



Comparison of Trastuzumab Deruxtecan and Sacituzumab Govitecan in HER2-Negative Metastatic Breast Cancer: A Large Real-World Data Analysis

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Background

Trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) are antibody-drug conjugates (ADCs) increasingly used in HER2-negative breast cancer. We hypothesized that treatment benefit would vary across HER2-null, HER2-ultra-low, and HER2-low subgroups of HER2-negative breast cancer patients. We also aimed to study the clinical impact of different sequencing of the two ADCs.

Methods

Patient data collection

- A total of 4,033 breast tumor specimens that received T-DXd and/or SG and underwent comprehensive tumor profiling at Caris Life Sciences (Phoenix, AZ, USA) were included.
- Real-world clinical data were obtained from insurance claims.
 - In patients treated with a single ADC, time-on-treatment (TOT) was determined as the interval from the initiation to the conclusion of that treatment
 - In patients treated with both ADCs, TOT2 was determined from the start of the first ADC to the last of the second ADC.
 - Overall survival (OS) was defined as the period from ADC treatment initiation to the date of the patient's last known clinical activity.
 - Kaplan-Meier survival estimates were generated for cohorts defined by molecular characteristics. Hazard ratios (HR) were computed utilizing the Cox proportional hazards model, and significant differences in survival times were assessed with the log-rank test, where P < 0.05 was considered significant.

HER2, Estrogen Receptor (ER), and Progesterone Receptor (PR) status

- HER2-positive: IHC 3+ with >10% of cells positive (excluded from analysis).
- HER2-low: IHC 1+ with >10% of cells positive, or IHC 2+ with >10% of cells positive combined with a negative CISH result.
- HER2-ultra-low: IHC 1+, 2+, or 3+ with ≤10% of cells positive.
- HER2-null: IHC 0+.

ASCO/CAP 2023 (Wolff 2023, *J Clin Oncol*) and DESTINY-Breast04 trial (Modi 2022, *NEJM*)

Additionally, the presence of ER and PR was determined by IHC using the CONFIRM Estrogen Receptor (SP1) antibody and CONFIRM Progesterone Receptor (1E2) antibody [Roche (Ventana)], with a positivity threshold of ≥1% for both.

Results

Table 1: Patient characteristics

	HER2 category	Single ADC-treated		P-value	Both ADCs		P-value	Total, N (%)
		T-DXd only, N (%)	SG only, N (%)		T-DXd before SG, N (%)	SG before T-DXd, N (%)		
Age	HER2-null	318 (22)	1218 (67)	<0.0001	127 (30)	151 (42)	0.0021	1815 (45)
	HER2-ultra-low	336 (23)	316 (17)		103 (25)	83 (23)		838 (21)
	HER2-low	789 (55)	273 (15)		190 (45)	126 (35)		1380 (34)
	Median Age	60	58		57.5	58		58
Gender	Interquartile Range	51-68	48-67	0.1	50-66	47-65	0.1	49-67
	Female	1427 (99)	1799 (100)		416 (99)	355 (99)		3997 (99)
Race	Asian or Pacific Islander	62 (4)	50 (3)	<0.0001	21 (5)	13 (4)	<0.0001	146 (4)
	Black or African American	175 (12)	343 (19)		56 (13)	64 (18)		638 (16)
	White	861 (60)	900 (50)		239 (57)	167 (46)		2167 (54)
	Other	47 (3)	74 (4)		2 (0)	18 (5)		141 (3)
	Unknown	298 (21)	440 (24)		102 (24)	98 (27)		938 (23)
Ethnicity	Hispanic or Latino	101 (7)	165 (9)	<0.01	29 (7)	31 (9)	0.6	326 (8)
	Not Hispanic or Latino	1065 (74)	1224 (69)		292 (70)	251 (70)		2832 (70)
	Unknown	277 (19)	418 (23)		99 (24)	78 (22)		872 (22)
Specimen Site	Primary/Local	433 (30)	726 (40)	<0.0001	128 (30)	139 (39)	<0.0001	1426 (35)
	Non-Visceral	461 (32)	588 (33)		118 (28)	125 (35)		1292 (32)
	Visceral	529 (37)	464 (26)		170 (40)	92 (26)		1255 (31)
	Unclear/Other	20 (1.4)	29 (1.6)		4 (1)	4 (1)		57 (1)
Total		1443	1807		420	360		4030

SG-only patients were preferentially HER2-null and T-DXd-only patients were far more commonly HER2-low.

