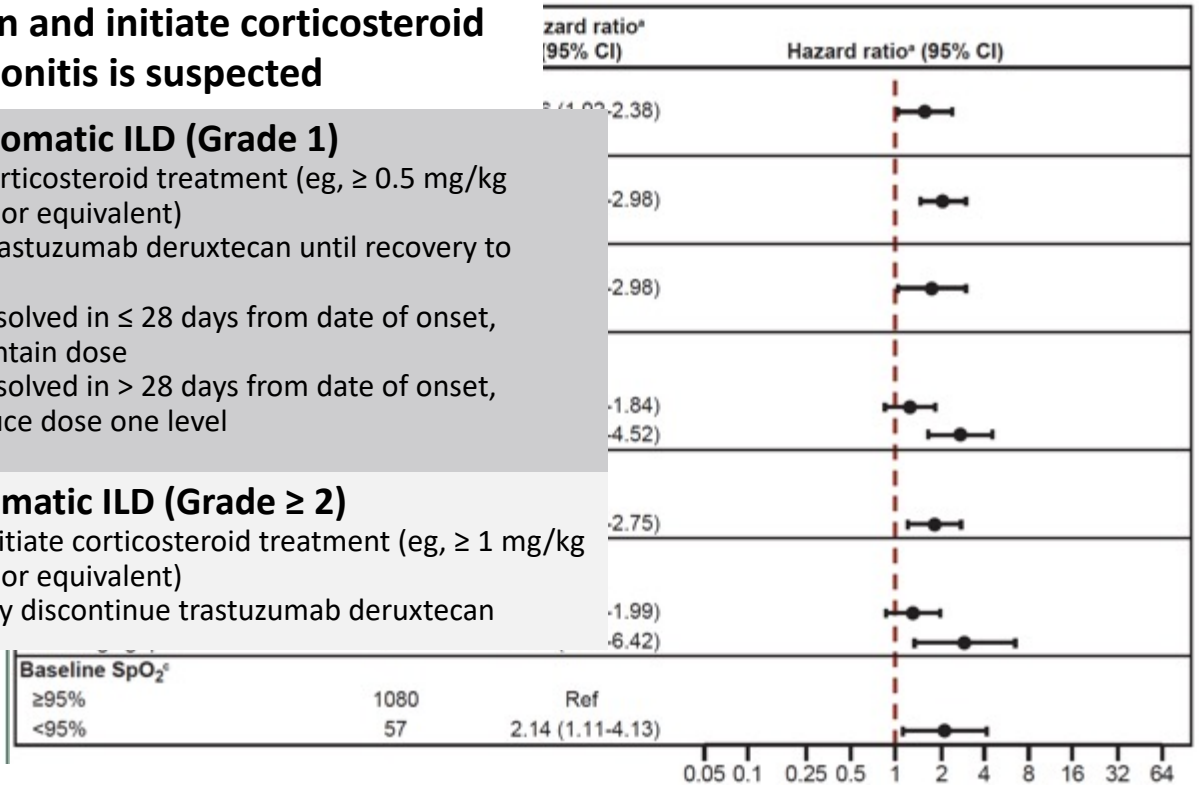
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

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)

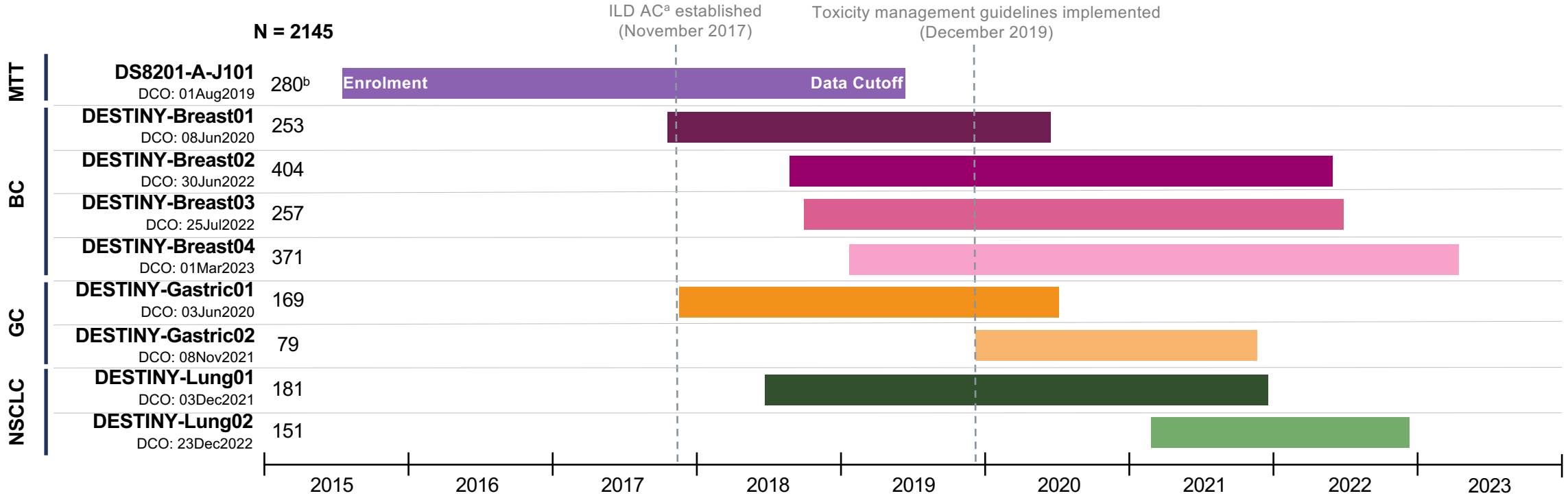
- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan



- 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

POOLED ANALYSIS FOR GRADE 1 ILD RECHALLENGE



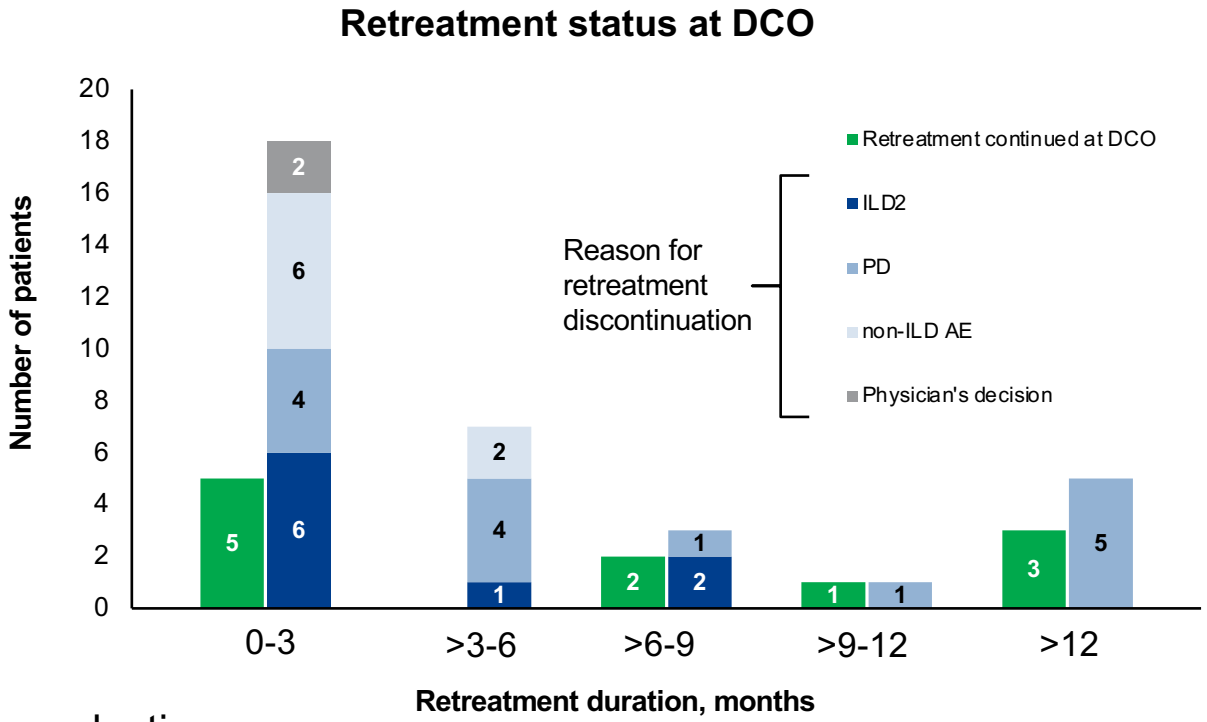
- Data were pooled from 9 clinical trials to identify patients with Gr 1 ILD as assessed by the investigators and confirmed by the adjudication committee (AC) who were retreated with T-DXd
  - All patients received at least 1 dose of T-DXd (5.4-8.0 mg/kg) monotherapy
- *T-DXd toxicity management guidelines recommend a dose reduction for retreatment if ILD takes longer than 28 days to resolve. At the time of study inclusions, guidelines recommended discontinuation of T-DXd if ILD had not resolved within 49 days from the last T-DXd dose[c]*

AC, adjudication committee; BC, breast cancer; DCO, data cutoff ; GC, gastric cancer; ILD, interstitial lung disease/pneumonitis; MTT, multiple tumor types; NSCLC, non–small cell lung cancer.
[a]Each AC session included an oncologist, a radiologist, and a pulmonologist. [b]Only patients who received at least 1 dose of T-DXd 5.4-8.0 mg/kg are included. The color bar for each study indicates the time from patient enrollment to data cut-off. [c]Guidelines have subsequently been updated to recommend discontinuation of T-DXd if ILD has not resolved within 126 days from the date of last drug dose.

