Nelle pazienti con carcinoma mammario metastatico HR- positivo/HER2-low e ultralow, non pretrattate con chemioterapia, è raccomandabile T-DXd rispetto a chemioterapia?

Q#2. Quale impatto nella pratica clinica ?

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Disclosure

Honoraria for Consultancy and Advisory Board from:

Roche, Novartis, Lilly, AstraZeneca, Pfizer, MSD, Daiichi Sankyo, Gilead, MenariniStemline, Merck, Exact Sciences.

DB-06 study design

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

HER2-low = 713
HER2-ultralow = 153†

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

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)

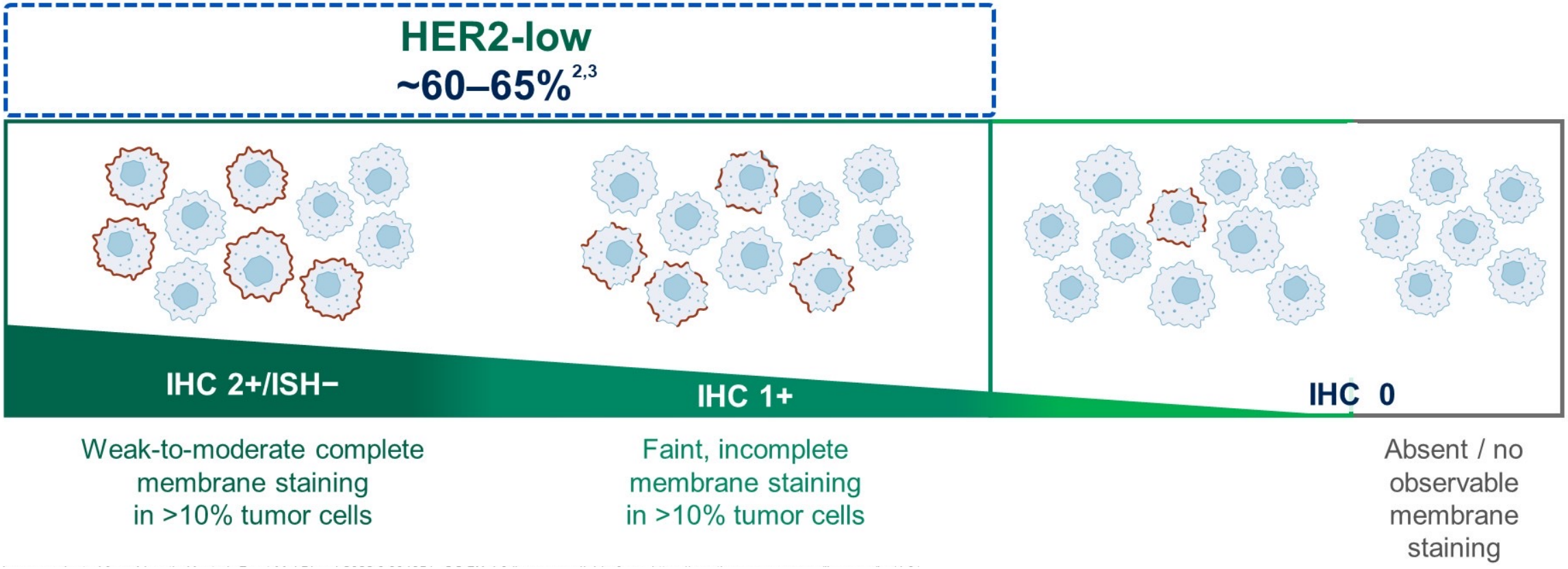
Other secondary

- 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‡

*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+); †HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data); ‡to be presented separately
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
NCT04494425. Updated. April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

DB-06: What about HER2-low

DB-06: What about HER2-low



HER2-status

Membrane staining pattern	Tumor cells	Score	Classical category	Expanded spectrum
Intense, complete	>10%	3+	HER2+	HER2+
Weak-to-moderate, complete	>10%	2+	HER2+ (if ISH+)	HER2+ (if ISH+)
			HER2- (if ISH-)	HER2-low (if ISH-)
Faint/barely perceptible, incomplete	>10%	1+	HER2-	HER2-low
Faint/barely perceptible, incomplete	≤10%	0	HER2-	HER2 Ultra low
No staining			HER2-	HER2-zero

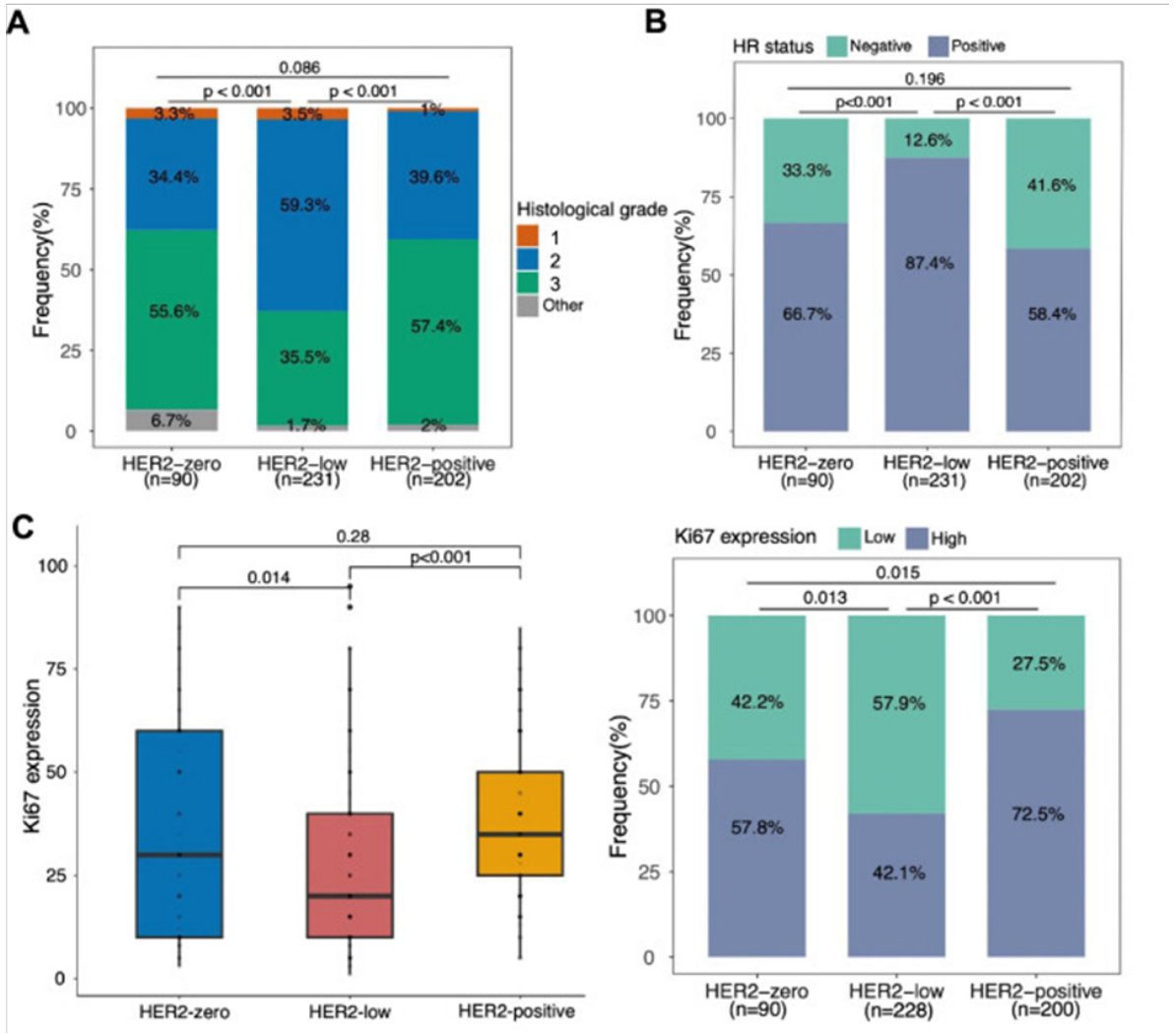
Abbreviations: IHC, immunohistochemistry; ISH, *in situ* hybridization; HER2, human epidermal growth factor receptor 2.

The introduction of novel anti-HER2 ADC fhas transformed the traditional dichotomy of HER2 status to an expanded spectrum. However, the identification of HER2-low tumors is challenged by methodological and analytical variables that might influence the sensitivity and reproducibility of HER2 testing

Fusco et al. Front Molec Path 2023

HER2-low heterogeneous phenotype

- More ER+
- Less Grade 3
- Lower Ki67

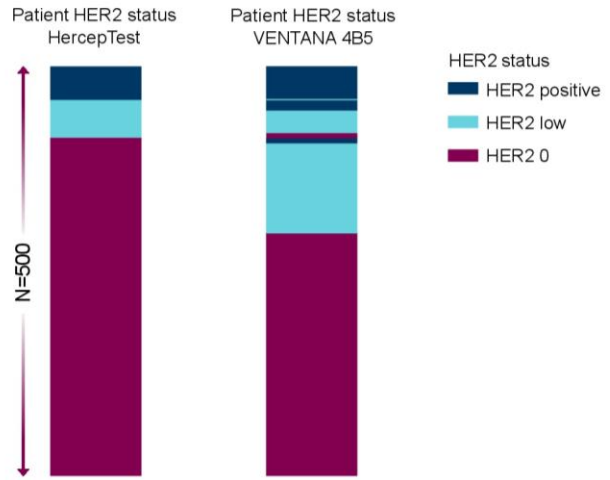


Zhang G, et al. BMC Med 2022

HER2-low heterogeneous characterization

Figure 2. Concordance Cohort: Concordance Between HercepTest and VENTANA 4B5 Assays Under Standard Scoring Conditions

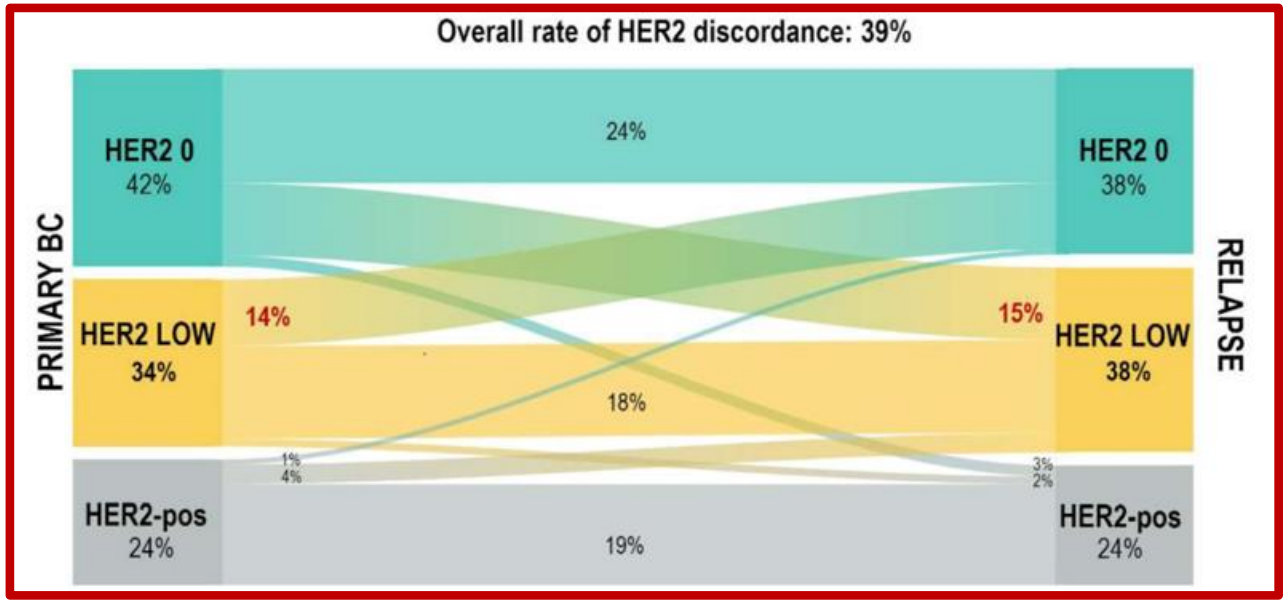
Breast Paired Classification N=500		Patient HER2 status (HercepTest IHC)			
		HER2 0, n (%)	HER2 low, n (%)	HER2 positive, n (%)	Total, n (%)
Patient HER2 status (VENTANA 4B5 IHC)	HER2 0, n (%)	298 (59.6)	5 (1.0)	0	303 (60.6)
	HER2 low, n (%)	108 (21.6)	28 (5.6)	1 (0.2)	137 (27.4)
	HER2 positive, n (%)	7 (1.4)	13 (2.6)	40 (8.0)	60 (12.0)
Total, n (%)		413 (82.6)	46 (9.2)	41 (8.2)	500 (100.0)



