SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM®
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Antibody Drug Conjugates: Solo and in Symphony – Real-World Performance Insights

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Disclosure Information

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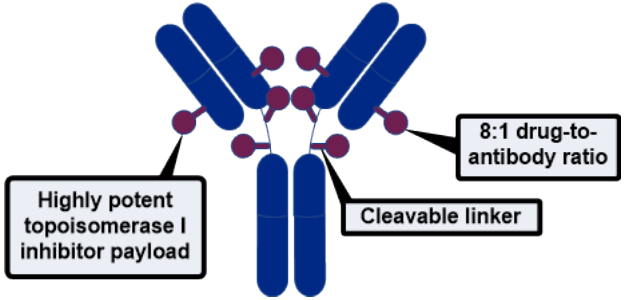
Current landscape of ADCs in HER2-negative MBC

Trastuzumab deruxtecan (T-DXd)

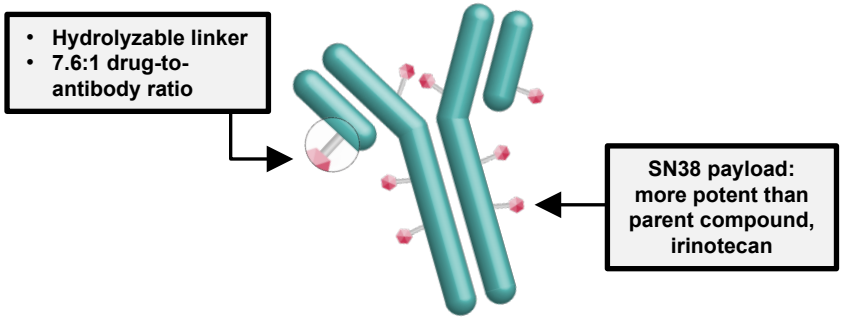
HER2-directed ADC



Unresectable or metastatic **HER2-low** breast cancer (IHC 1+ or IHC 2+/ISH-) after a prior chemotherapy in the metastatic setting or disease recurrence during or within 6 months of completing adjuvant chemotherapy

Sacituzumab govitecan (SG)

TROP2-directed ADC



Unresectable locally advanced or metastatic **HR+/HER2-** breast cancer after endocrine therapy and ≥2 additional systemic therapies for metastatic disease

Unresectable locally advanced or metastatic **TNBC** after ≥2 prior systemic therapies, at least one of them for metastatic disease

Modified from Bardia A et al. ESMO 2020; Modi S et al. ASCO 2022.