Fig. 1: Time-on-treatment (TOT) with TDX-d and SG according to HER2 status. Kaplan-Meier survival analysis of TOT with TDX-d (a) and SG (b) in HER2-null (blue lines), HER2-ultra-low (orange lines), and HER2-low (green lines).

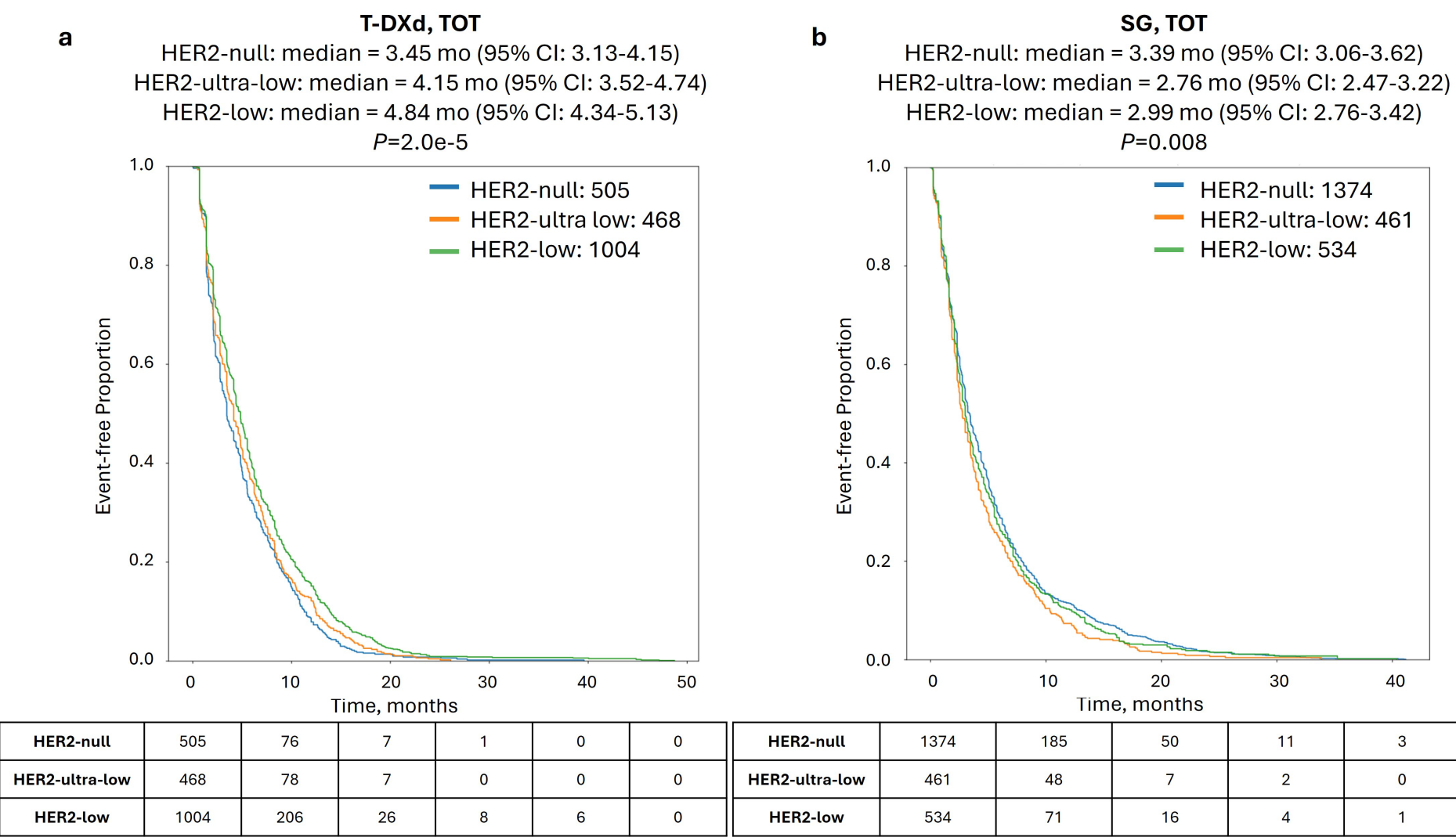