Rugo et al, ESMO Breast 2024

T-DXd Retreatment Characteristics

	T-DXd retreatment (N = 45)
Dose level of T-DXd retreatment	
Same dose, n (%)	31 (68.9)
Reduced dose, n (%)	14 (31.1)
Median time to retreatment after ILD1 onset (range), days	28 (8-48)
Median retreatment cycles (range)	5.0 (1-37)
Patients with ILD2 (n = 15)	5.0 (2-23)
Patients without ILD2 (n = 30)	4.5 (1-37)
Median retreatment duration (range), days	85.0 (1-848)
Patients with ILD2 (n = 15)	85.0 (22-648)
Patients without ILD2 (n = 30)	82.5 (1-848)

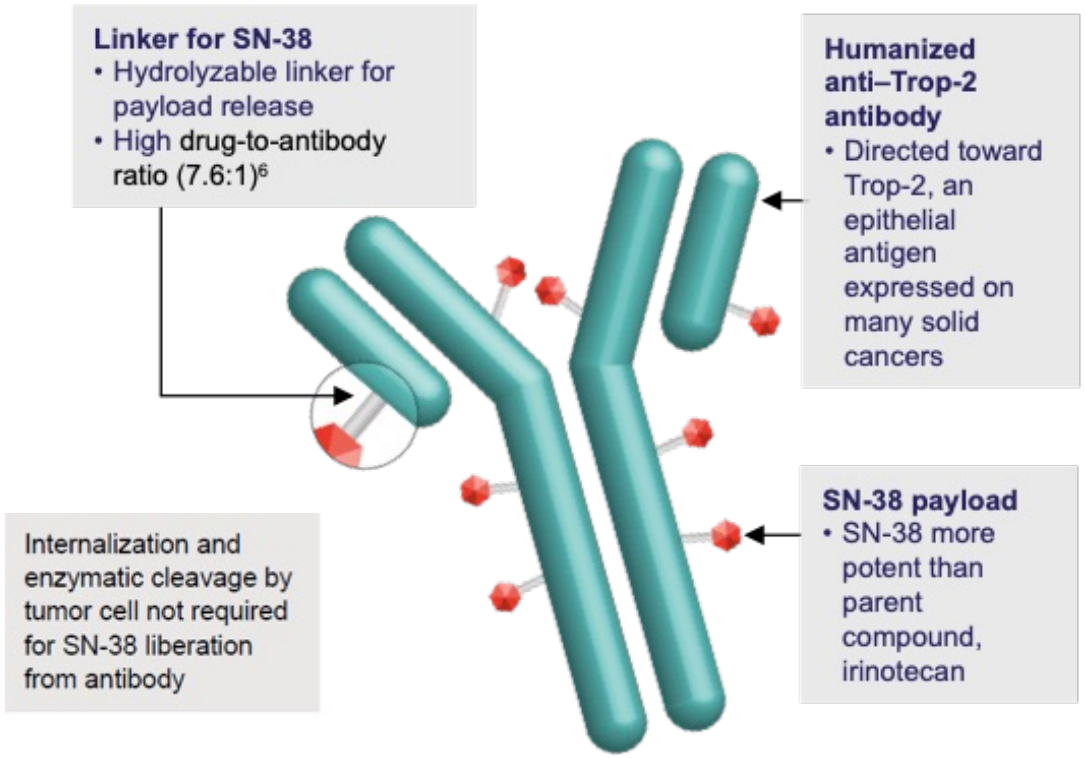


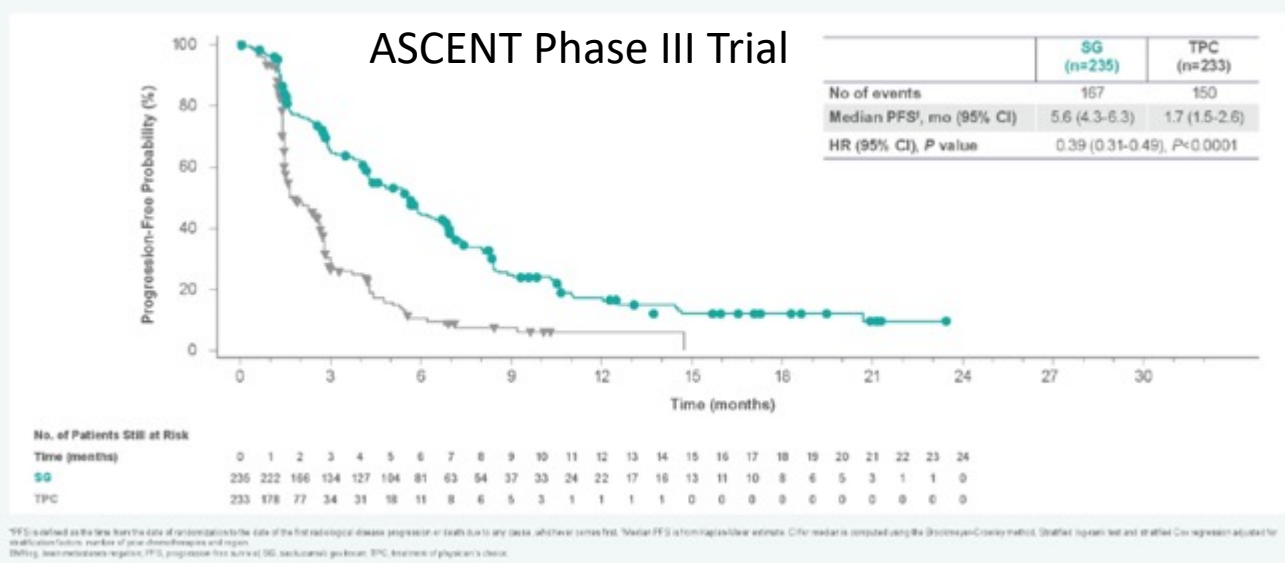
- 68.9% (31/45) of patients were retreated without any dose reductions
- 24.4% (11/45) of patients were still receiving T-DXd retreatment at the DCOs of each respective study
- Progressive disease was the main reason for T-DXd retreatment discontinuation (33.3% [15/45] of patients)
  - 20.0% (9/45) of patients discontinued retreatment due to recurrent ILD (ILD2)
- **33.3% (15/45) of patients were retreated for >6 months and 17.8% (8/45) of patients were retreated for >12 months**