Current landscape of ADCs in HER2-negative MBC

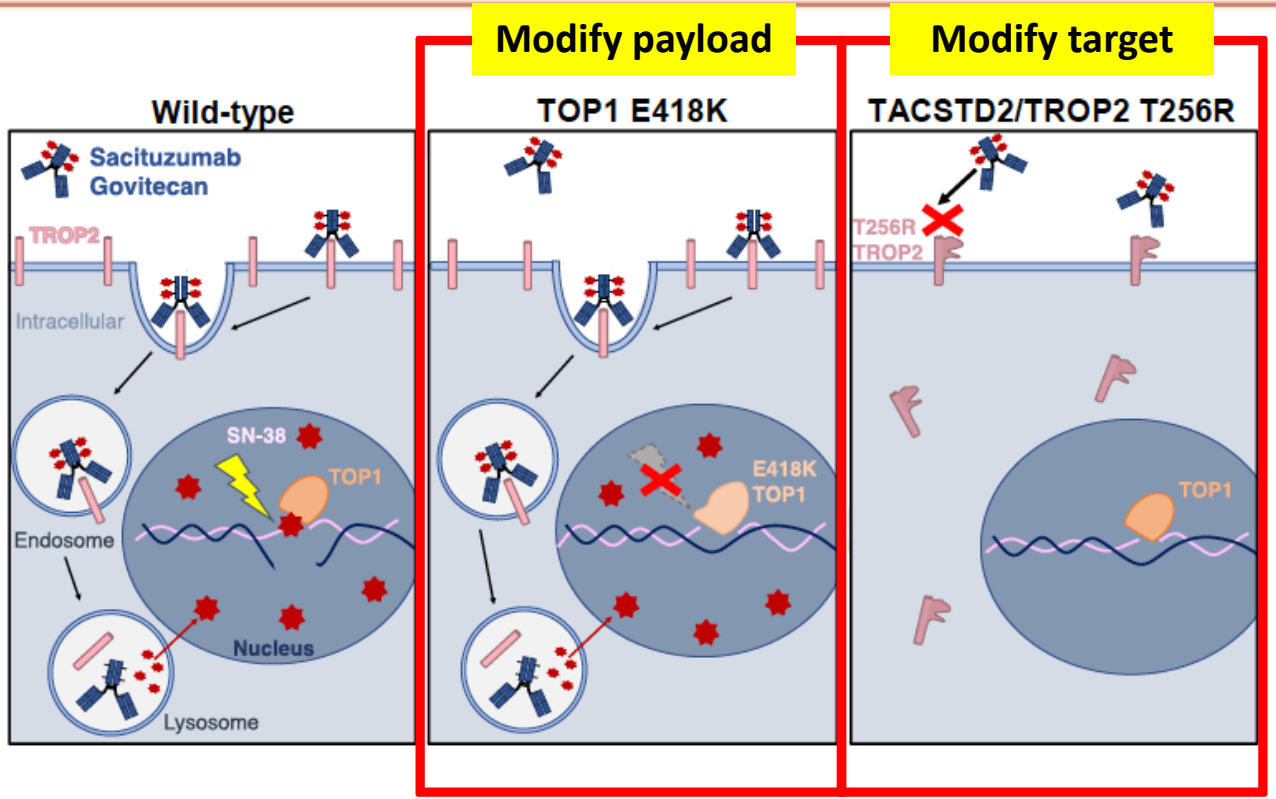
	HR+/HER2- BC			TNBC	
ADC trials in MBC	**DESTINY-Breast04**	**TROPION-Breast01**	**TROPiCS-02**	**DESTINY-Breast04**	**ASCENT**
Treatment arms	T-DXd (HER2) vs TPC	Dato-DXd (TROP2) vs TPC	SG (TROP2) vs TPC	T-DXd (HER2) vs. TPC	SG (TROP2) vs. TPC
HER2 status	1+, 2+/ISH-	0, 1+, 2+/ISH-	0, 1+, 2+/ISH-	1+, 2+/ISH-	0, 1+, 2+/ISH-
Prior chemotherapy for MBC	1-2	1-2	2-4	1-2	≥1
Median PFS HR (95% CI)	9.6 vs 4.2 mo. HR 0.37 (0.30-0.56)	6.9 vs 4.9 mo. HR 0.63 (0.52-0.76)	5.5 vs 4.0 mo. HR 0.65 (0.53-0.81)	6.3 vs 2.9 mo. HR 0.29 (0.15-0.57)	5.6 vs 1.7 mo. HR: 0.41 (0.32-0.52)
Median OS HR (95% CI)	23.9 vs 17.6 mo. HR 0.69 (0.55-0.87)	N/A HR 0.84 (0.62–1.14)	14.5 vs 11.2 mo. HR 0.79 (0.65-0.95)	17.1 vs 8.3 mo. HR 0.58 (0.31-1.08)	12.1 vs 6.7 mo. 0.48 (0.38-0.59)
ORR	52.6% vs 16.3%	36.4% vs 22.9%	21% vs 14%	50.0% vs 16.7%	35% vs 5%

1. Is there a preferred initial ADC?

2. Is there a role for sequencing of ADCs?

Modi S et al. ESMO 2023; Bardia A et al. ESMO 2023; Tolaney S et al. ASCO 2023; Bardia A et al. NEJM 2021.