- There was a 73.2% (95% CI: 69.1-77.0%) overall percentage agreement between assays in classification
- VENTANA 4B5 tends to classify patients into higher HER2 categories than HercepTest, which was the primary driver of the discordance between the assays (**Figure 2**)

Scott M, et al. Poster 1021, ASCO 2021

	Central IHC Testing			
Local IHC Testing	**Score 0**	**Score 1+**	**Score 2+**	**Score 3+**
Score 0	15	78	9	0
Score 1+	1	35	8	4
Total	16	113	17	4

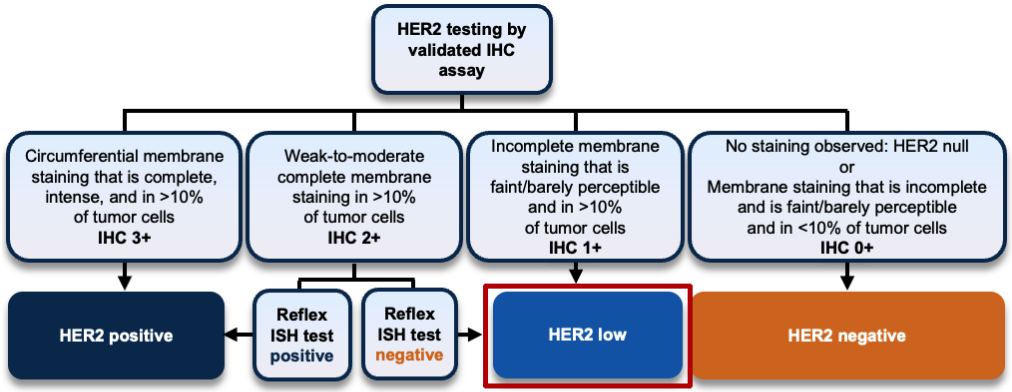


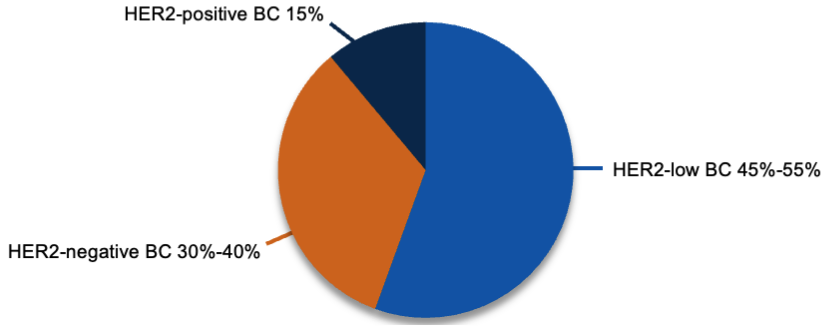
Miglietta F, et al. ESMO Breast 2021; Lambein K, et al. AJCP 2013

When test for HER2-low

the dynamic of HER2

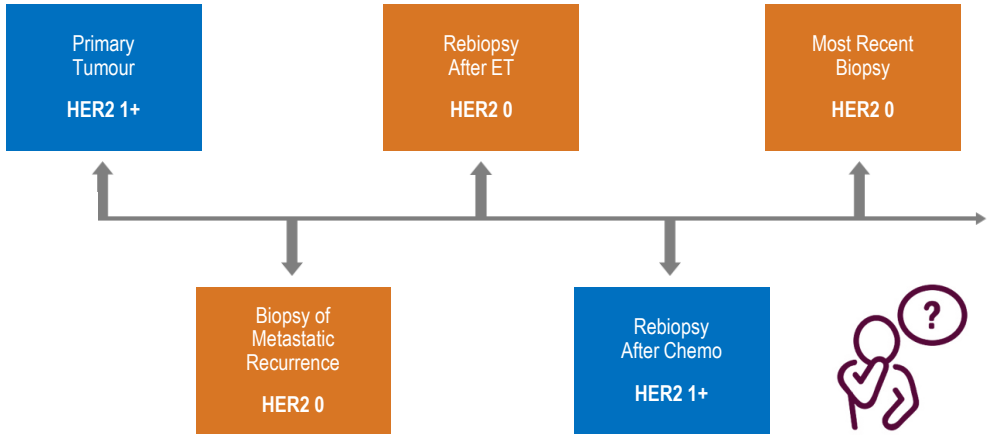
Static definition





Dynamic definition (real life)

- HER2-low status changes over time
- Which timepoint to use to define a tumour as HER2 low?

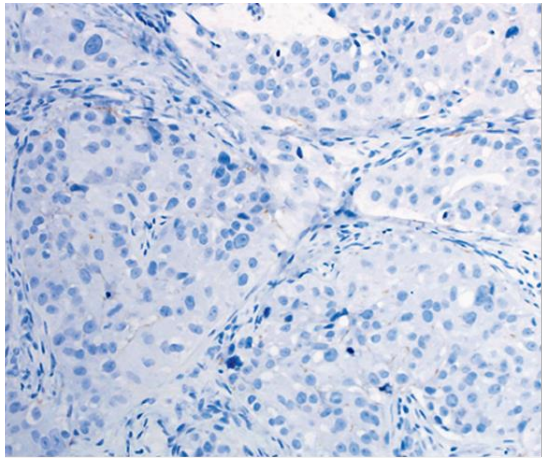


Tarantino P, *et al.* HER2-Low Breast Cancer: Pathological and Clinical Landscape. J Clin Oncol 2020;38(17):1951–62.

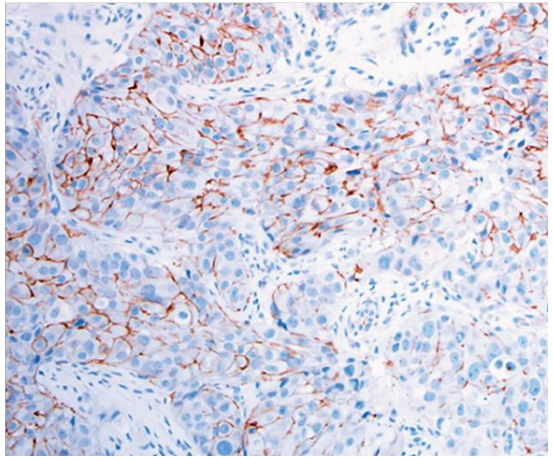
How test for HER2-low

different results with different assays

DAKO Poly-HercepTest



Ventana 4B5 antibody

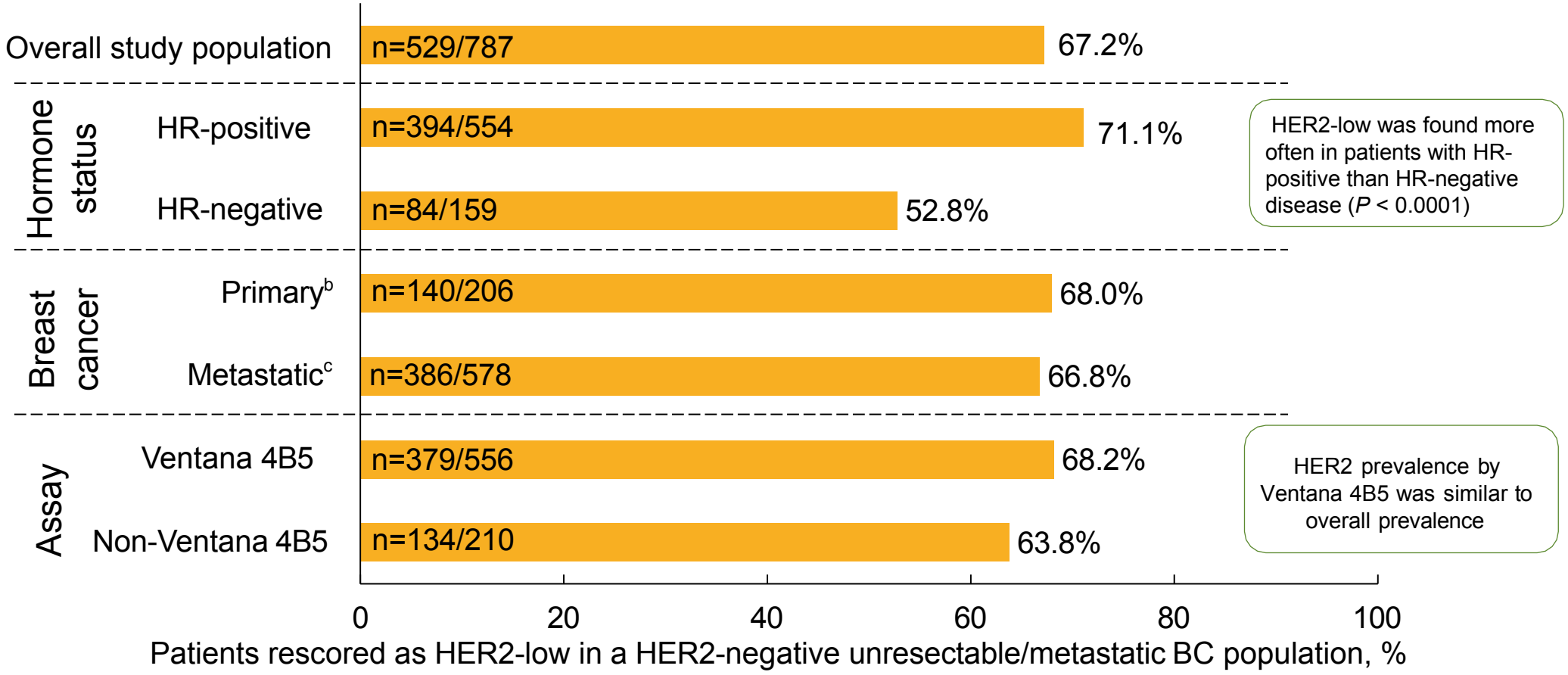


Zhang H, et al. Am J Clin Pathol. 2022;157:328-336

		PATHWAY 4B5				
		0	**1+**	**2+**	**3+**	**Total**
HercepTest (mAb)	**0**	35	0	0	0	**35**
	1+	17	8	0	0	**25**
	2+	4	12	13	1	**30**
	3+	0	0	2	27	**29**
	Total	**56**	**20**	**15**	**28**	**119**

Rueshoff J, et al. Virchows Arch 2022

HER2-low: different results at rescoring



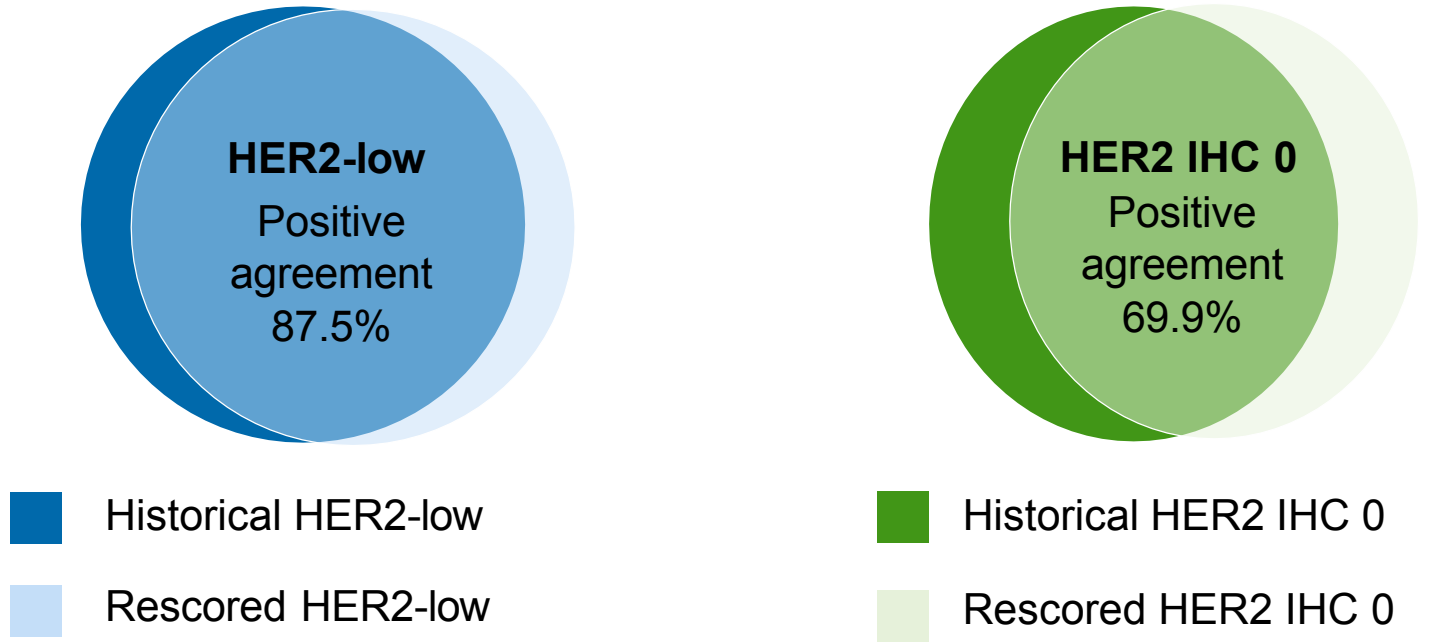
BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

[a] Two patients were missing HER2 rescore data. [b] Rescored biopsy sample dated before 30 days prior to unresectable/metastatic BC diagnosis date. [c] Rescored biopsy sample dated on/after 30 days prior to unresectable/metastatic BC diagnosis date.