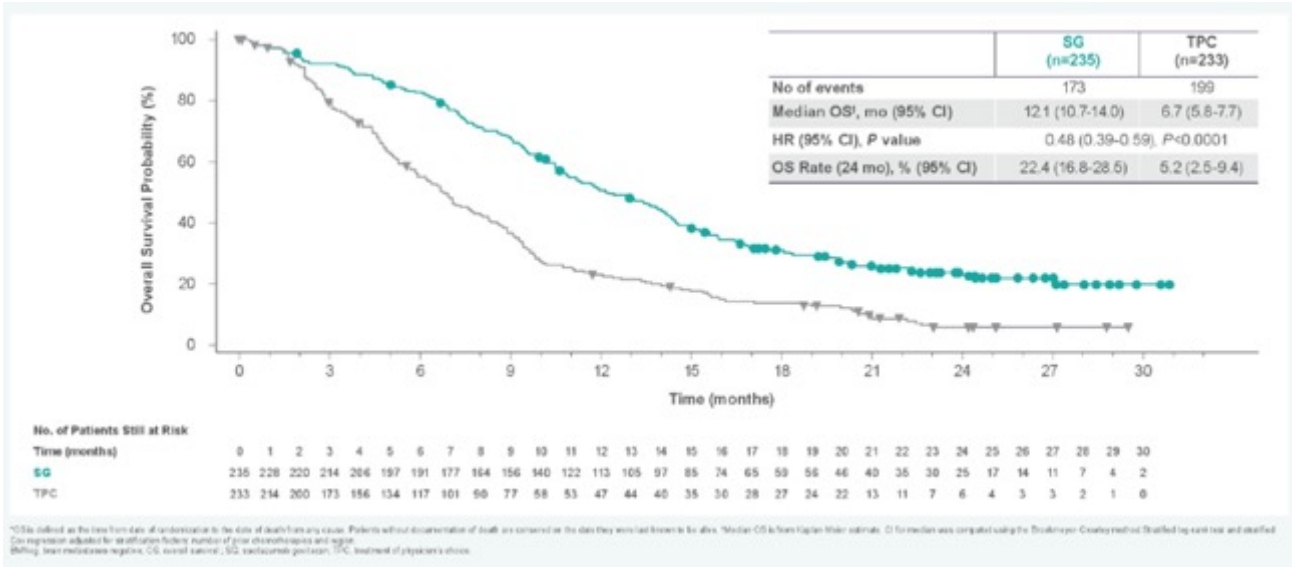
AE, adverse event; DCO, data cutoff; ILD, interstitial lung disease/pneumonitis; ILD1; first Gr 1 ILD event; ILD2, any-grade recurrent ILD event; PD, progressive disease; T-DXd, trastuzumab deruxtecan.

Rugo et al, ESMO Breast 2024

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







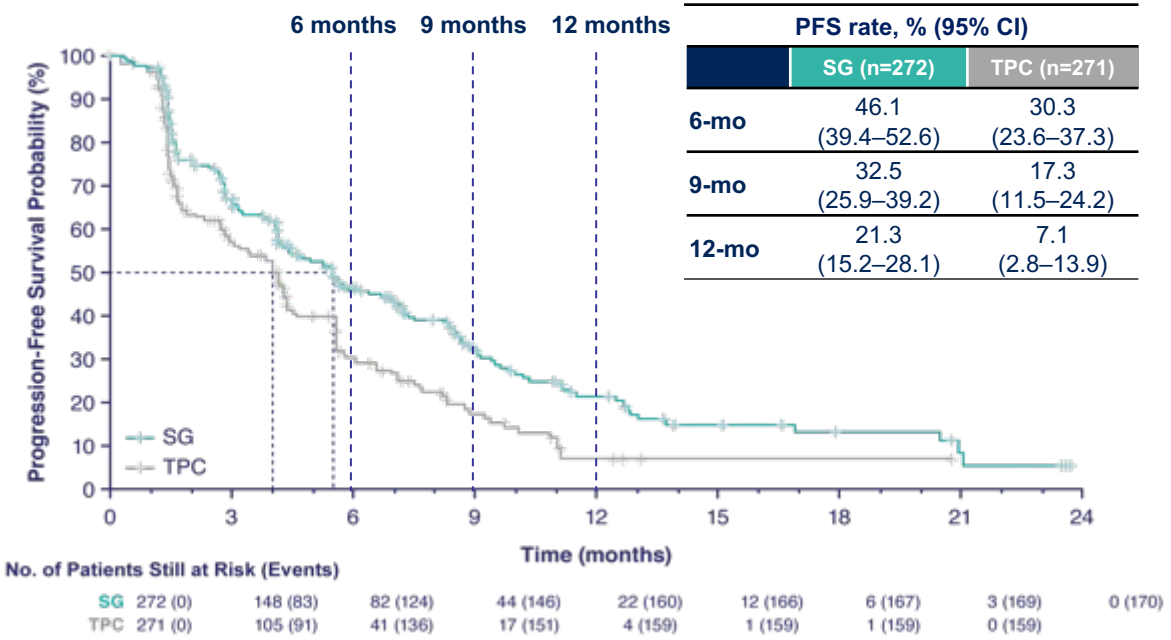
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- **Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), FN (6% vs 2%)**
  - G-CSF: 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due 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]

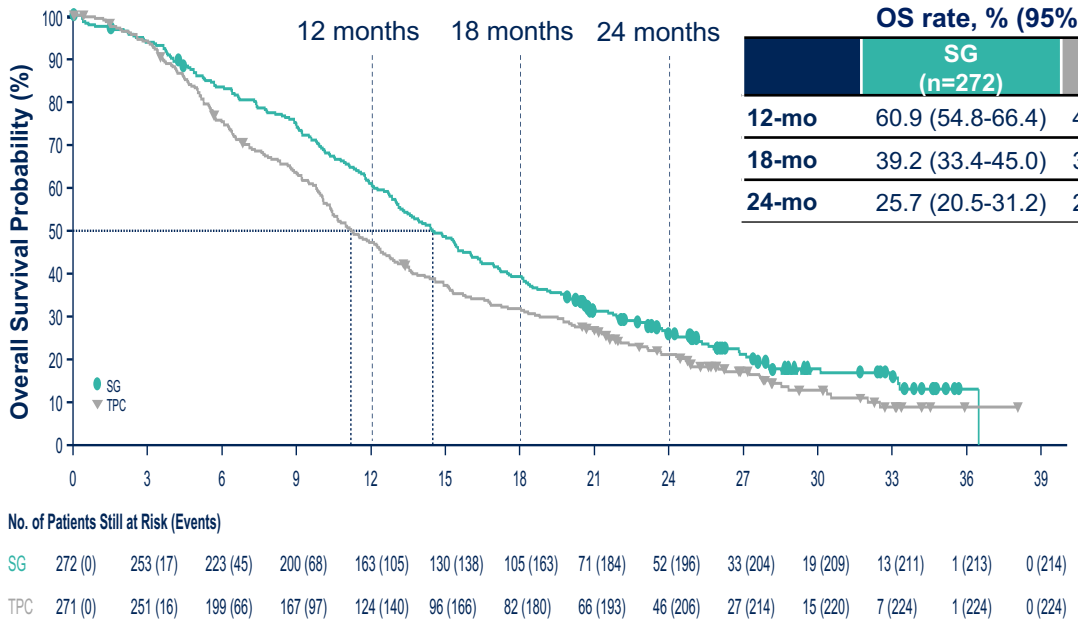
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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

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

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

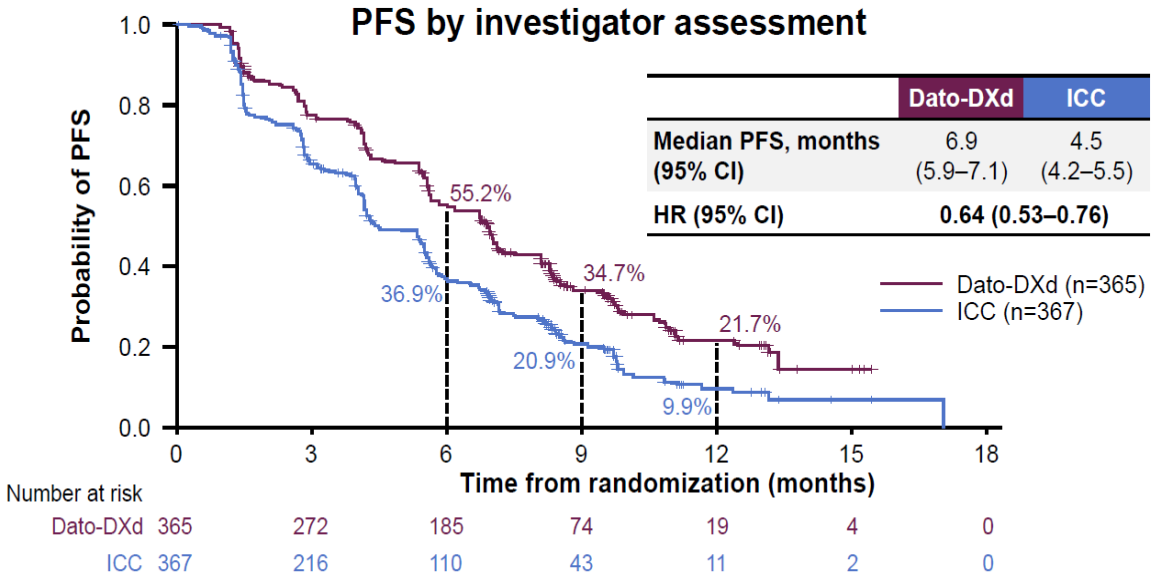
- Lines of chemo in unresectable/ metastatic setting (1 vs 2)
- Geographical location (US/Canada/ Europe vs ROW)
- Previous CDK4/6 inhibitor (yes vs no)