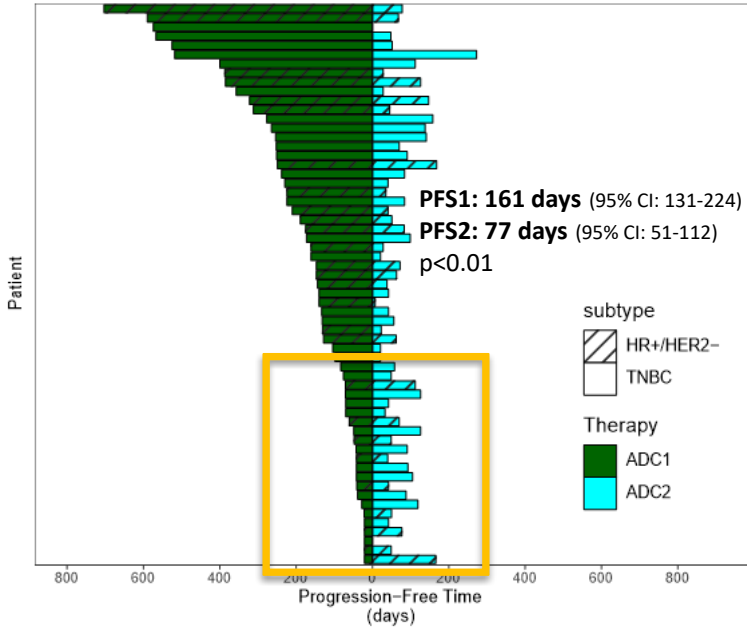
Mechanisms of resistance to ADCs

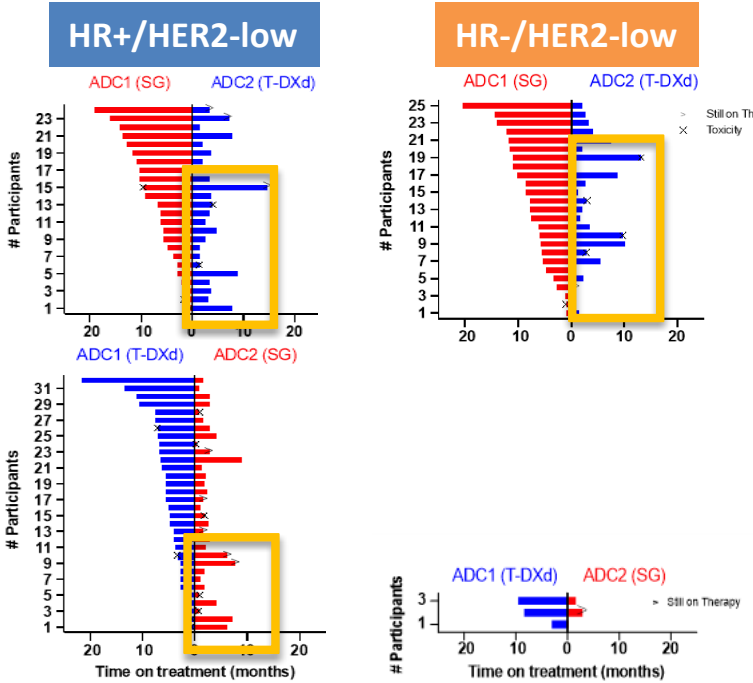


Coates et al. Cancer Discov 2021;11(10):2436-45.

Is there benefit with ADC2 after ADC1?

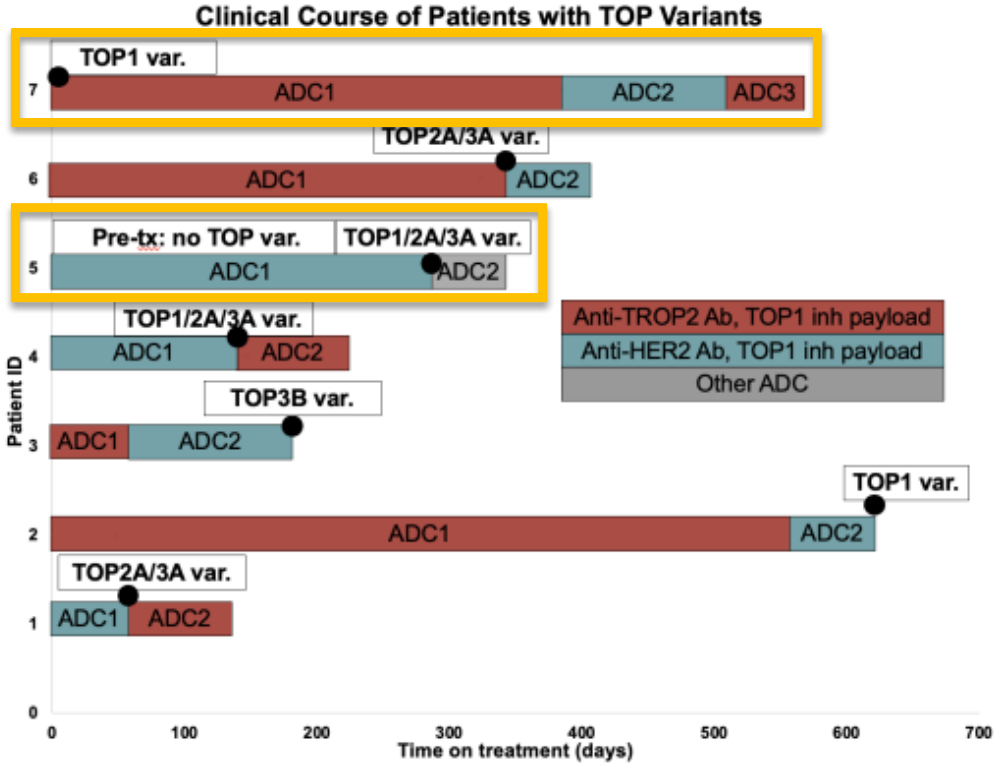
- Significantly shorter median TTP with ADC2 vs ADC1: >, ≈, or < than other standard therapy (i.e., chemotherapy)?
- How to identify patients who appear to derive similar or greater benefit from ADC2 than ADC1?