Viale G et al. San Antonio Breast Cancer Symposium 2022

HER2-low and HER2 0: different results at rescoring

Overall concordance 81.3% (n = 639/786)[a]
Cohen K (95% CI): 0.583 (0.523-0.643)[b]



[a] Concordance includes only patients with both historical and rescored IHC scores available. [b] Indicates moderate agreement (defined as κ 0.4 to ≤ 0.6).[2]
BC, breast cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
1. Viale G et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-15. 2. Landis JR, Koch GG. *Biometrics*. 1977;33(1):159-174.

Viale G et al. San Antonio Breast Cancer Symposium 2022

Open issues

- Distinction b/w IHC score 0 vs 1+ is not pursued in the daily clinical practice
- Definition of 1+ score is not univocal (ASCO/CAP vs 4B5 Ventana)
- Definition of 2+ score (>reflex ISH) may include or not intense but incomplete membrane staining and 10% or less pos cells
- Concordance among different Ab/assay for score 0 and 1+ has not been fully evaluated (Ventana 4B5 vs old HercepTest vs newHerceptest vs Others)

In clinical practice

- HER2 negative
- Score 2+ (20% of tumor cells)
- ISH: not amplified

In clinical practice

- HER2 negative
- Score 2+ (20% of tumor cells)
- ISH: not amplified

- What about the remaining 80% tumor cells?
- Important to know if they (and how many of them) are 1+?
- Should we report on the % of tumor cells without any staining (null)?
- Should we adopt the HER2-low terminology in the report?

Precision or Prediction ?

The exciting results of the clinical studies for HER2-low disease were obtained by selecting pts with an usual IHC test (4B5) and with the ASCO scoring system

Neither the test nor the scoring system were developed to identify tumors with HER2-low
Do we need «precision» or «prediction» ?

DB-06: What about HER2-ultralow

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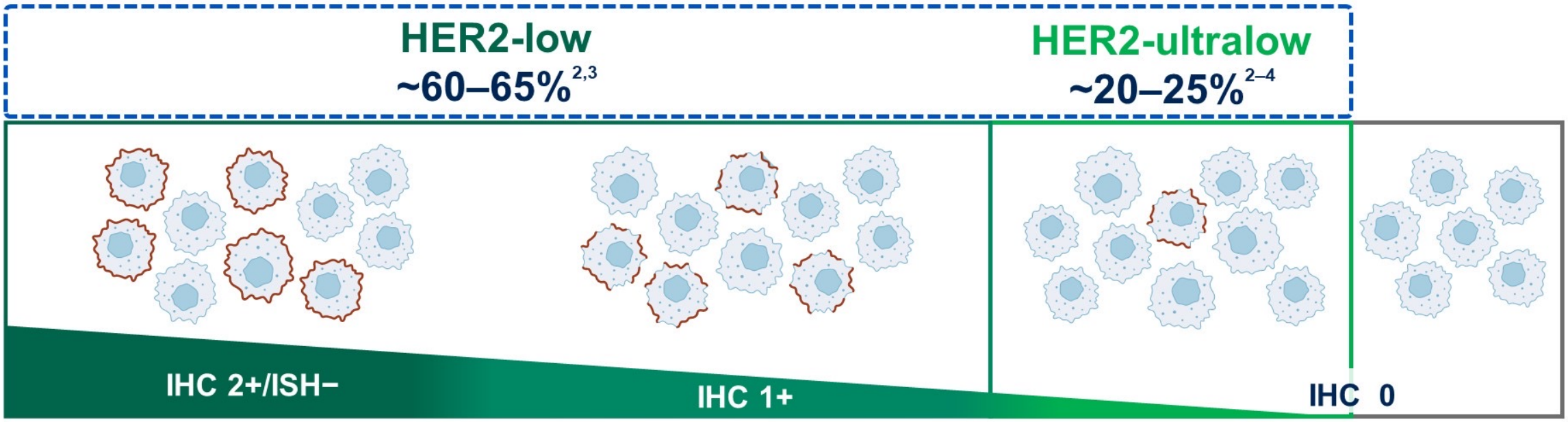
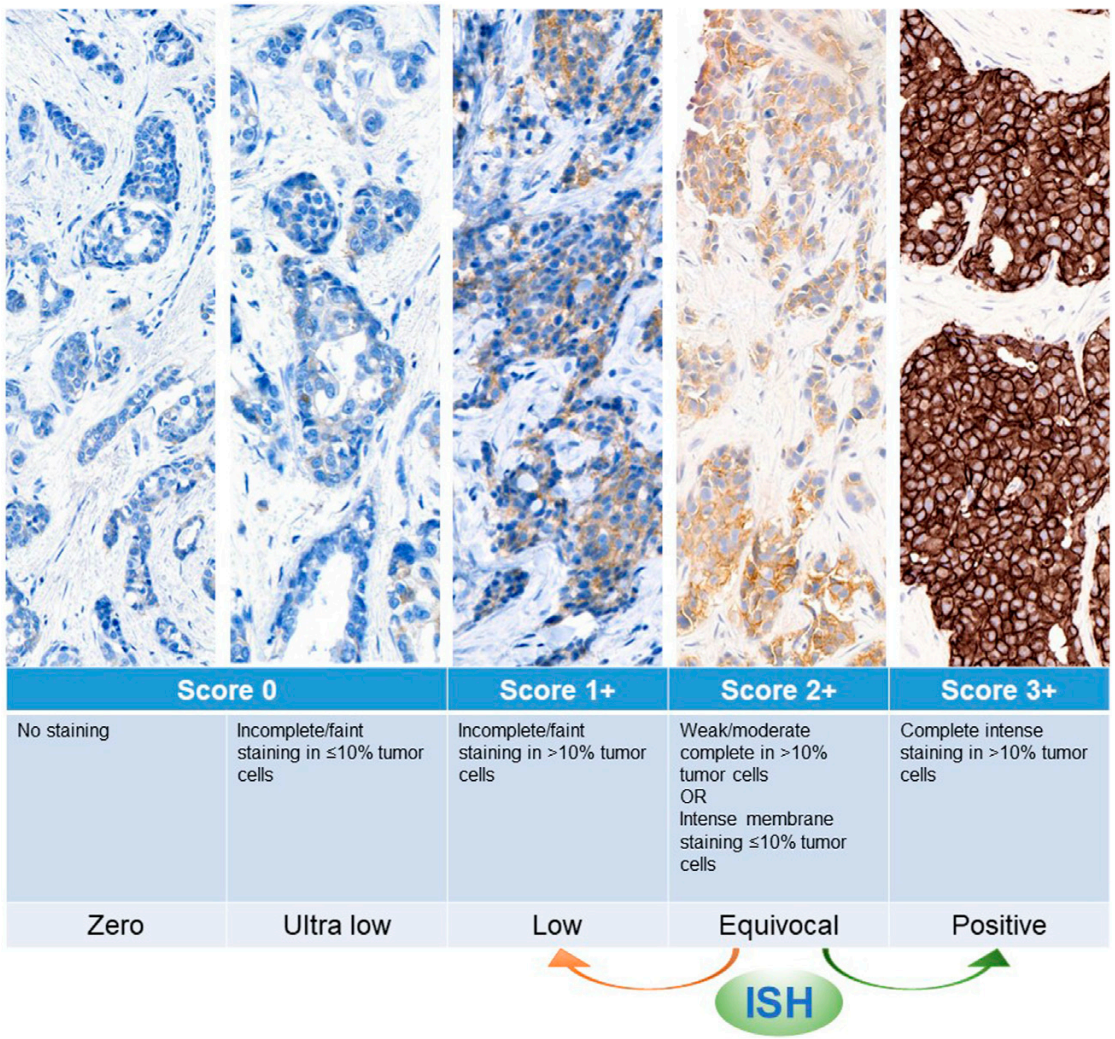


Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022;9:834651. CC BY 4.0 license available from: https://creativecommons.org/licenses/by/4.0/

1. Wolff AC, 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; 4. Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):Abstract e13156

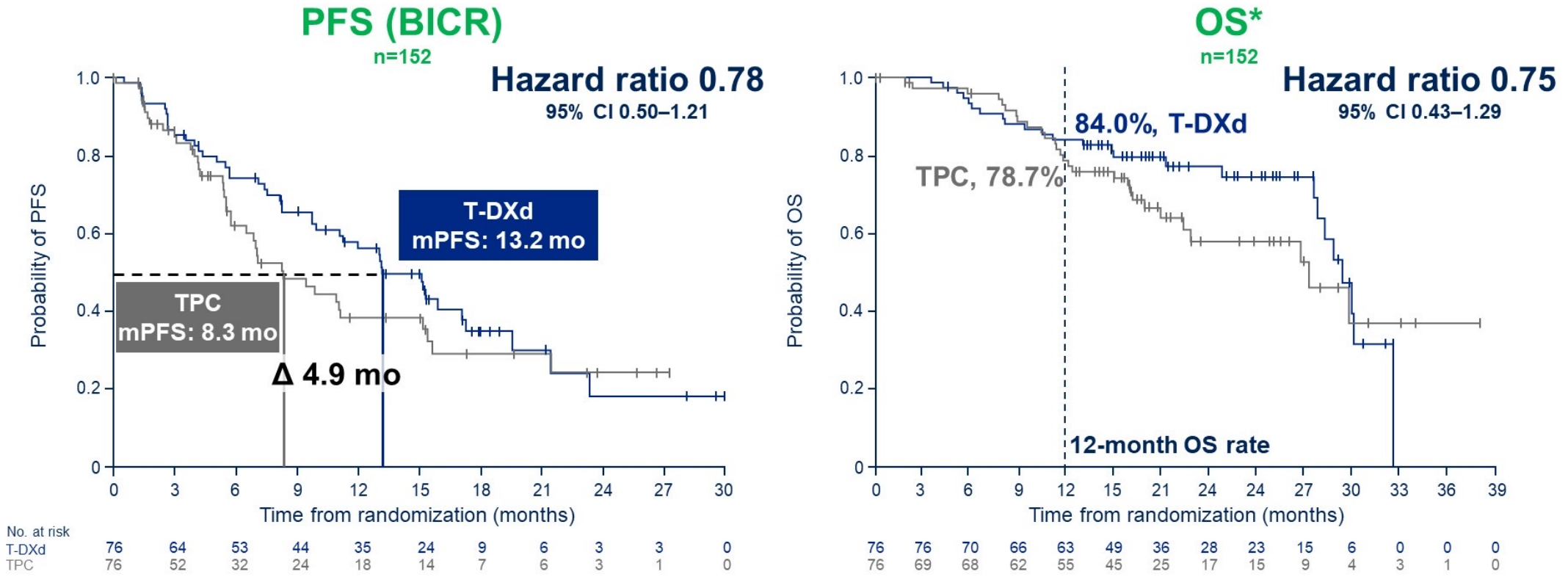
Slide adapted from Curigliano et al ASCO 2024

HER2 status



The identification of low HER2 expression levels is not a trivial task particularly for the discrimination between HER2-low score 1+ and “HER2- zero” (i.e., IHC score 0), which comprises also the subset of “HER2 ultra-low” (i.e., score 0 with incomplete and faint staining in ≤10% of tumor cells)

PFS/OS in HER2-ultralow: pre-specified exploratory analysis



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

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Slide adapted from Curigliano et al ASCO 2024

In whom should we use T-DXd ?