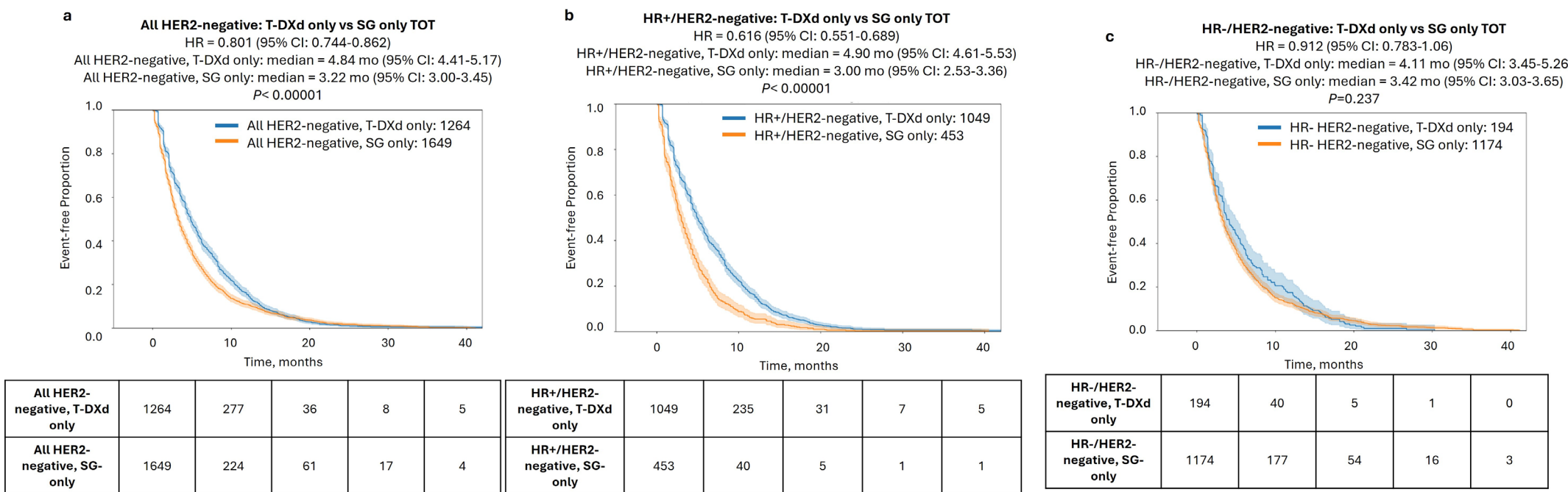


Fig. 2: Time-on-treatment (TOT) with T-DXd only vs. SG only. Kaplan-Meier curves show TOT with T-DXd only vs. SG only in all HER2-negative patients (a), HR+/HER2-negative patients (b), and HR-/HER2-negative patients (c).