Abelman RO et al. SABCS 2023; Huppert LA et al. SABCS 2023.

Cross-resistance to TOP1inh ADCs



N=20 pts with available tissue WES

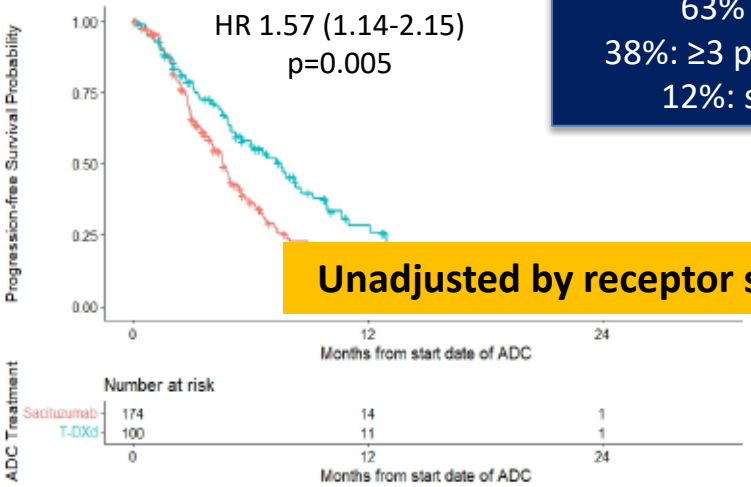
- TOP variants (resistance to payload): time point of emergence?
- Genomic alterations that confer resistance to target?
- Other mechanisms of resistance?
  - ADC intracellular trafficking
  - Lysosomal metabolism
  - Increased drug efflux of payload (ABC transporters)

Abelman RO et al. SABCS 2023.

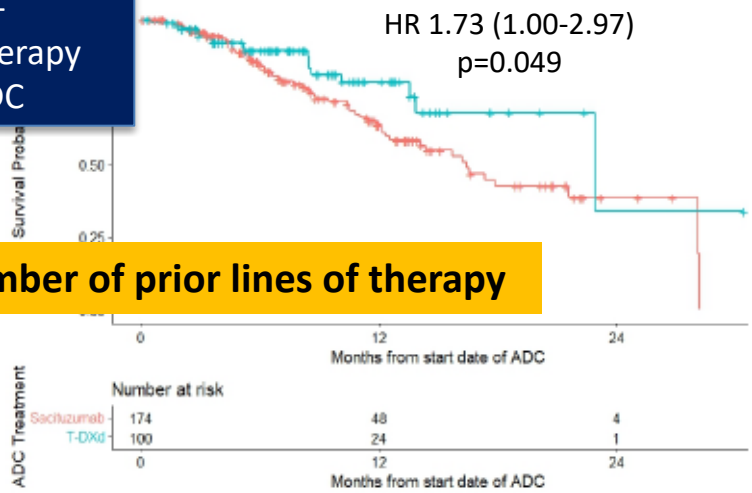
Is there a preferred initial ADC: TROP2 vs HER2?