In case of ultra-low

- Apparent efficacy benefit but differences not evaluated for significance (small sample size)
- More toxicity (>G3 AEs and fatal AEs) than TPC
- No OS impact
- No QoL data

What is missing ?

- no data of T-DXd in ultra-low in 2L
- no data of T-Dxd in ultra-low HR-neg

What line of Tx should we use T-DXd ?

Given substantial OS benefit and high PFS/ORR of T-DXd in 2nd line, who should receive T-DXd in 1st line vs 2nd line?

1st line T-DXd

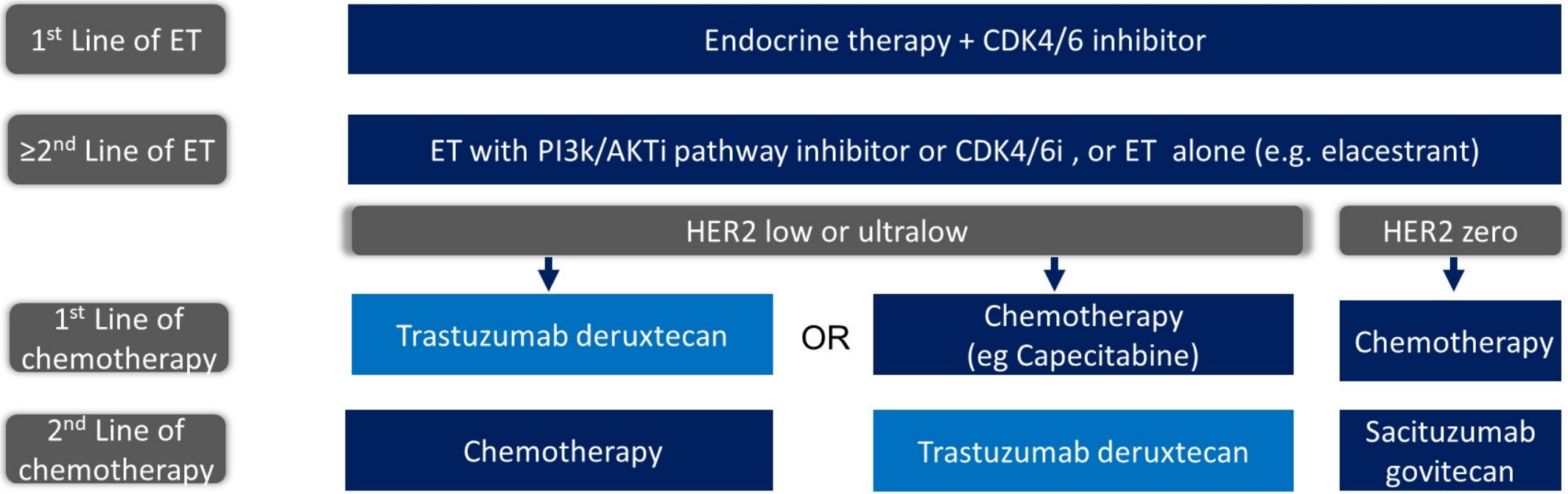
- Symptomatic/ Need for objective disease response
- Short interval after adjuvant chemotherapy
- Patient preference

2nd line T-DXd

- Asymptomatic/ low burden of disease
- Long interval after adjuvant chemotherapy
- Patient preference

These selection criteria may change as data evolve

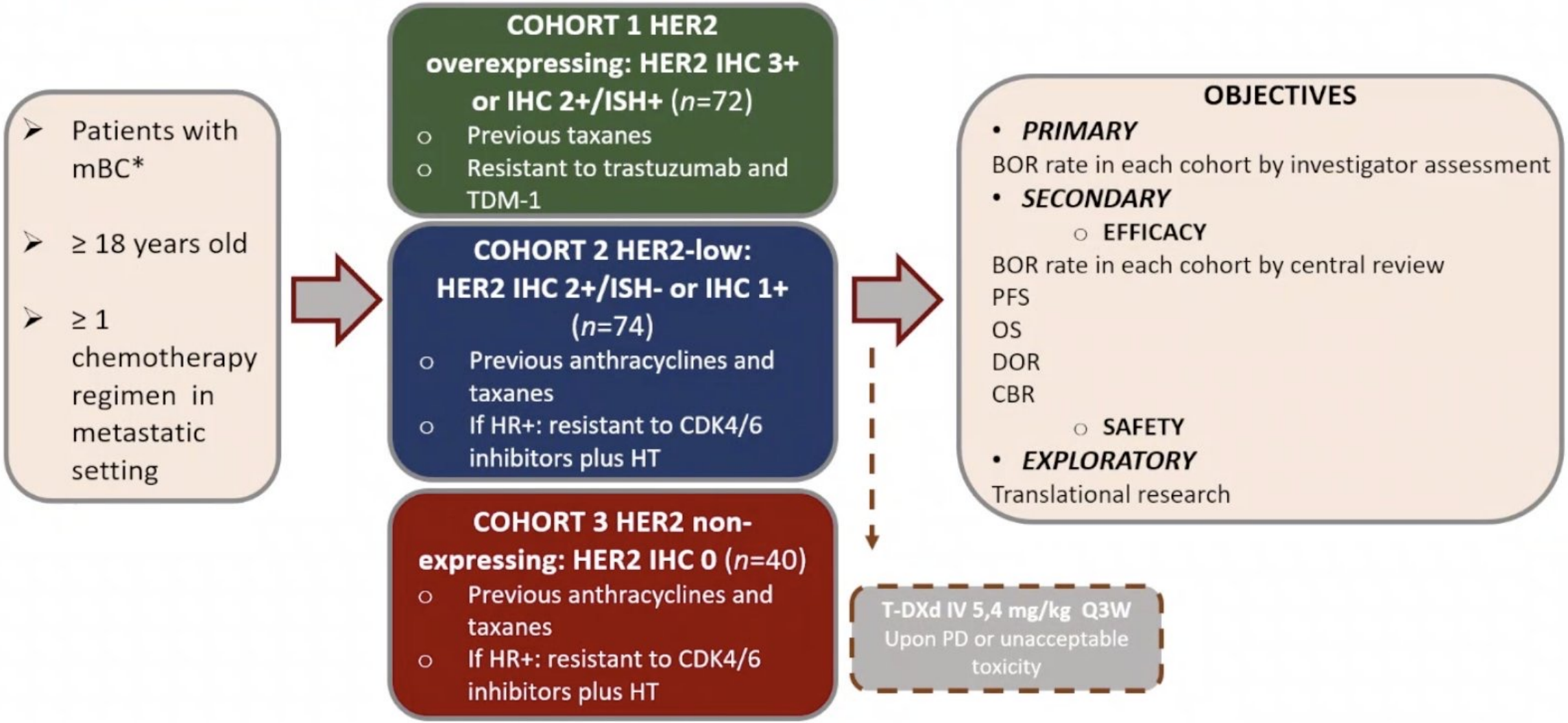
Possible algorhitm in HR+/HER2-



What about HER2 score 0

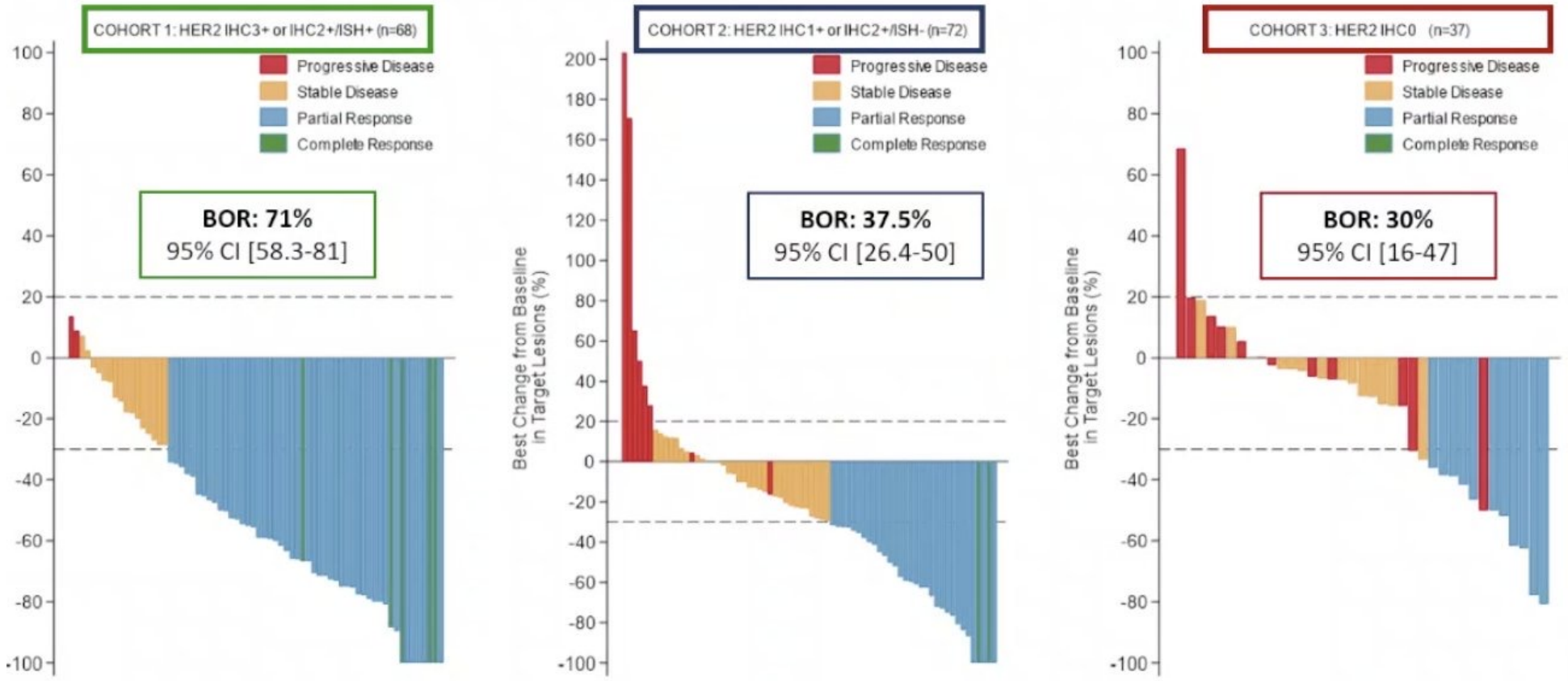
DAISY trial

- *A multicenter, open-label, phase 2 trial (NCT04132960)*



*Patients enrolled from November 2019-March 2021. HR+: hormone receptor-positive; CDK4/6: cyclin-dependent kinase 4/6; HT: hormone therapy; BOR: best objective response; OS: overall survival; DOR: duration of response; CBR: clinical benefit rate; IV: intravenously; Q3W: every 3 weeks; PD: progressive disease