- 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

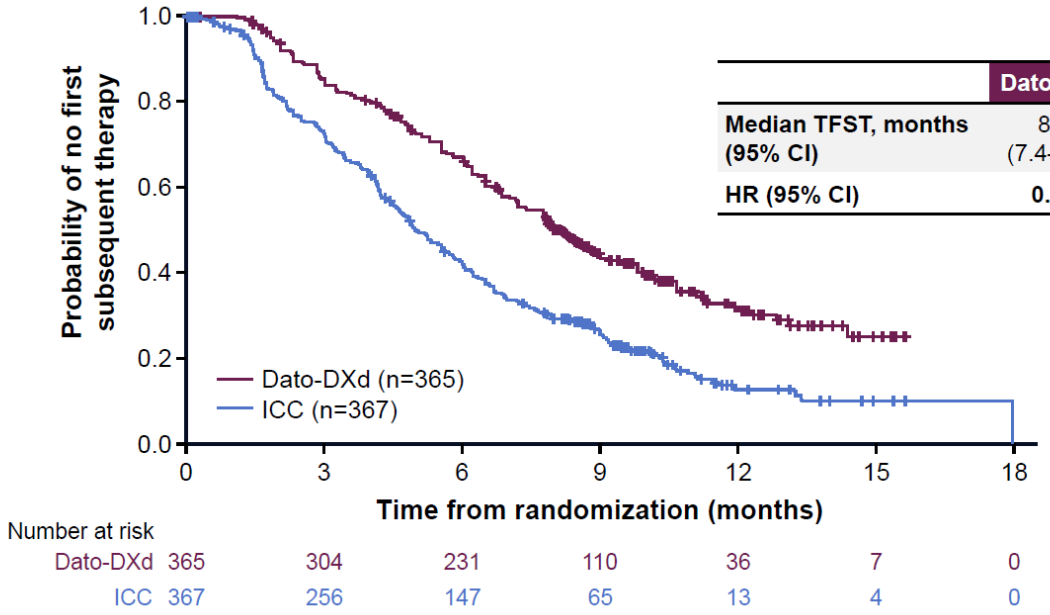
TROPION-Breast01: PFS and time to subsequent therapy

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)	

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)	

PFS by BICR (primary endpoint)

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

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)	

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

Tropion-Breast01 Safety

- Compared to ICC, less dose reduction and interruption
- The most common toxicity is low grade nausea (51%)
- Alopecia: 36%
- AESIs
  - Oral mucositis/stomatitis
    - 56% all grade, 7% grade $\geq$ 3
    - Steroid mouthwash under evaluation
  - Ocular surface events (dry eye, keratitis)
    - 40%, almost all low grade
  - Drug-related ILD
    - 3.3% all grade, 0.8% $\geq$ grade 3
    - One patient with adjudicated grade 5 drug related event

Jhaveri and Rugo et al, ESMO BC 2024

Proposed Mechanism of ADC + IO Synergy

1: ADCs bind to the cancer cell

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

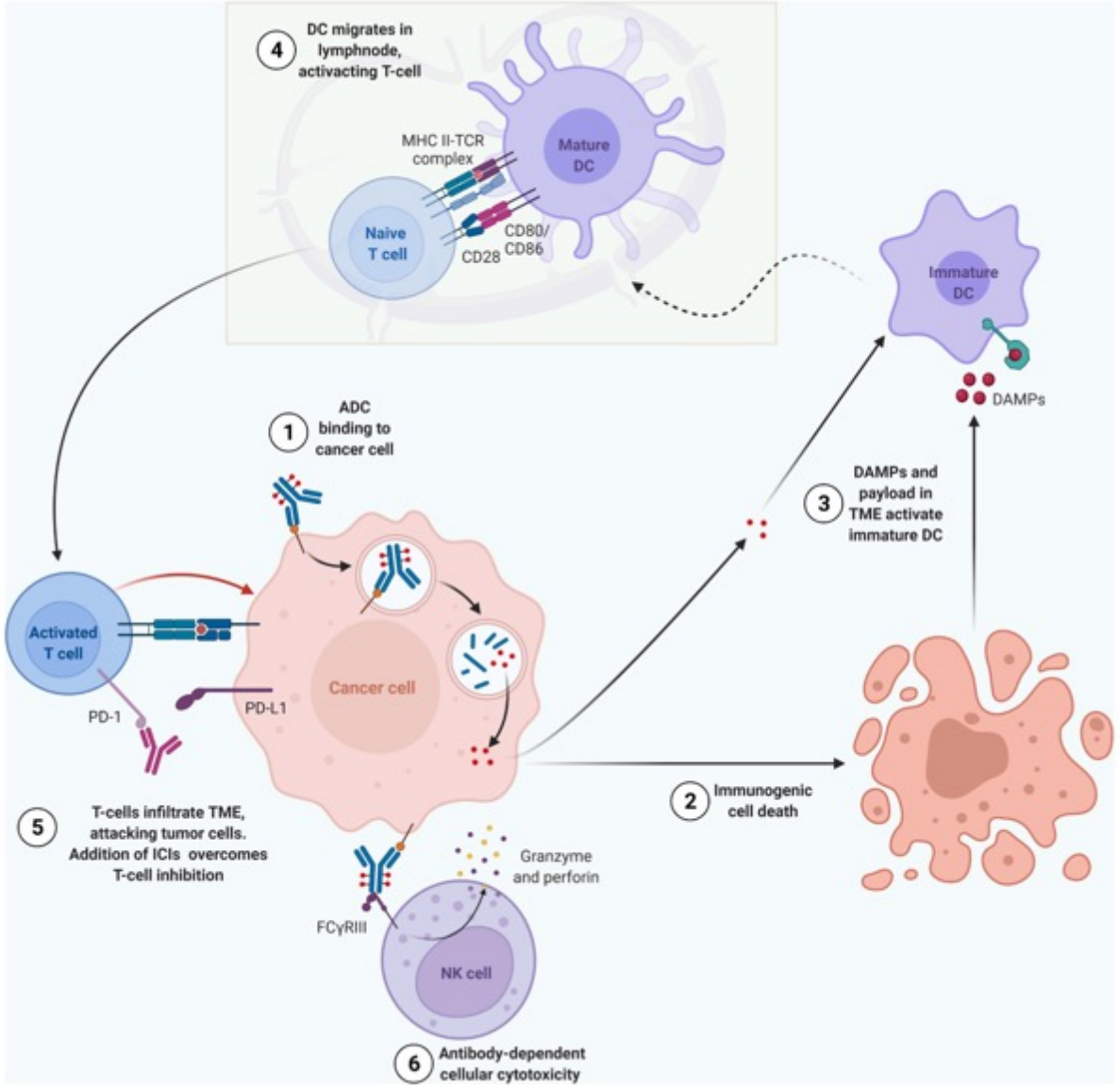
3: Damage-associated molecular patterns (DAMPs) are released in the tumor microenvironment (TME), stimulating the maturation of dendritic cells