N=274 pts with HER2-low MBC
63% HR+ / 37% HR-
38%: ≥3 prior lines of therapy
12%: subsequent ADC

PFS for Initial ADC treatment
HR 1.57 (1.14-2.15)
p=0.005



OS for Initial ADC treatment
HR 1.73 (1.00-2.97)
p=0.049



Unadjusted by receptor status or number of prior lines of therapy

PFS	Level	Events (Rec: Deaths)	Median (95% CI)	p-value	HR (95% CI)	p-value
Initial treatment	T-DXd	100:56	7.6 mo (5.3 – 9.9)	0.005	Ref	
	SC	174:131	4.6 mo (4.0 – 5.5)		1.57 (1.14 – 2.15)	0.005

OS	Level	Events (Rec: Deaths)	Median (95% CI)	p-value	HR (95% CI)	p-value
Initial treatment	T-DXd	100:17	22.9 mo (22.9 – NE)	0.049	Ref	
	SC	174:58	16.4 mo (12.6 -NE)		1.73 (1.00 – 2.97)	0.049

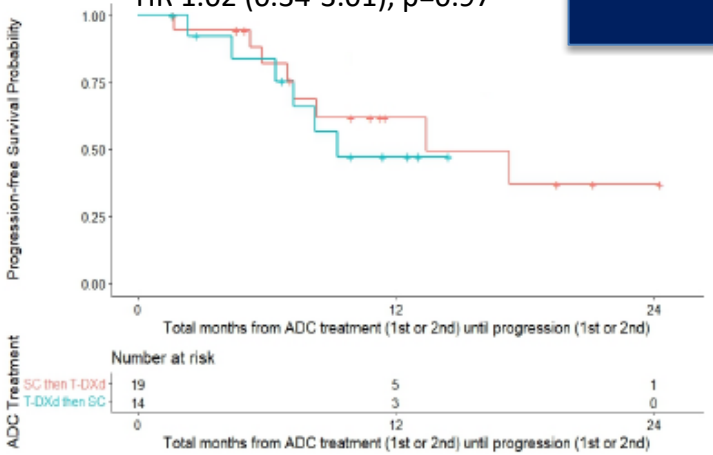
Raghavendra AS et al. SABCS 2023.

Is there a preferred sequence of TROP2/HER2 ADCs?

PFS2 for Sequential ADC Treatments (=progression on both ADCs)

HR 1.02 (0.34-3.01), p=0.97

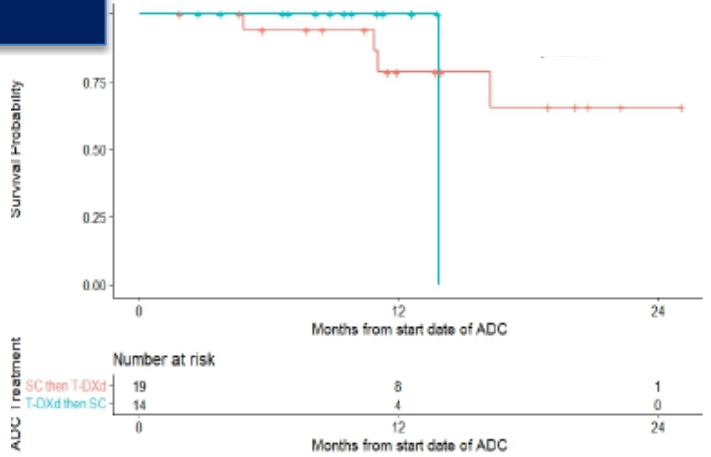
33 pts received sequential ADC:
19 SG → T-DXd
14 T-DXd → SG



PFS	Events (Rec: Deaths)	Median (95% CI)	p-value	HR (95% CI)	p-value
SC →T-DXd	19:8	5.5 mo (2.1 – NE)	0.97	Ref	
T-DXd → SC	14:6	2.4 mo (1.6 – NE)		1.02 (0.34 – 3.01)	0.97

OS for Sequential ADC Treatments

HR 0.78 (0.08-7.94), p=0.984



OS	Events (Rec: Deaths)	Median (95% CI)	p-value	HR (95% CI)	p-value
SC →T-DXd	19:4	NE (16.2 – NE)	0.84	Ref	
T-DXd → SC	14:1	13.9 mo (NE - NE)		0.78 (0.08 – 7.94)	0.84

Raghavendra AS et al. SABCS 2023.