Results

Table 2: Time-on-treatment (TOT) with T-DXd only and SG only in HER2 stratified cohorts

HER2 category	All			
	TOT (T-DXd; SG), months	N (T-DXd; SG)	HR (95% CI)	P-value
HER2-null	4.7; 3.4	262; 1116	1.1 (1-1.3)	0.053
HER2-ultra-low	4.8; 3.0	295; 289	1.4 (0.59-0.83)	<0.001
HER2-low	4.9; 3.5	707; 244	1.2 (0.83-1)	0.011

HER2 category	HR+				HR-			
	TOT (T-DXd; SG), months	N (T-DXd; SG)	HR (95% CI)	P-value	TOT (T-DXd; SG), months	N (T-DXd; SG)	HR (95% CI)	P-value
HER2-null	4.8; 3.0	209; 277	0.67 (0.56-0.83)	<0.001	4.6; 3.5	48; 822	0.91 (0.71-1.3)	0.6
HER2-ultra-low	5.1; 2.5	245; 99	0.56 (0.45-0.71)	<0.001	3.2; 3.0	46; 188	0.91 (0.63-1.3)	0.4
HER2-low	5.1; 3.1	595; 77	0.67 (0.53-0.83)	<0.001	4.2; 3.9	100; 164	0.91 (0.77-1.3)	0.7

Fig. 3: T-DXd outcomes according to HER2 and HR status. (a, b) Forest plots summarize hazard ratios (HRs) for T-DXd-only time-on-treatment (TOT) (a) and overall survival (OS) (b) in HR+ vs. HR- groups in all HER2-negative tumors and HER2-negative subsets.