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

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

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

Nicolo et. al. *Cancer Treatment Reviews* 2022

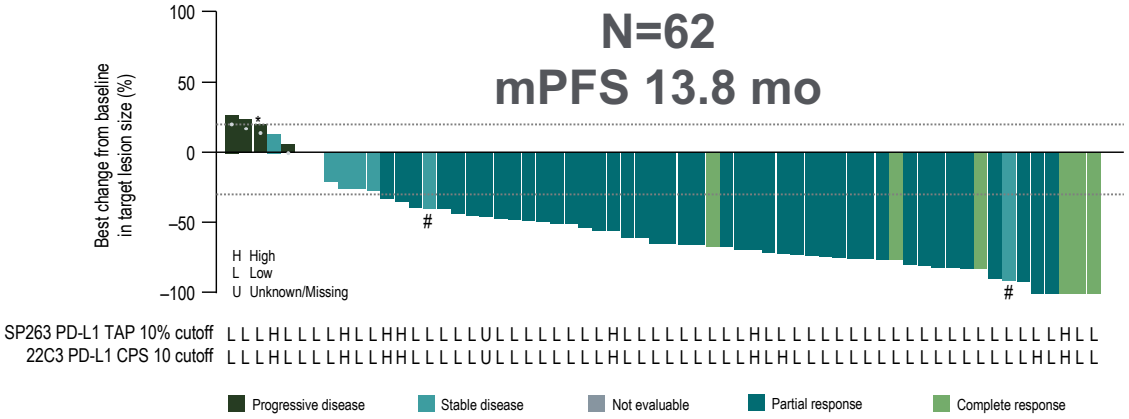


ADCs plus Checkpoint Inhibitors: 1st line mTNBC

Dato-DXd + Durvalumab in the Begonia Trial

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

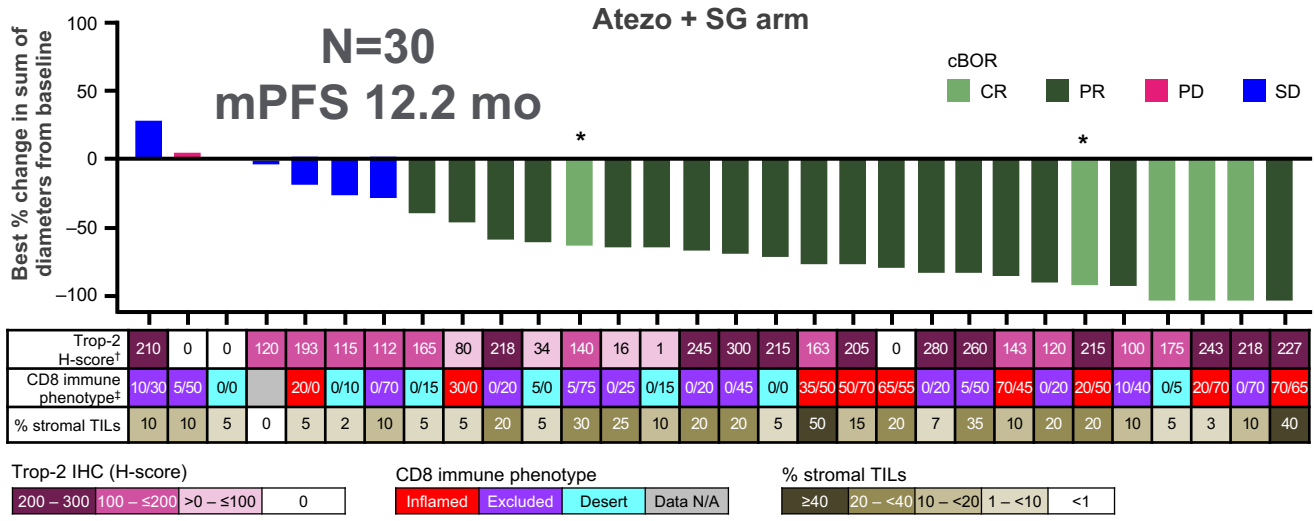
- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Schmid et al, ESMO 2023

Sacituzumab Govitecan + Atezolizumab in the Morpheus-PAN BC Trial (PD-L1+)

Confirmed ORR 76.7%, 5 CR, 18 PR



Schmid et al, ESMO BC 2024

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+

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

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

N=110 → 1:1 → N=110

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

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

Endpoints
Primary
- PFS

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

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

Ascent-07:
First-line Chemotherapy in HR+

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

N = 654
2:1 randomization

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

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

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

Primary Endpoint
- PFS by BICR

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

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

GBG: SASCIA Post-Neoadjuvant Trial
NCT04595565

N=1200
HER2-negative early breast cancer

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

R 1:1

→ Sacituzumab govitecan (8 cycles d1, 8 q3w)

→ Treatment of physician´s choice*

Follow-up

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

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

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

R 1:1

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

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

Follow-up

PI: Sara Tolaney; Alliance Foundation Trial

TROPION-Breast02 (n=625)

NCT05374512
PD-L1 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

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

TROPION Breast05 (n=625)

NCT06103864
PD-L1+

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

Sacituzumab Tirumotecan (sac-TMT)

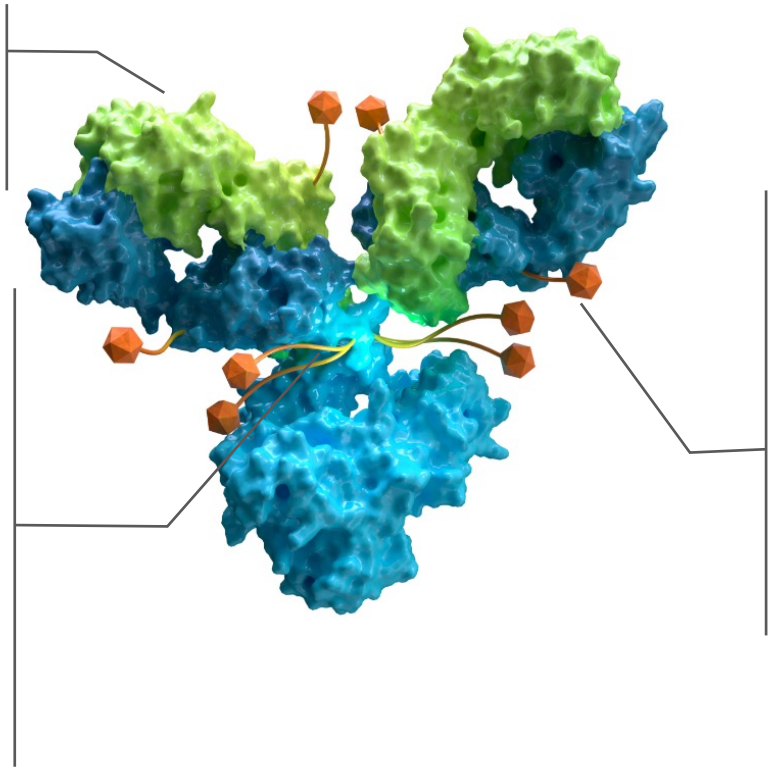
Sac-TMT is a TROP2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor at DAR 7.4. The features of sac-TMT lead to release of the payload both in the tumor microenvironment (TME) and inside tumor cells, achieving a balance between the safety and efficacy of the ADC.

Antibody

- hRS7, a recombinant humanized anti-TROP2 antibody with high affinity

Linker

- **Kthiol conjugation:** irreversible coupling to improve stability of ADC
- **Payload release:** intracellular enzymatic cleavage and extracellular hydrolysis in TME
- **Balanced stability:** balance between efficacy and safety to expand therapeutic window



Payload

- **Novel topo I inhibitor** (belotecan derivative named T030), highly active
- Average **DAR: 7.4** (range:7–8)
- **Bystander effect**
- Methylsulfonyl derivatization enhances linker stability and toxin permeability

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; TME, tumor microenvironment; TROP2, trophoblast cell surface antigen 2.

Phase III OptiTROP-Breast01 Study: Sacituzumab Tirumotecan

A randomized, controlled, and open-label phase III study (NCT05347134)

Patients with locally recurrent or metastatic TNBC

- Relapsed or refractory to 2 or more prior chemotherapy regimens for unresectable, locally advanced or metastatic disease
  - For prior therapy, 1 could be in the (neo)adjuvant setting, provided progression occurred during treatment or within 12 months after treatment discontinuation
- Received taxane(s) in any setting

R 1:1

Sac-TMT, 5 mg/kg IV, days 1 &15 every 28-day cycle

Physician's choice of chemotherapy: eribulin, capecitabine, gemcitabine, or vinorelbine **every 21-day cycle**

Treatment until disease progression, unacceptable toxicity or any other reason for discontinuation

Endpoints[a]

Primary
- PFS by BICR

Secondary
- OS
- PFS by investigator assessment
- ORR, DOR
- Safety

Stratification factors
- Line of prior therapy (2–3 *vs* >3)
- Presence of liver metastases (yes vs. no)

N=263

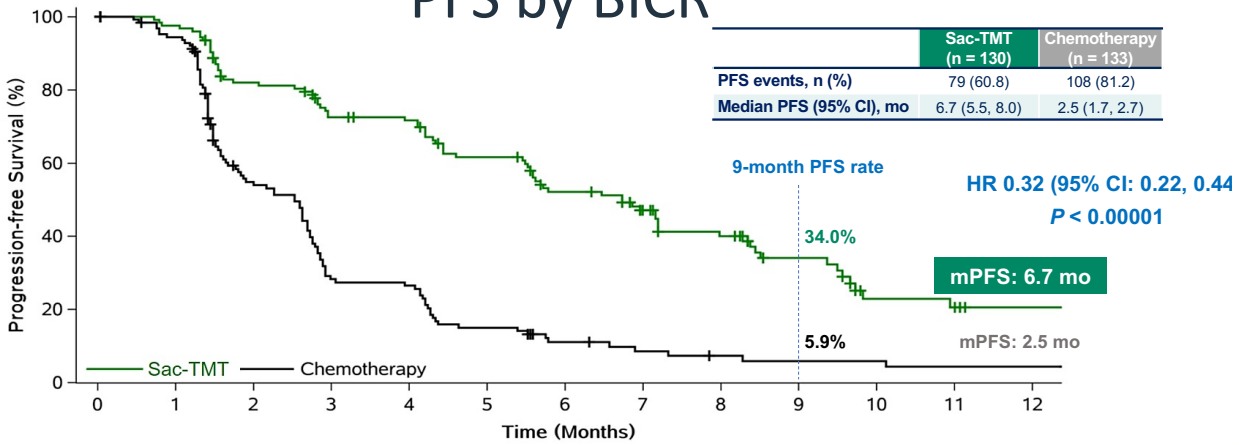
Tumor assessment
- Every 6 weeks for the first year and every 12 weeks afterward.