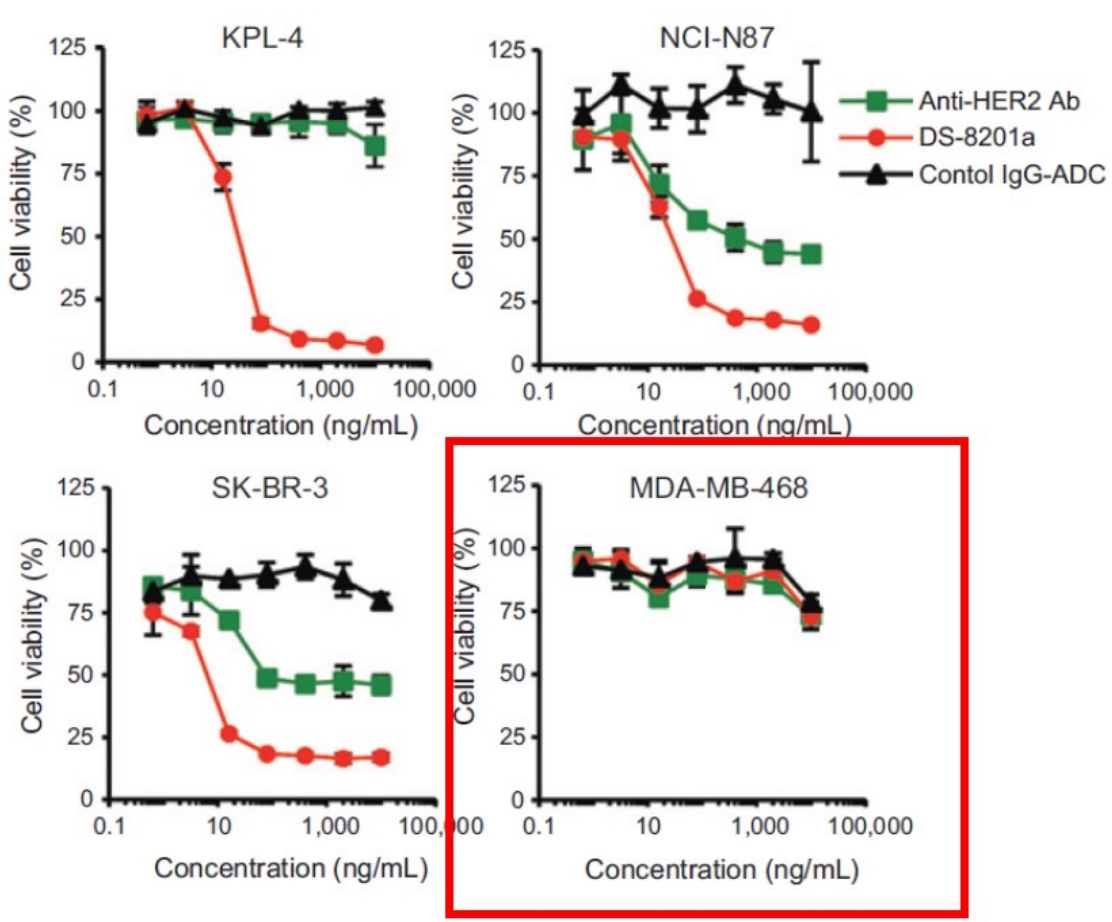
Best Objective Response rate according to HER2

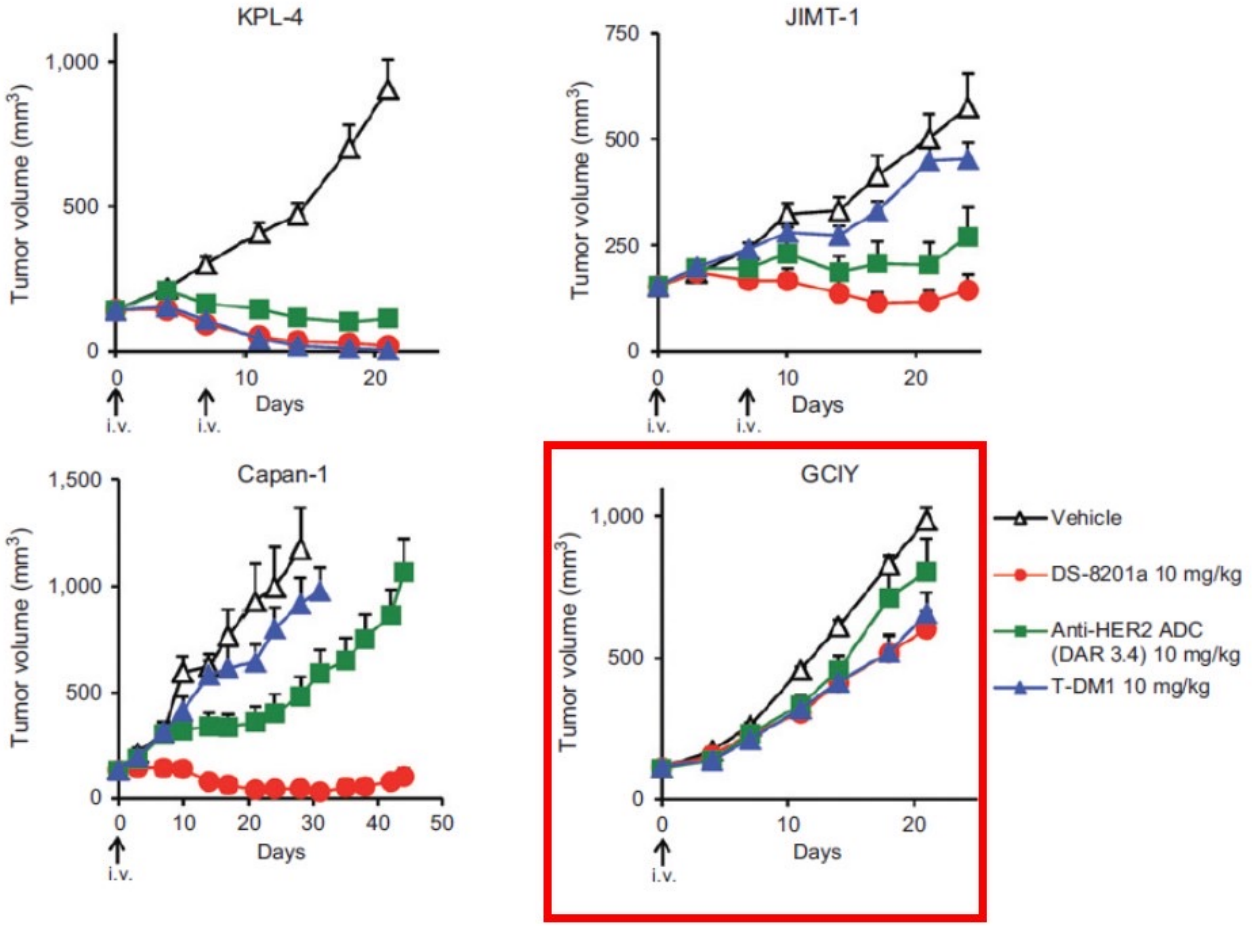


THE BOR RATE IS DEFFERENT BETWEEN THE THREE COHORTS p <0.0001

T-DXd in HER 0 (null) ?

No clinical data. Preclicnial evidences suggest limited or null effect in HER20 (IHC)





Ogitani et al Clin Cancer Res; 22(20) 2016. 5103

T-DXd in HER 0 (null) ?

If is true, it imples there is a lower limit of HER2 expression below which T-DXd is not beneficial

Consider that if this subset would be very small then the testing may be not worthwhile

Consider the heterogeneity

How do we test for these patients ?

What's going on?

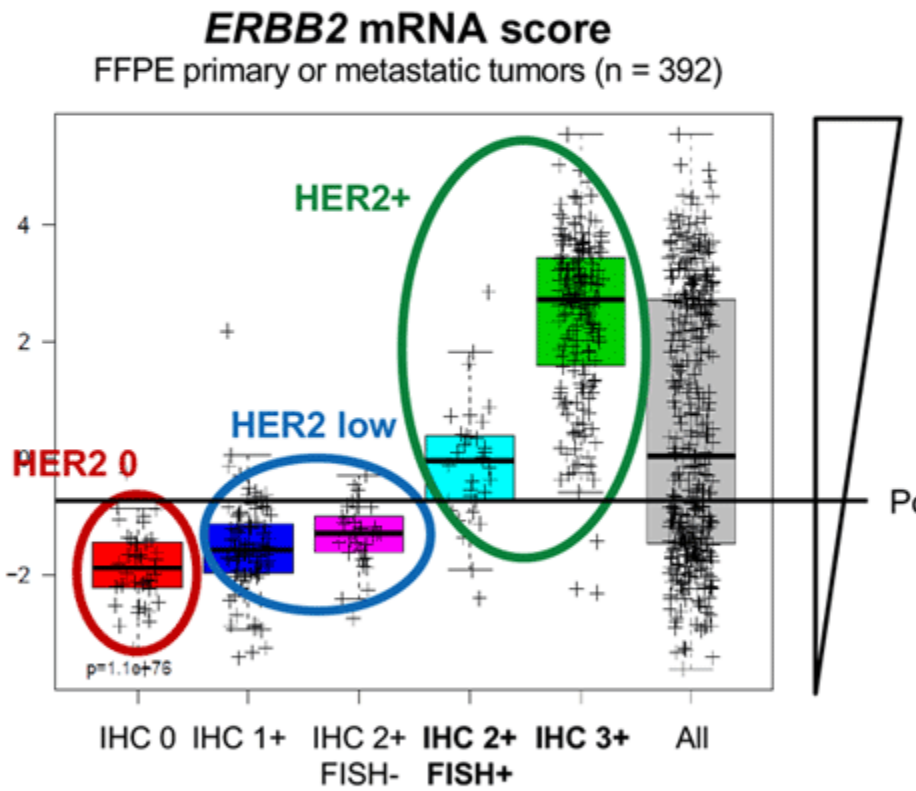
Current IHC is not accurate for distiguishing HER2-low or ultralow cancers from HER2 0 cancers

- Test designed to distinguish IHC 3+ from everything else
- NOT designed to distinguish ultra-low vs null (what is the lowest cut-off)?

What's next?

- Multiple new assys in R/D (HER2 mRNA, heterogeneity)
- Trials to evaluate these assyas (DB-15 evaluating IHC HER2=0)

ERBB2 mRNA vs. IHC



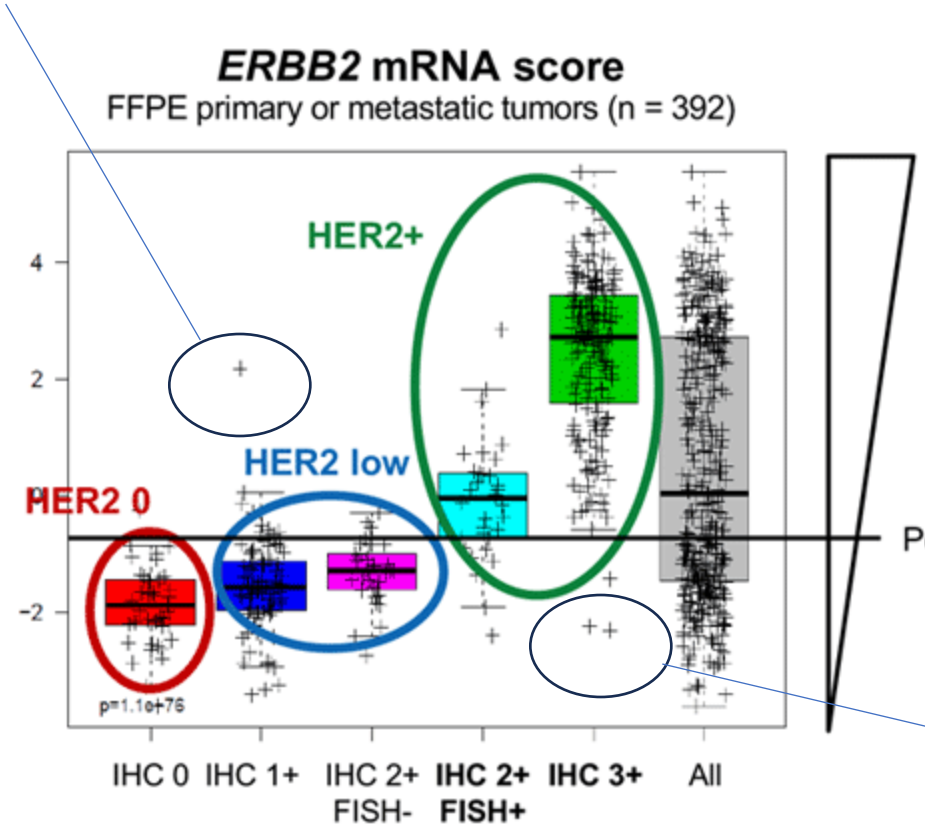
- A large dynamic range of *ERBB2* mRNA expression exists in breast cancer (>16-fold change)
- HER2 3+ tumors have the largest range of *ERBB2* expression
- HER2 2+ vs 3+ is very different based on *ERBB2* expression
- Difference between HER2 0 vs HER2 low is small

Potential optimal cutoff to predict HER2 ASCO/CAP status

1. Griguolo G et al. *Cancers (Basel)*. 2020;12:1902.

ERBB2 mRNA vs. IHC

antiHER2 active ?