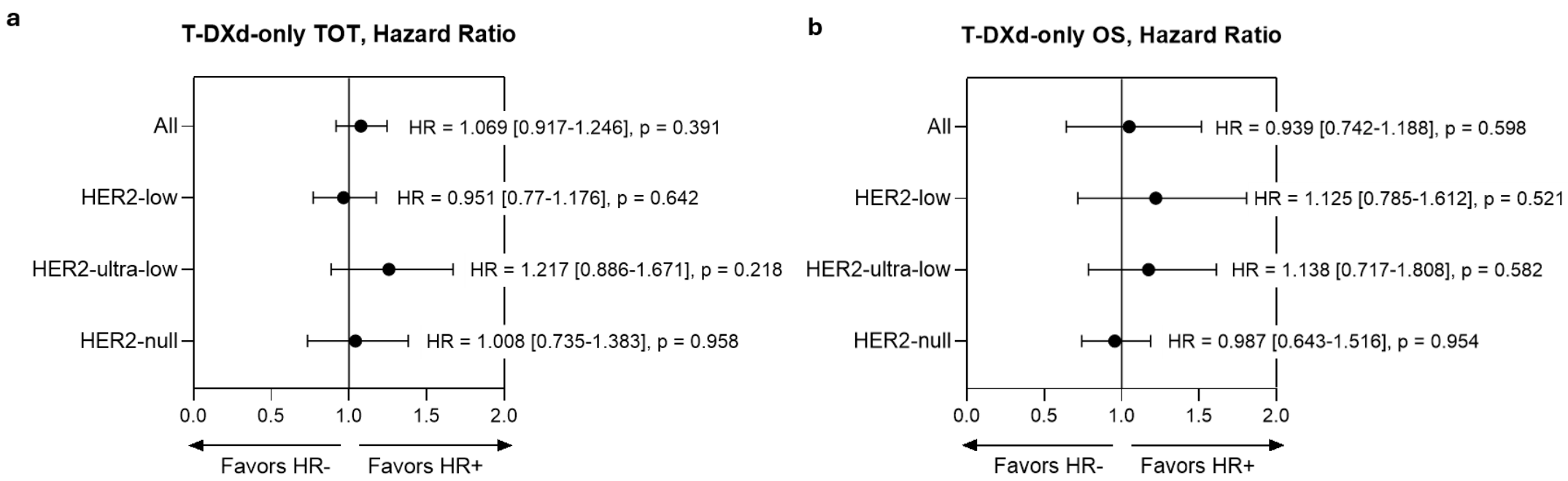
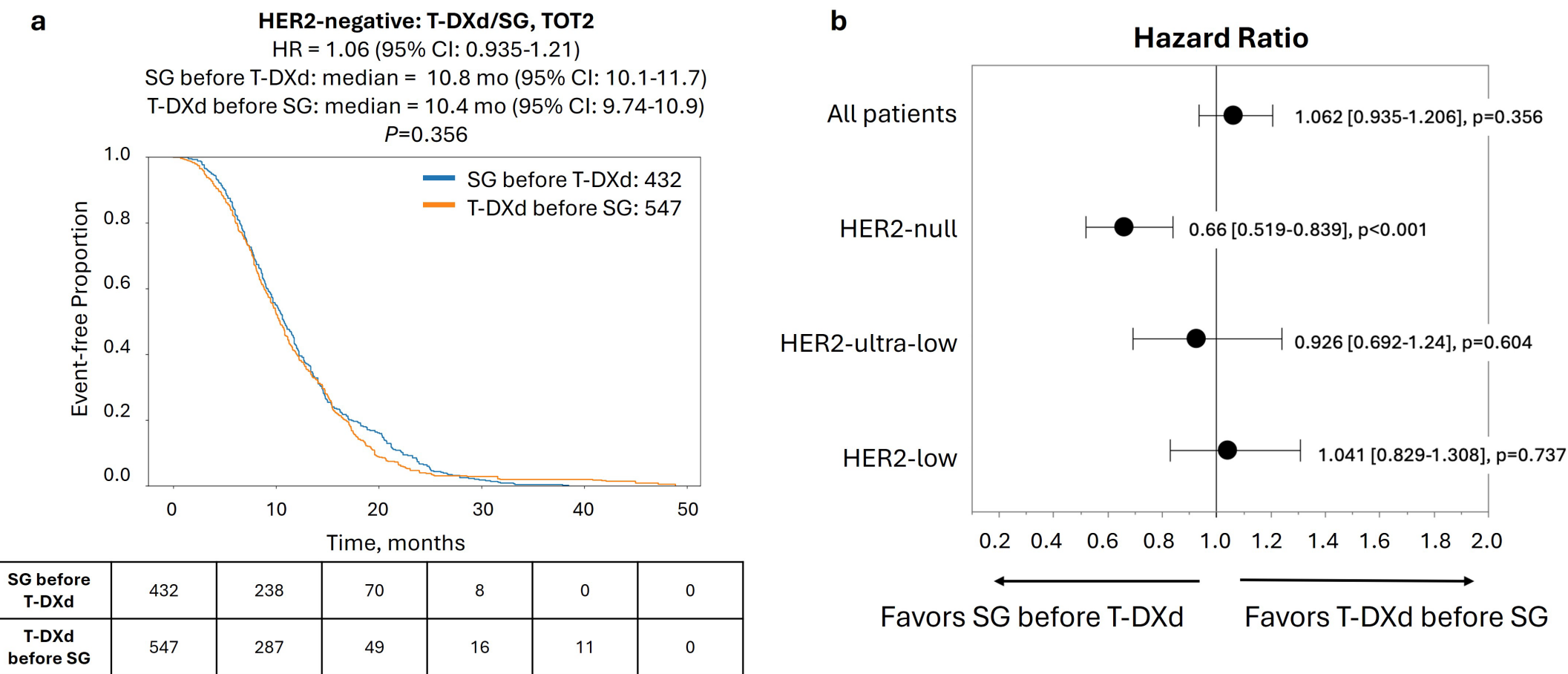