Choice of chemotherapy
- Eribulin: 88 (66.2%)
- Capecitabine: 4 (3.0%)
- Gemcitabine: 20 (15.0%)
- Vinorelbine: 21 (15.8%)

Patient population
- Median 3 vs 2 lines of prior chemotherapy
- 87% visceral mets
  - 35% liver

Safety
- Neutropenia 74%
  - 32% grade 3
- Stomatitis 40%
  - 9% grade 3
- 12% grade 3 thrombocytopenia
- ILD, eye tox rare

PFS by BICR

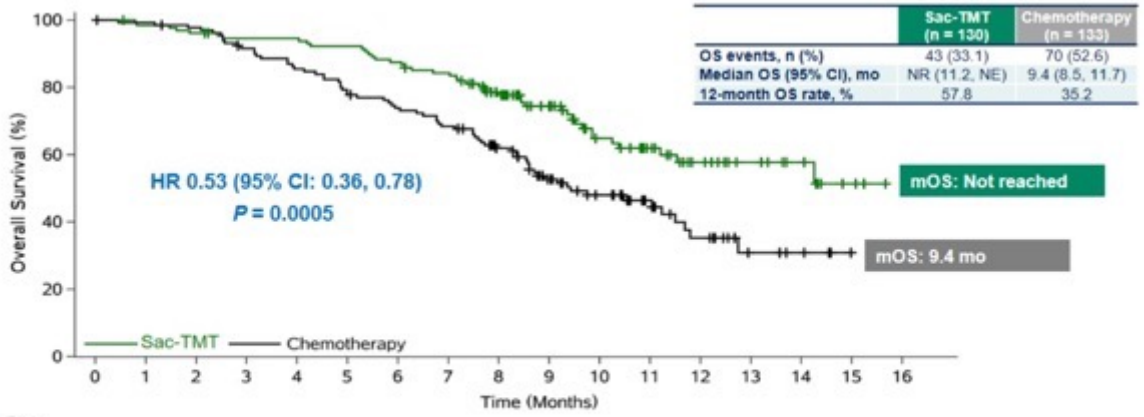


	Sac-TMT (n = 130)	Chemotherapy (n = 133)
PFS events, n (%)	79 (60.8)	108 (81.2)
Median PFS (95% CI), mo	6.7 (5.5, 8.0)	2.5 (1.7, 2.7)

No. at Risk													
Sac-TMT	130	122	97	83	80	67	54	42	33	20	10	9	6
Chemotherapy	133	119	62	32	30	17	10	7	5	4	4	3	3

- PFS by investigator assessment (secondary endpoint): Median 6.5 *vs* 2.6 mo; HR 0.32 (95% CI: 0.24, 0.44)

OS (interim)



	Sac-TMT (n = 130)	Chemotherapy (n = 133)
OS events, n (%)	43 (33.1)	70 (52.6)
Median OS (95% CI), mo	NR (11.2, NE)	9.4 (8.5, 11.7)
12-month OS rate, %	57.8	35.2

No. at Risk																		
Sac-TMT	130	127	124	120	120	117	111	106	85	66	44	33	22	15	11	4	0
Chemotherapy	133	131	128	119	111	101	95	88	71	50	37	24	15	6	4	0	

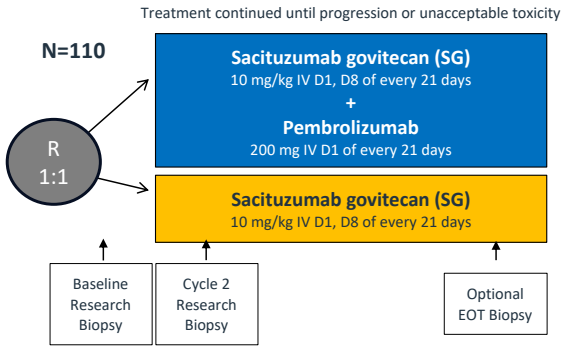
- Efficacy boundary (corresponding to actual OS events of 113): 0.0042. The study crossed OS efficacy boundary.

Binghe Xu et al, ASCO 2024

SACI-IO HR+ (Phase 2): Sacituzumab govitecan with or without pembrolizumab in patients with HR+/HER2

Metastatic or locally advanced unresectable breast cancer

- HR-positive (ER ≥ 1% or PR ≥ 1%), HER2-negative (IHC 0, 1+, or 2+/ISH-)
- No restriction on PD-L1 status
- ≥1 endocrine therapy for mBC or progression on or within 12 months of adjuvant endocrine therapy
- 0-1 prior chemotherapy for mBC



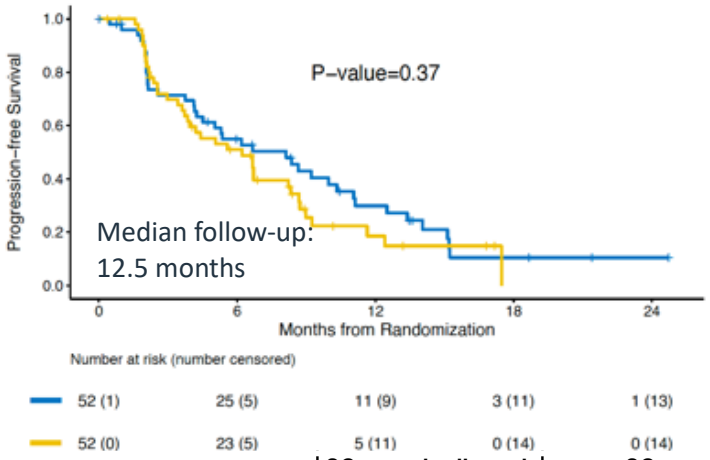
Endpoints

Primary:
- PFS (ITT)

Secondary:
- PFS (PD-L1+)[b]
- OS (ITT, PD-L1+)
- ORR, DOR, TTOR, CBR (ITT, PD-L1+)
- Safety

Exploratory:
- Correlative
- HRQoL

PFS



	SG + pembrolizumab (n=52)	SG (n=52)
N PFS events	38	38
Median PFS, months (95% CI)	**8.12** (4.51, 11.12)	**6.22** (3.85, 8.68)
HR (95% CI)	**0.81** (0.51, 1.28); P=0.37	

	SG + pembrolizumab (n=52)		SG (n=52)	
	n (%)	95% CI	n (%)	95% CI
Confirmed PR	11 (21.2%)	11.1, 34.7%	9 (17.3%)	8.2 30.3%
SD	25 (48.1%)	34, 62.4%	26 (50.0%)	35.8, 64.2%
PD	11 (21.2%)	11.1, 34.7%	14 (26.9%)	15.6, 41%
NE	5 (9.6%)	3.2, 21%	3 (5.8%)	1.2, 15.9%
Objective response rate	**11 (21.2%)**	**11.1-34.7%**	**9 (17.3%)**	**8.2-30.3%**
PD-L1-positive	**3/16 (18.8%)**	4.0, 45.6%	**5/24 (20.8%)**	7.1, 42.2%
PD-L1-negative	**8/35 (22.9%)**	10.4, 40.1%	**4/28 (14.3%)**	4.0, 32.7%
Clinical benefit rate	26 (50.0%)	35.8, 64.2%	24 (46.2%)	32.2, 60.5%
Median DOR, mo	12.9	4.4, NA	4.5	4.5, NA
Median TTOR, mo	2.3	1.8, 8.7	4.1	2.0, 10.2

TROFUSE 010: PD-L1-
Sacituzumab tirumotecan in HR+
N=1200

Key inclusion criteria:
- Unresectable locally advanced or metastatic centrally-confirmed **HR+/HER2-** breast cancer
- Disease recurrence on/after **CDK4/6i** (in the early or metastatic setting)

Key exclusion criteria:
- Previously treated with **chemotherapy** in metastatic setting
- Disease **recurrence** within **6 months** after completion of adjuvant/neoadjuvant chemotherapy

Stratification Factors:
1) PD-L1 status (CPS<1 vs CPS 1-9 vs CPS≥10)
2) TROP2 expression (low+medium vs high)
3) Geographical Region (WE vs NA vs ROW)

R
3:3:2

- **Arm A: MK-2870**
- **Arm B: MK-2870 + Pembrolizumab**
- **Arm C: TPC***

***Treatment of Physician's Choice:**
Paclitaxel/ Nab-Paclitaxel/ Capecitabine/ Liposomal Doxorubicin

Role in PD-L1+ vs negative?