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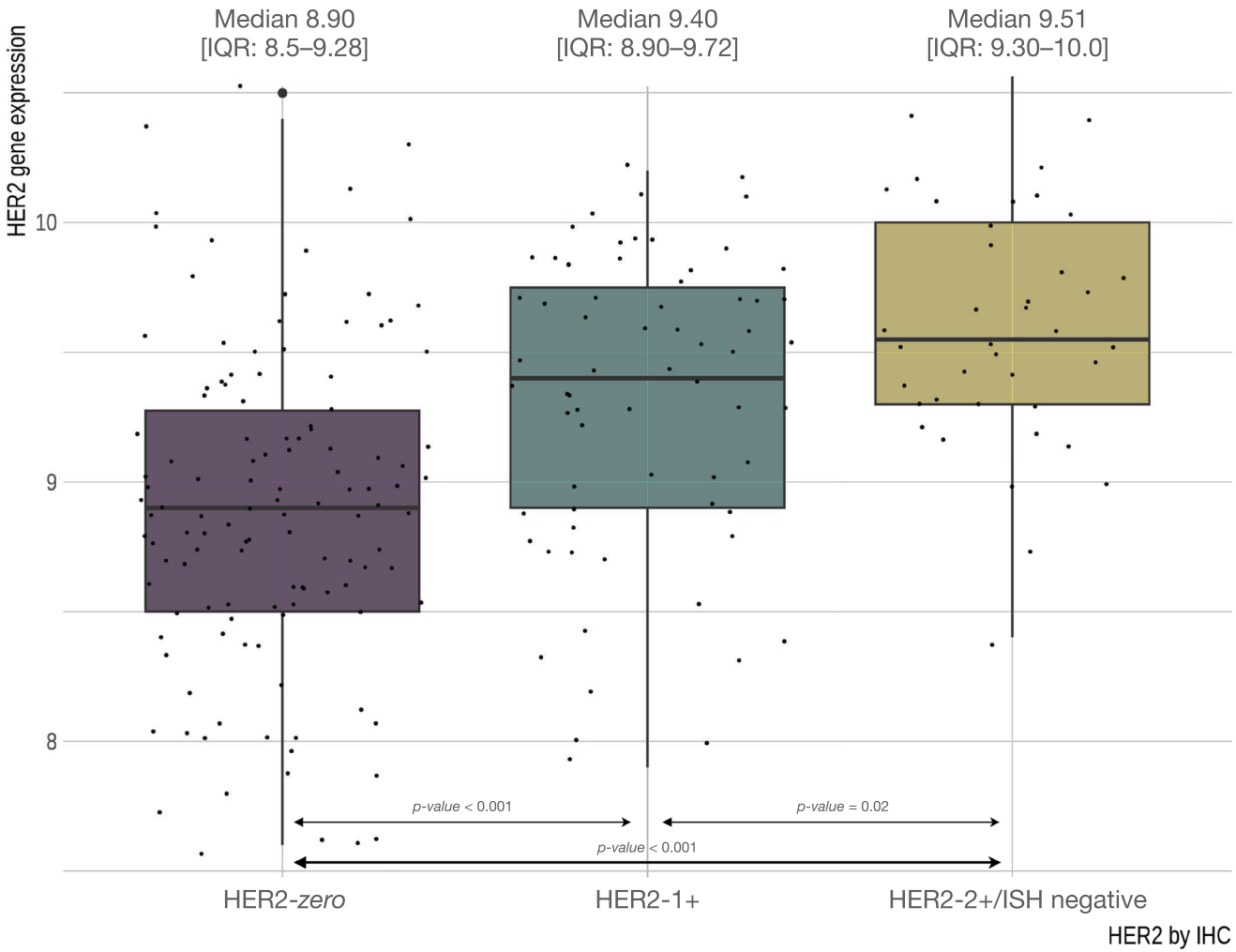


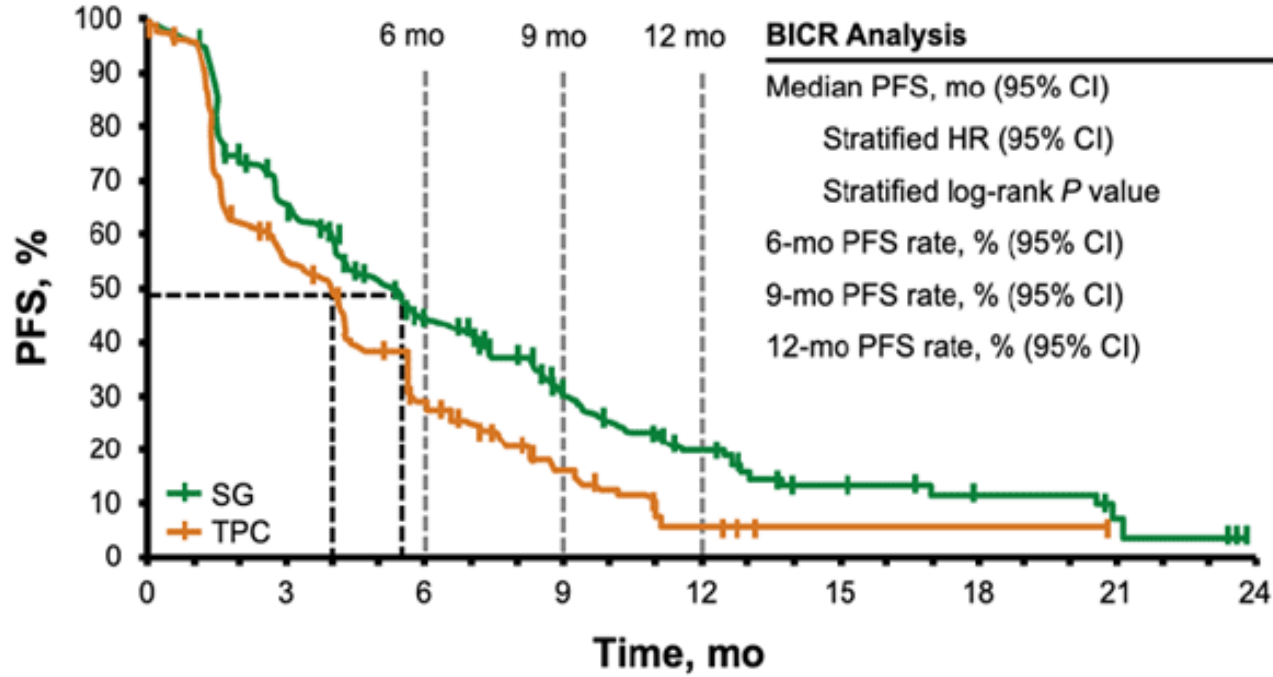
B/w Jan 2021 and Jan 2023, 229 consecutive HR-positive HER2-negative early BC (T1-3 N0-1) have been characterised by IHC and ODX

Due to the substantial overlap, the HER2 gene expression is unable to properly distinguish HER2-low and HER2-zero IHC whose accurate identification is critical in the context of HER2-negative BC

In case oif HER2-*null:* TROPICS-02

Sacituzumab Govitecan (SG) for HR+/HER2- MBC

SG demonstrated a statistically significant improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death; a higher proportion of patients were alive and progression-free at all landmark timepoints



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	.0003	
6-mo PFS rate, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-mo PFS rate, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-mo PFS rate, % (95% CI)	21.3 (15.2-28.1)	7.1 (2.8-13.9)

PFS ∆1.5 mo; *P* = .0003
ORR benefit: 21% vs 14%, *P* = .03

No. at Risk (Events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

Median follow-up was 10.2 months.
1. Rugo HS et al. ASCO 2022. Abstract LBA1001.

ADCs sequencing

ADCs sequencing

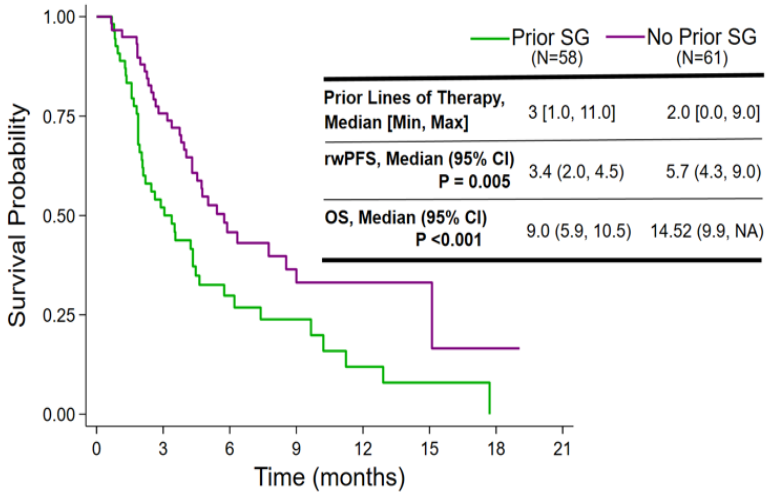
HR+ mBC (except few "HER2-null")

→ **Exhaust endocrine treatment strategies**

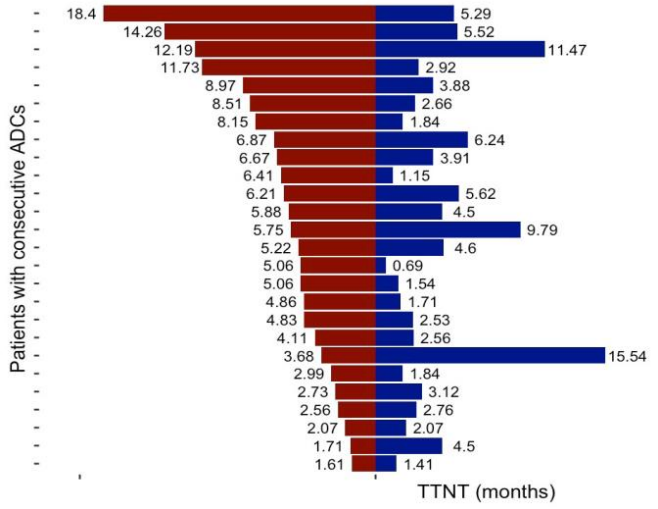
→ **T-DXd** (DB06)

→ **Dato-DXd** (TB01) → **SG** (TROPiCS02)

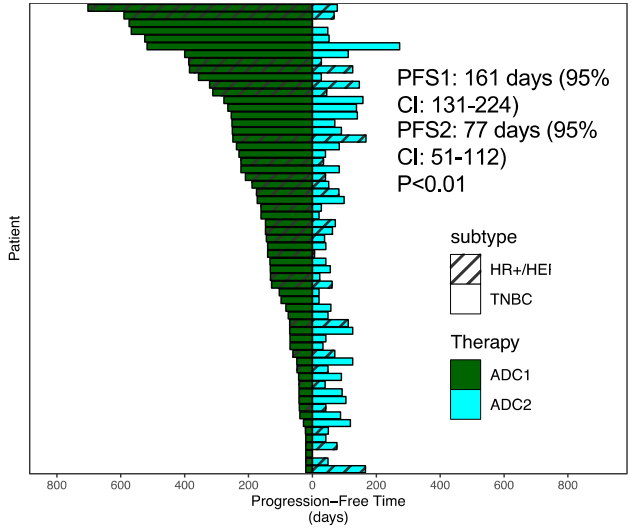
→ **SG** (TROPiCS02) → **Dato-DXd** (TB01)



Tarantino P et al. ASCO 2024



Morganti S. et al. ESMO Breast 2024



Abelman R. et al. ASCO 2023

1. Tarantino P, *et al*. Presented at ASCO 2024. By permission of Dr P. Tarantino; 2. Morganti S, *et al*. Presented at ESMO 2024. By permission of Dr S. Morganti. 3. Abelman R, *et al.* Presented at ASCO 2023.