Is there a preferred sequence of TROP2/HER2 ADCs?

Median PFS			Abelman et al.		Poumeaud et al.		Huppert, Mahtani et al.	
HR+	SG → T-DXd	ADC1 (SG)	N=7	8.3 mo	N/A		N=24	8.0 mo
		ADC2 (T-DXd)		5.6 mo				3.7 mo
	T-DXd → SG	ADC1 (T-DXd)	N=11	4.9 mo	N=56	2.7 mo	N=32	5.5 mo
		ADC2 (SG)		1.7 mo		2.3 mo		2.6 mo
HR-	SG → T-DXd	ADC1 (SG)	N=14	7.7 mo	N=100	4.9 mo	N=25	7.8 mo
		ADC2 (T-DXd)		2.8 mo		3.2 mo		2.8 mo
	T-DXd → SG	ADC1 (T-DXd)	N=7	1.4 mo	N/A		N=3	NR
		ADC2 (SG)		3.1 mo				NR

Is there a preferred sequence of TROP2/HER2 ADCs?

Median PFS			Abelman et al.		Median 2 (0-9) before ADC1 Poumeaud et al.		Median 2 (0-5) before ADC1* Huppert, Mahtani et al.	
HR+	SG → T-DXd	ADC1 (SG)	N=7	8.3 mo	N/A		N=24	8.0 mo
		ADC2 (T-DXd)		5.6 mo				3.7 mo
	T-DXd → SG	ADC1 (T-DXd)	N=11	4.9 mo	N=56	2.7 mo	N=32	5.5 mo
		ADC2 (SG)		1.7 mo		2.3 mo		2.6 mo
HR-	SG → T-DXd	ADC1 (SG)	N=14	7.7 mo	N=100	4.9 mo	N=25	7.8 mo
		ADC2 (T-DXd)		2.8 mo		3.2 mo		2.8 mo
	T-DXd → SG	ADC1 (T-DXd)	N=7	1.4 mo	N/A		N=3	NR
		ADC2 (SG)		3.1 mo				NR

Median 4 lines before ADC2

Median 4 (1-11) before ADC2

*HR- T-DXd → SG: median 3 (1-5) lines

Is there a preferred sequence of TROP2/HER2 ADCs?