Garrido-Castro, ASCO 2024

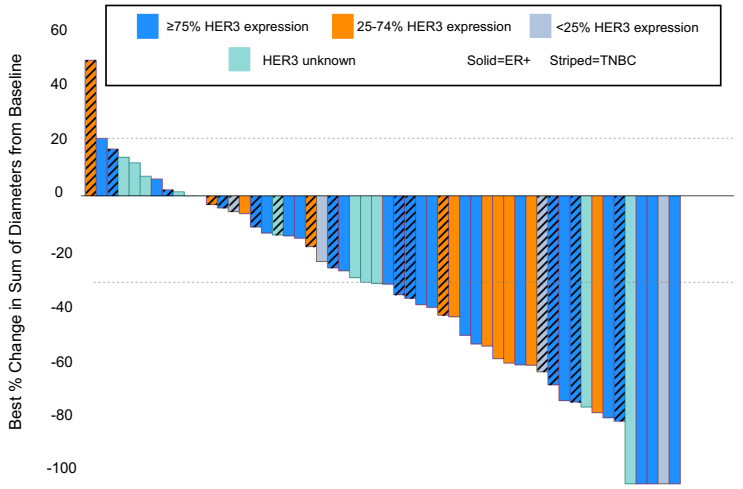
Patritumab Deruxtecan: Phase 2 Study of HER3-DXd in MBC

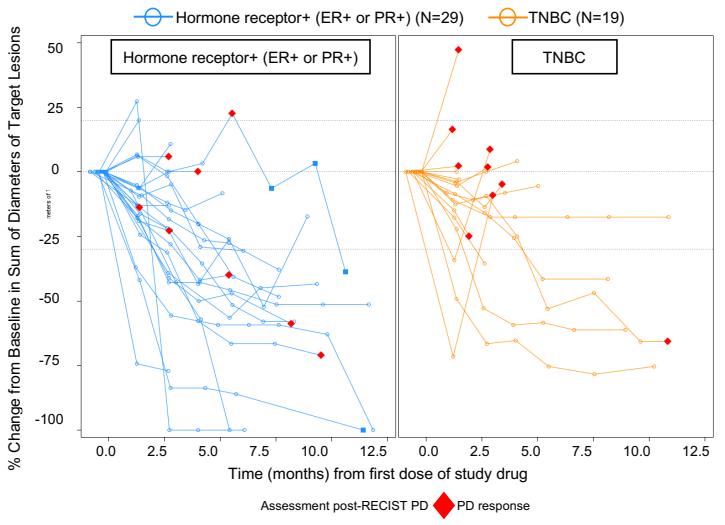
- 60 pts:
  - HR+: Prior CDKi, 0-2 chemo
  - TN: 1-3 chemo
  - 27 HR+/19 TN (n=48)
  - 64% HER3 ≥75%; 8% <25% (n=47)
- ORR 35%, CBR 43%,
  - No relationship to HER3 expression
- DOR ≥ 6mo: 47.6% in responders (n=10)
- Most common AE:
  - Nausea/diarrhea/fatigue
  - TEAE: 2 ILD, 1 low plt

	(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)

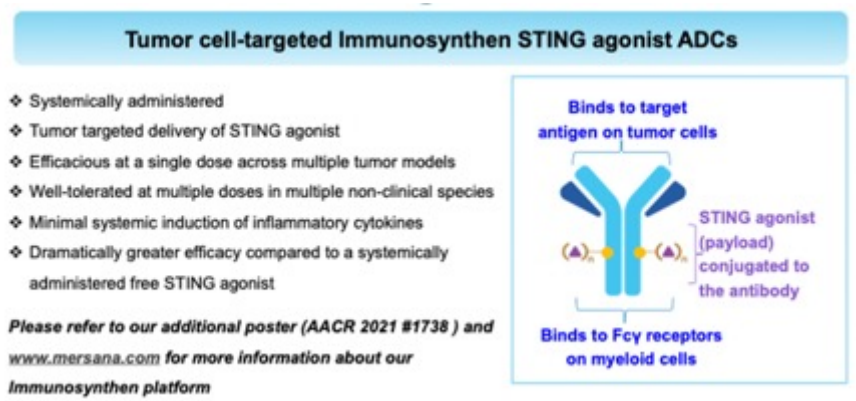


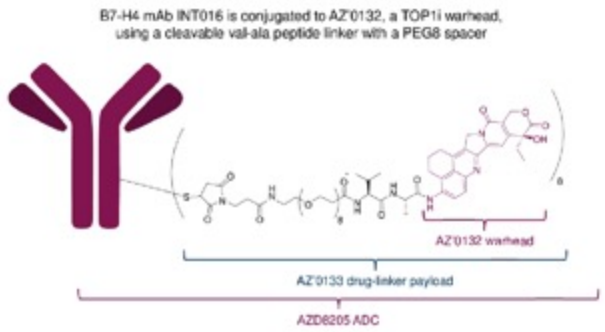


Hamilton et al, ASCO 2023

New Directions

- Newer ADCs
  - ADCs (HER2) with immune payload
  - Immune antibody with TOPO1i payload
  - HER2 Ab with eribulin payload: BB1701
- Combination Therapies
  - ADCs plus checkpoint inhibitors to enhance immunotherapy
  - ADCs plus anti-CD47 antibodies
- Understanding mechanisms of resistance
- Sequencing ADCs
  - Change the payload
  - Change the target
  - Why is safety so different?





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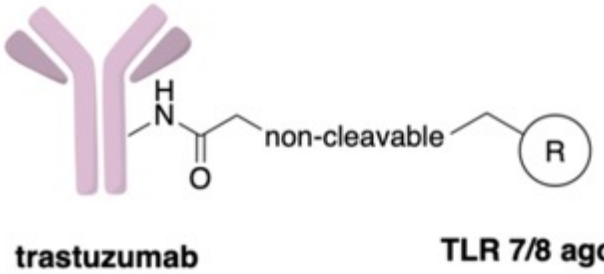
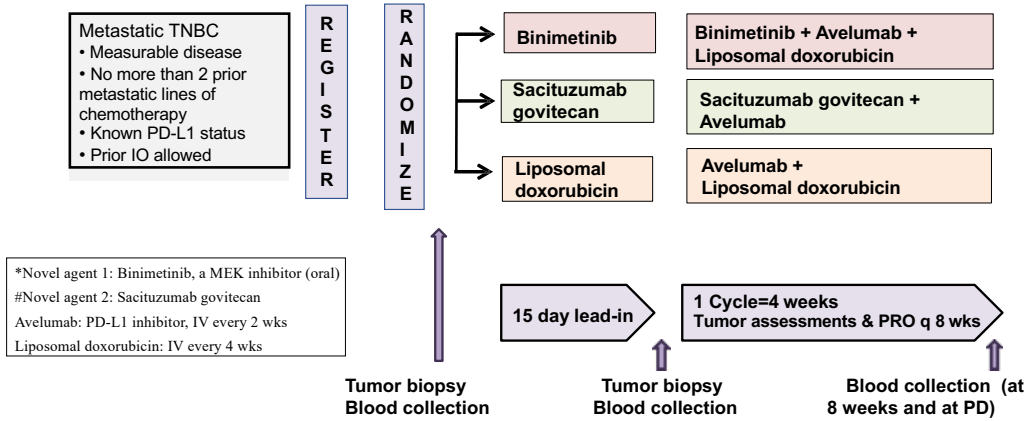