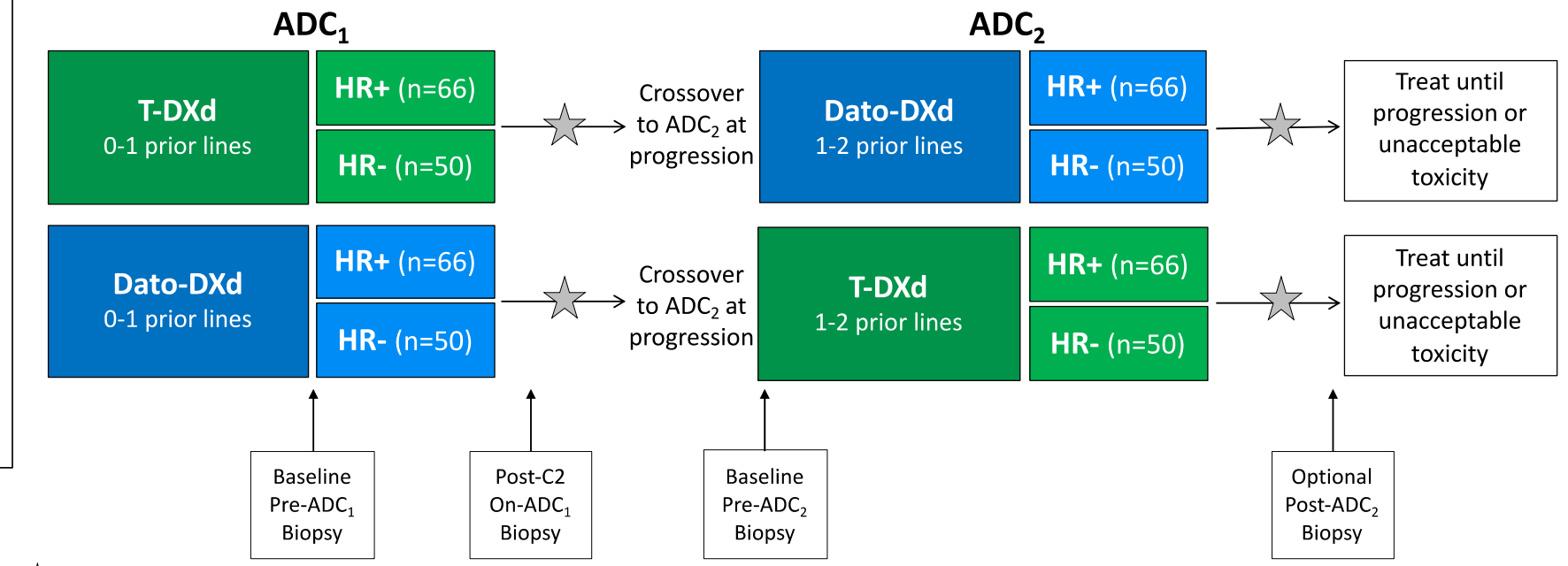
TRADE DXd Ph2 trial

Eligibility:

- Confirmed unresectable LA or metastatic disease
- History of HER2-low BC (any prim or met) defined as IHC 1+ or 2+/ISH-
- Most recent pathology: HER2-0 or HER2-low
- Measurable disease
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

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

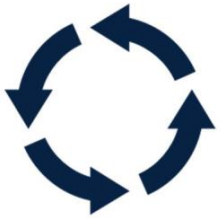
Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR



Tumor assessments + Blood collection q9w

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

Toxicity of Special Interest: ILD

1	2	3	4	5
				
Screen	**Scan**	**Synergy**	**Suspend Treatment**	**Steroids**
• Careful patient selection is warranted before initiating T-DXd to optimise the monitoring strategies based on the baseline risk • Screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD	• The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest • A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks	• Minimising the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected	• T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves	• The mainstay for treating T-DXd- induced ILD remains corticosteroids, with the dose to be adapted to the toxicity grade

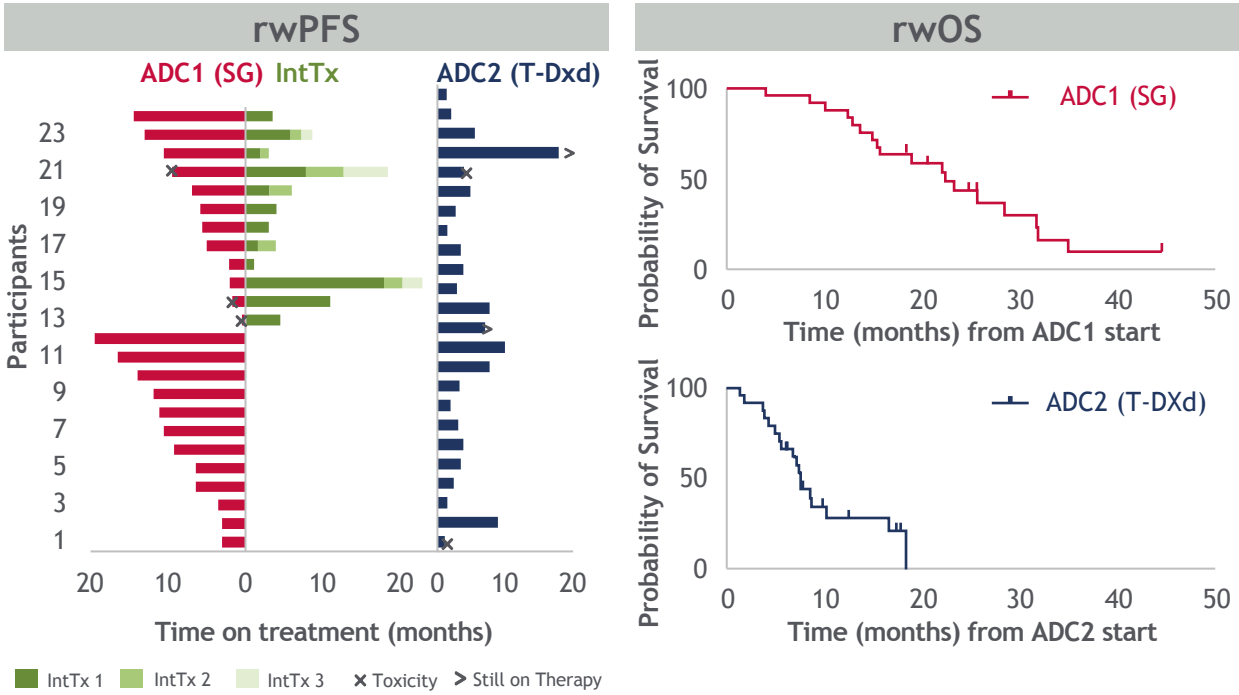
ADCs sequencing

Retrospective RWD

1. University of California, San Francisco
2. Toulose/Paris, France
3. Dana Farber, Boston
4. Mass Gen, Boston
5. Memorial SKCC, New York

UCSF RWD (N=84, HR+=56)

HR+/HER2-low (SG to T-DXd; n=24) rwPFS and rwOS Outcomes[1]



SG → T-DXd
(n=24, 42.9%)

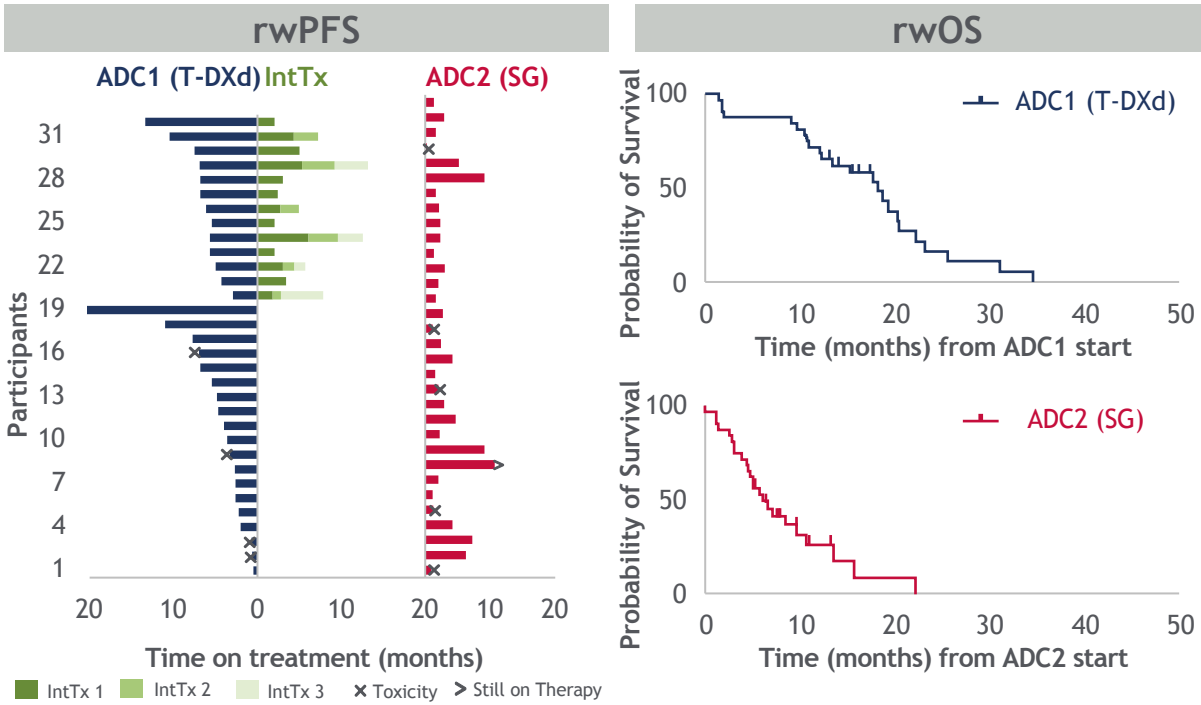
- Median lines of therapy for MBC prior to SG:[1]
  - Median lines chemo: **2.0** (range 0-7)
  - Median total lines of therapy: **3.0** (range 0-9)
- IntTx between ADCs: 50.0%[1]

	ADC1 (SG)	ADC2 (T-DXd)
Median rwPFS from time of each ADC start, months	6.5	3.6
Median rwOS from time of each ADC start, months	20.1	7.7

1. Huppert L, et al. Presented at ASCO 2024. Poster #61.
2. Huppert L, et al. Presented at SABCS 2023. Poster #PS08-04.

UCSF RWD (N=84, HR+=56)

HR+/HER2-low (T-DXd to SG; n=32) rwPFS and rwOS Outcomes[1]



T-DXd → SG
(n=32, 57.1%)

- Median lines of therapy for MBC prior to T-DXd:[1]
  - Median lines chemo: **2.0** (range 0-6)
  - Median total lines of therapy: **4.5** (range 2-10)
- IntTx between ADCs: 40.6%[1]

	ADC1 (T-DXd)	ADC2 (SG)
Median rwPFS from time of each ADC start, months	5.3	2.1
Median rwOS from time of each ADC start, months	15.1	5.6

1. Huppert L, et al. Presented at ASCO 2024. Poster #61.
2. Huppert L, et al. Presented at SABCS 2023. Poster #PS08-04.

Tentative take home message #1

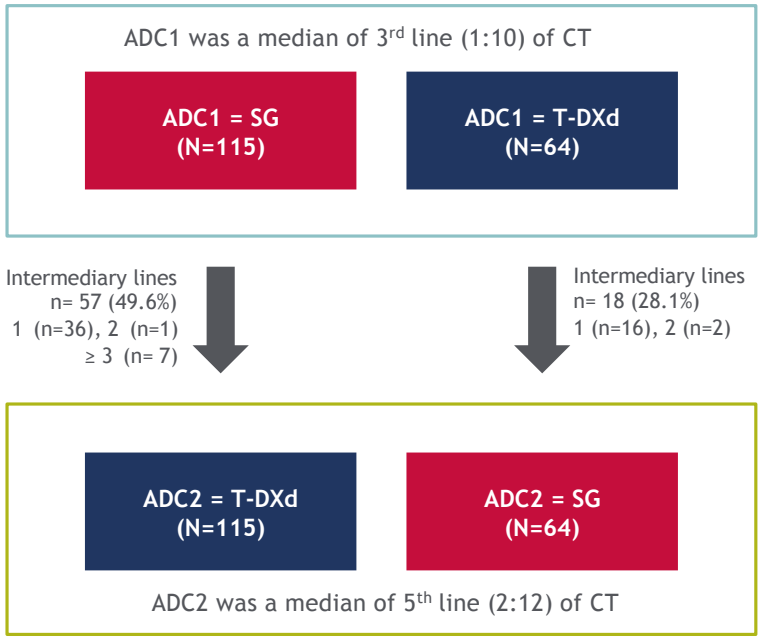
The performance of ADC2 is expected to be inferior than ADC1, with exceptions