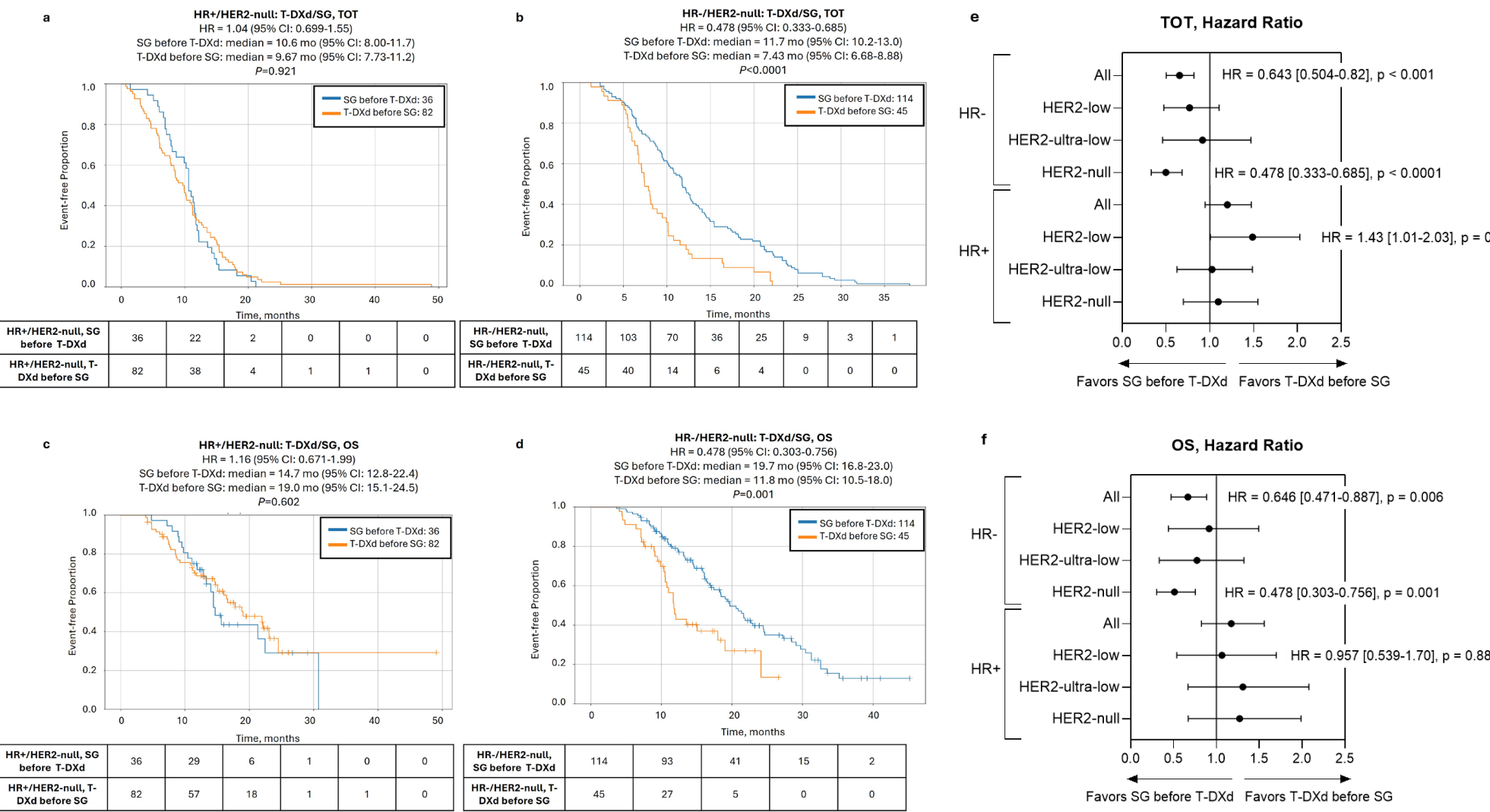