B7-H4 ADC

BDC-1001

TBCRC 047: InCITe Trial Design



*Safety combination data from MiLO trial
#Safety combination data from several ongoing trials

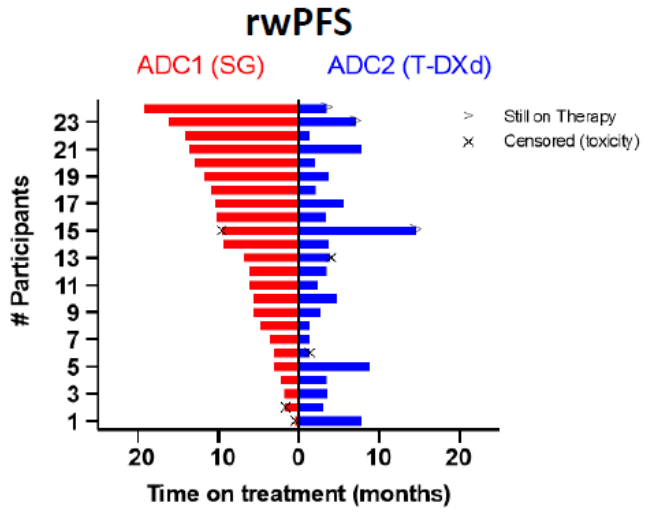
PI: Hope S. Rugo

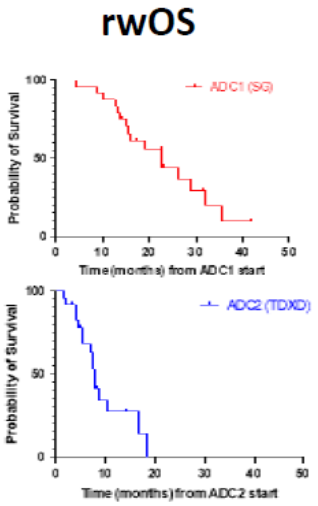
HR+/HER2-low efficacy data (n=56)

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

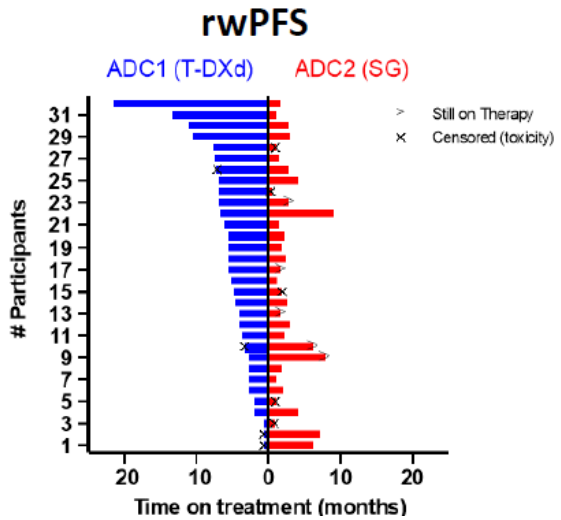


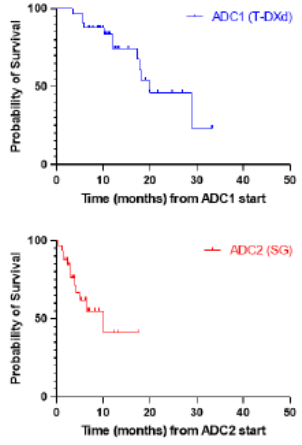


T-DXd → SG
(n=32, 57.1%)

- 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





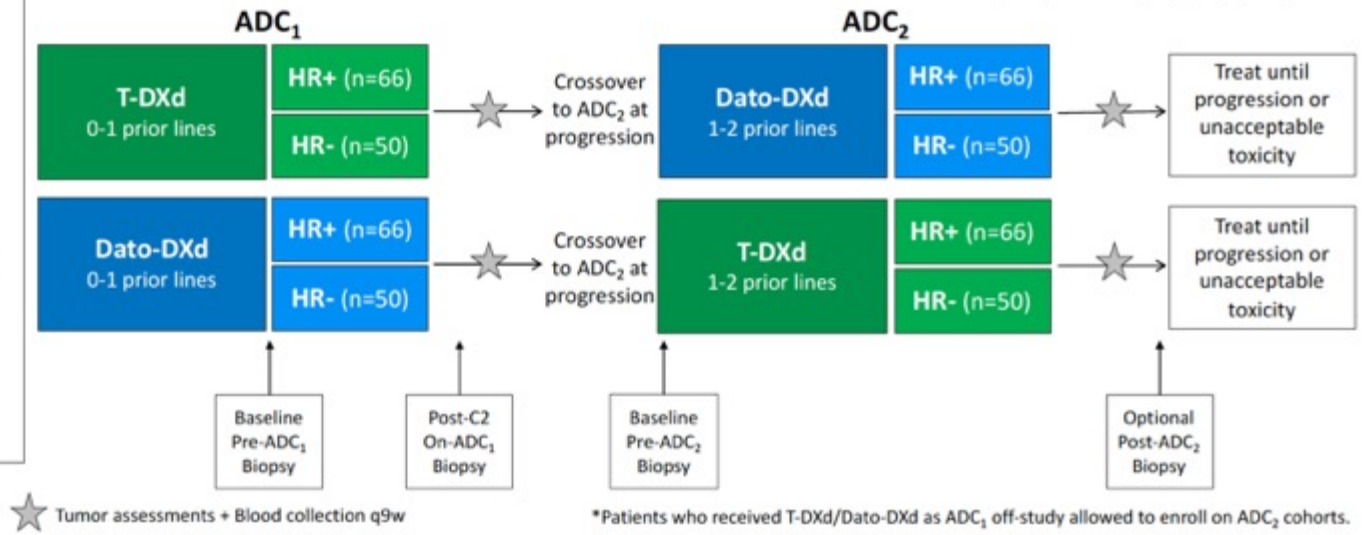
Huppert L, et al. SABCS 2023. Abstract PS08-04

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.

Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR



Role of SG after T-DXd in HER2 low:
- US Series trial
- BC Cancer trial (HR+)

SERIES Study:
PI: Reshma Mahtani

N=75

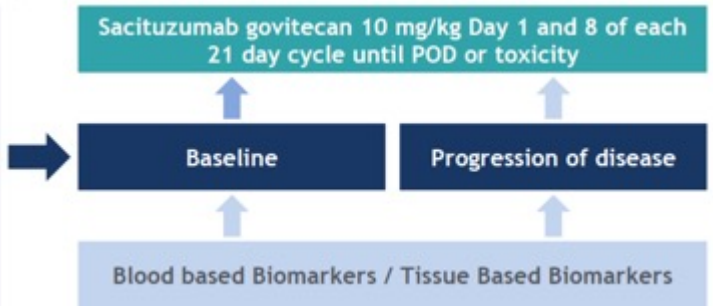
HR+/HER2 LOW (IHC 1+/2+ &ISH-) mBC

Refractory to at least one prior endocrine therapy

Received >1≤ 4 chemotherapies in the metastatic setting

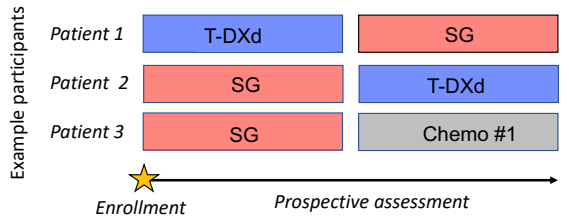
CDK4/6i (in adjuvant or metastatic setting)

Trastuzumab deruxtecan*



Registry Sequencing Study:
PI: Laura Huppert

Cohorts 1 & 2: Enrollment Prior to ADC #1



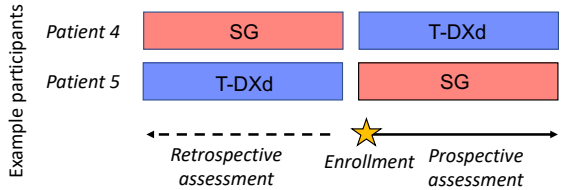
Cohort 1: HR+/HER2- HER2 low
~35 patients

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
    - Sequencing with standard chemotherapy – best foot forward or individualize for tumor biology/extent of 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!**
  - Do we need to define HER2 low?
  - Sequencing of ADCs
  - Understanding resistance.
- **Toxicity management is critical**
  - Combination data with radiation largely lacking


Thank you!