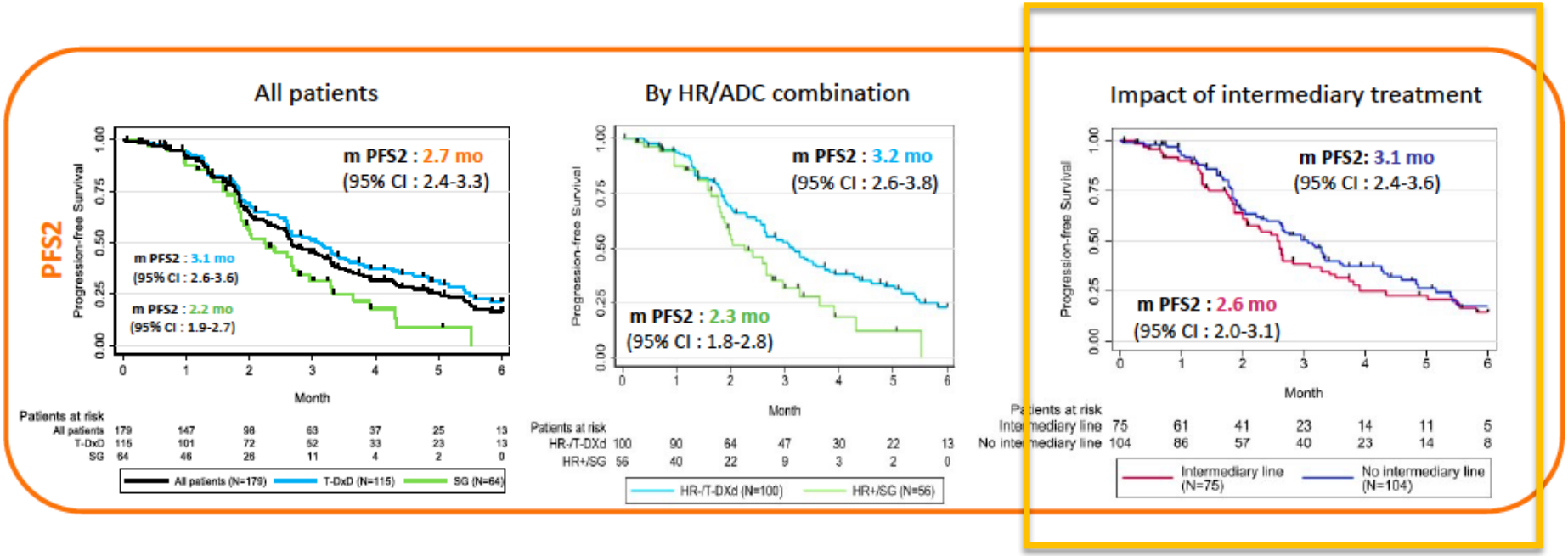
Median PFS			Abelman et al.		Poumeaud et al.		Intervening therapies	Huppert, Mahtani et al.		Intervening therapies
HR+	SG → T-DXd	ADC1 (SG)	N=7	8.3 mo	N/A			N=24	8.0 mo	47.8%
		ADC2 (T-DXd)		5.6 mo					3.7 mo	
	T-DXd → SG	ADC1 (T-DXd)	N=11	4.9 mo	N=56	2.7 mo	28.1%		5.5 mo	42.4%
		ADC2 (SG)		1.7 mo		2.3 mo			2.6 mo	
HR-	SG → T-DXd	ADC1 (SG)	N=14	7.7 mo	N=100	4.9 mo	49.6%		7.8 mo	40.0%
		ADC2 (T-DXd)		2.8 mo		3.2 mo			2.8 mo	
	T-DXd → SG	ADC1 (T-DXd)	N=7	1.4 mo	N/A			N=3	NR	66.7%
		ADC2 (SG)		3.1 mo					NR	

Median 4 lines before ADC2

Median 4 (1-11) before ADC2

*HR- T-DXd → SG: median 3 (1-5) lines

Does immediate vs delayed sequential therapy matter?

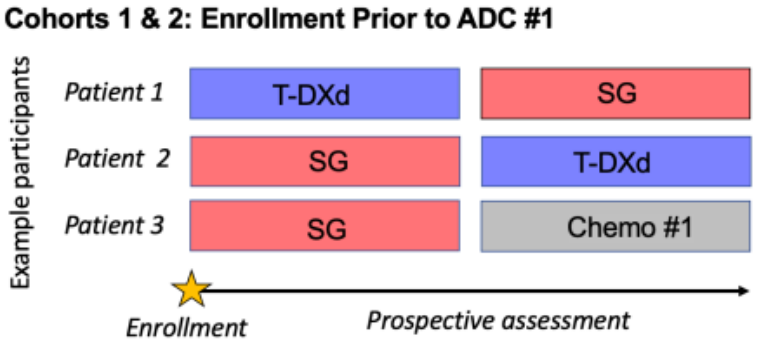


Poumeaud F et al. SABCS 2023.

Conclusions

- Preferred initial ADC approach remains unclear and may depend on multiple factors (e.g., receptor status, cell surface target expression, intrinsic resistance to payload):
  - With new ADCs in development, will there be a preferred ADC1 (“one size fits all” vs. biomarker-informed approach): direct comparisons of ADCs, correlative science
- After progression on ADC1:
  - Unknown if clinical outcomes with ADC2 are >, <, or ≈ to other therapies: If/how will ADC2 (and beyond) be compared to standard chemotherapy?
  - Subgroup of patients derive clinical benefit from ADC2: How to identify these patients?
- Optimal sequence of TROP2 or HER2 approved ADCs remains unclear
- Understanding the primary mechanism(s) that drive ADC resistance is key to inform subsequent treatment strategies
- Given limitations of real-world data (retrospective, tumor heterogeneity, patient selection bias, lines of prior therapy), prospective concerted research efforts are needed