Fig. 4: Time-on-treatment from start of first ADC to end of second ADC (TOT2) for patients in the full HER2-negative cohort according to treatment sequence of T-DXd and SG. (a) Kaplan-Meier curve shows median TOT2 of patients treated with SG before T-DXd (blue lines) vs. T-DXd before SG (orange lines). (b) Forest plot of hazard ratios for TOT2 with T-DXd before SG vs. SG before T-DXd in patient cohorts according to HER2 status.

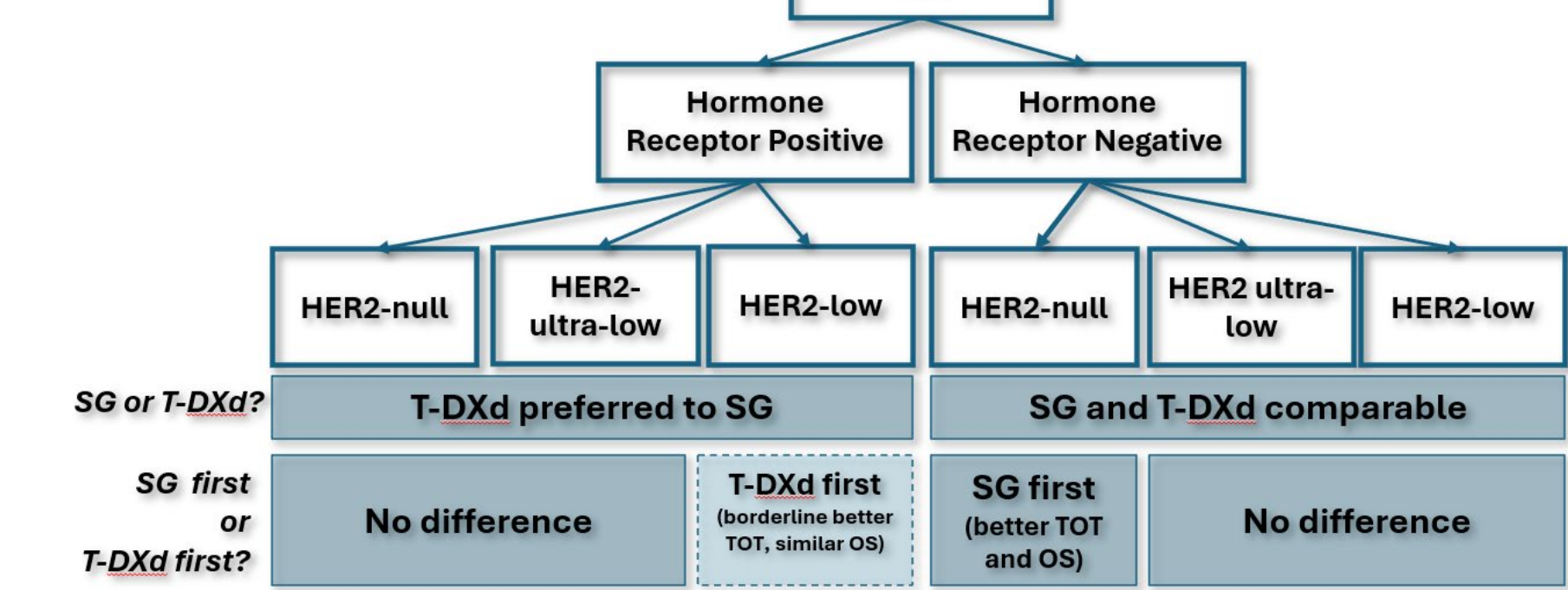


Results

Fig. 5: ADC sequencing-associated outcomes in patients with HER2-null tumors according to HR status. Kaplan-Meier curves show time-on-treatment from start of first ADC to end of second ADC (TOT2) (a, b) and overall survival (OS) (c, d) comparing SG before T-DXd (blue lines) vs. T-DXd before SG (orange lines) in HR+/HER2-null (a, c) and HR-/HER2-null groups (b, d)



Conclusions



- T-DXd offers a significantly prolonged TOT compared to SG in HR+ MBC across HER2-negative categories, while both agents perform comparably in HR- tumors.
- Sequencing preferences emerge only in HR- tumors lacking any HER2 expression (HR-/HER2-null), favoring SG-first as is shown by both TOT and OS; while outcome remains largely unaffected by sequence across other groups.

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