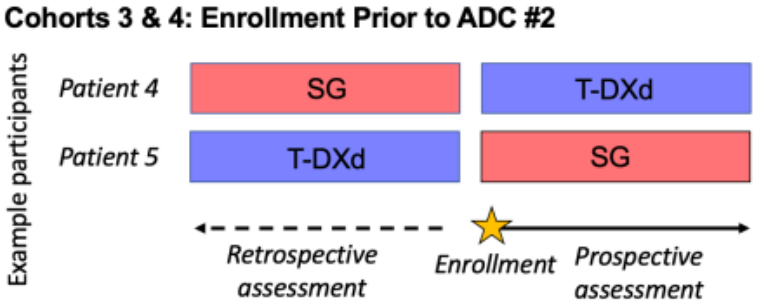
TBCRC Registry of Sequential Use of ADCs for HER2-low MBC



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



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

Study Chairs: L. Huppert, H. Rugo

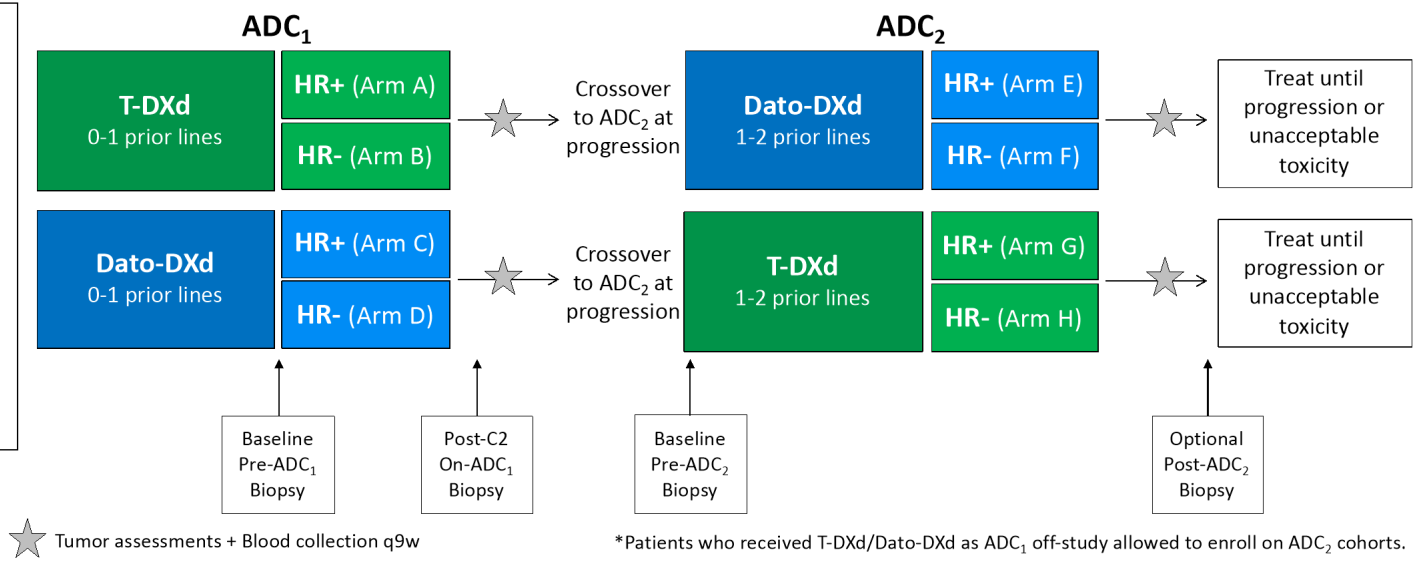
TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd: TRADE-DXd

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

Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low breast cancer (any prior primary or metastatic tumor) defined as IHC 1+ or 2+/ISH non-amplified
- Most recent pathology: HER2 IHC 0 or HER2-low
- Measurable disease
- No prior topo-I inhibitor-based therapy

Allocation 1:1 to T-DXd or Dato-DXd as ADC_1



*Patients who received T-DXd/Dato-DXd as ADC_1 off-study allowed to enroll on ADC_2 cohorts.

Study Chair/Overall PI: A. Garrido-Castro

Acknowledgements

- Hal Burstein
- Nancy U. Lin
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