France RWD (N=179, TNBC=108)

Main patient characteristics

Characteristics	Total (N=179)
Median age, years (range)	54 (30-80)
De novo MBC, n (%)	39 (21.8)
Histological subtype, n (%)	
Invasive ductal carcinoma	152 (84.9)
Invasive lobular carcinoma	23 (12.8)
Other	4 (2.2)
Germline *BRCA/PALB2* status, n (%)	146 (81.6)
Wild Type	126 (86.3)
Germline pathogenic variant	20 (13.7)
BRCA1 / BRCA2	10 (6.8) / 9 (6.2)
PALB2	1 (0.7)
Tumor phenotype, n (%)	
HR positive (HR+)	71 (39.7)
HR negative (HR-)	108 (60.3)
HER2-low	179 (100)
Systemic treatment, n (%)	
(Neo) adjuvant chemotherapy	123 (89.8)
iCDK4/6 for HR+ patients	65 (91.5)

ADC treatment

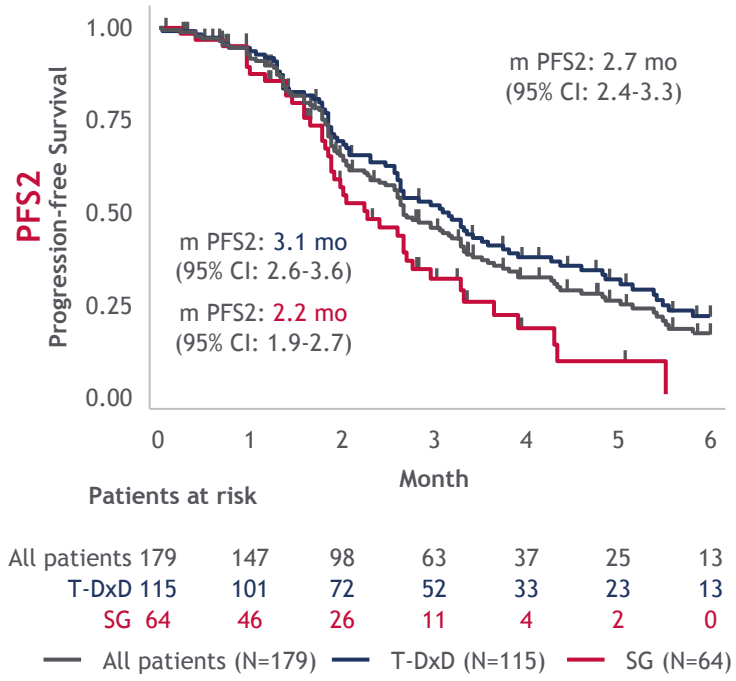


1. Poumeaud F, et al. Presented at SABCS 2023. Poster #PS08-02.

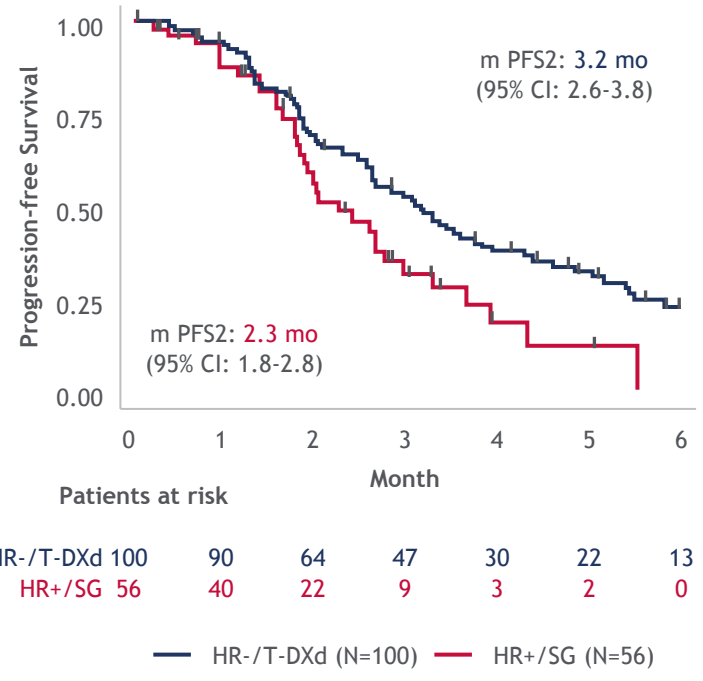
France RWD (N=179, TNBC=108)

ADC2 PFS Outcomes

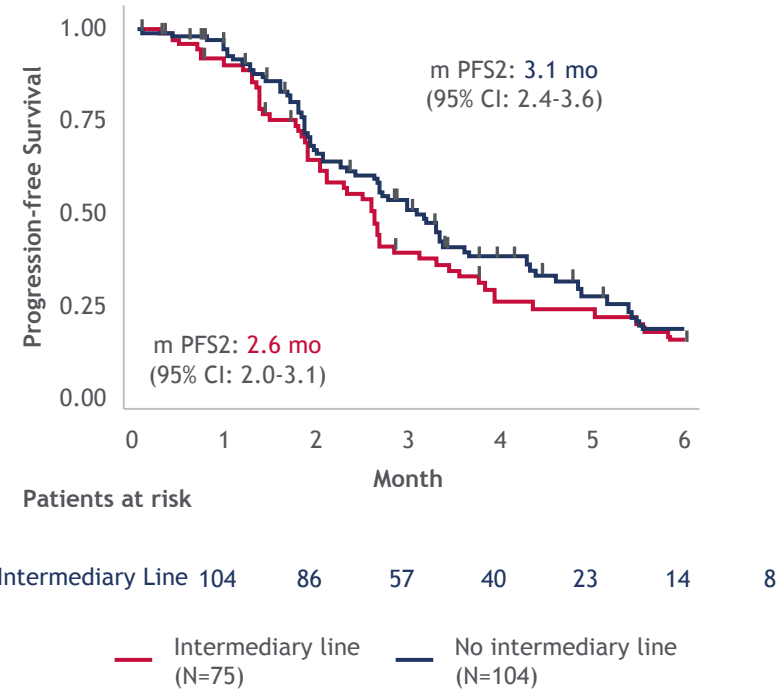
All patients



By HR Status/ADC combination



Impact of intermediary treatment



Nearly 40% of pts with primary resistance to ADC1 had initial disease control with ADC2

1. Poumeaud F, et al. Presented at SABCS 2023. Poster #PS08-02.

Tentative take home message #1

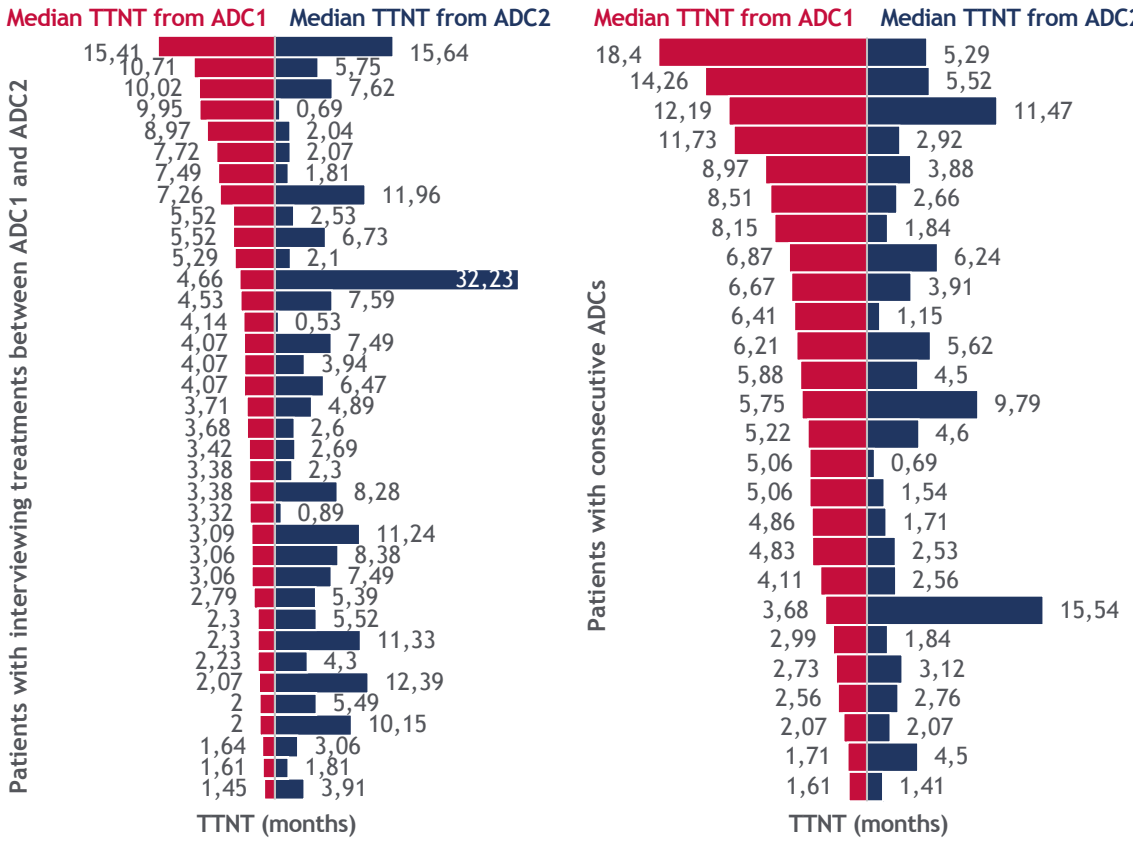
The performance of ADC2 is expected to be inferior than ADC1, with exceptions

Sequencing of ADCs with a similar payload results in modest outcomes in pretreated pts.
However, a non-negligible subset of pts exhibits an increased responses to ADC2 vs ADC1.

Dana Farber RWD (N=62 HER2-)

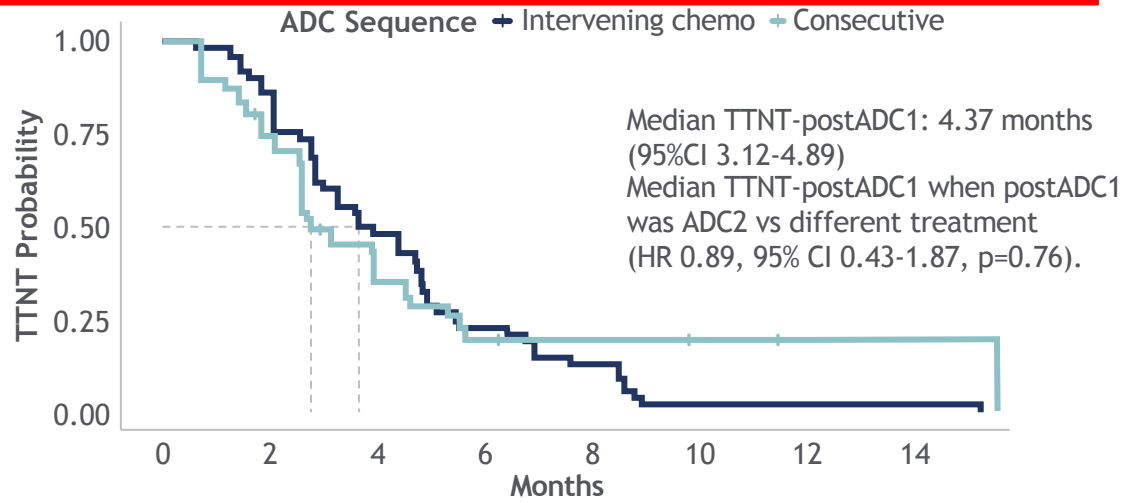
26 (41.9%) pts received consecutive ADCs and 36 (58.1%) pts received intervening treatments bw ADC1 and ADC2

HR+/HER2−



Median TTNT from ADC1 and ADC2

	Median TTNT from ADC1 (months)	Median TTNT from ADC2 (months)
Overall population (n=62)	4.34 (95% CI 3.68-5.52)	5.39 (95% CI 3.91-8.38)
HR+/HER2- (n=33, 53%)	4.66 (95% CI 3.09-5.75)	5.62 (95% CI 3.91-NA)
TNBC (n=29, 47%)	4.11 (95% CI 3.68-6.87)	5.29 (95% CI 2.66-NA)



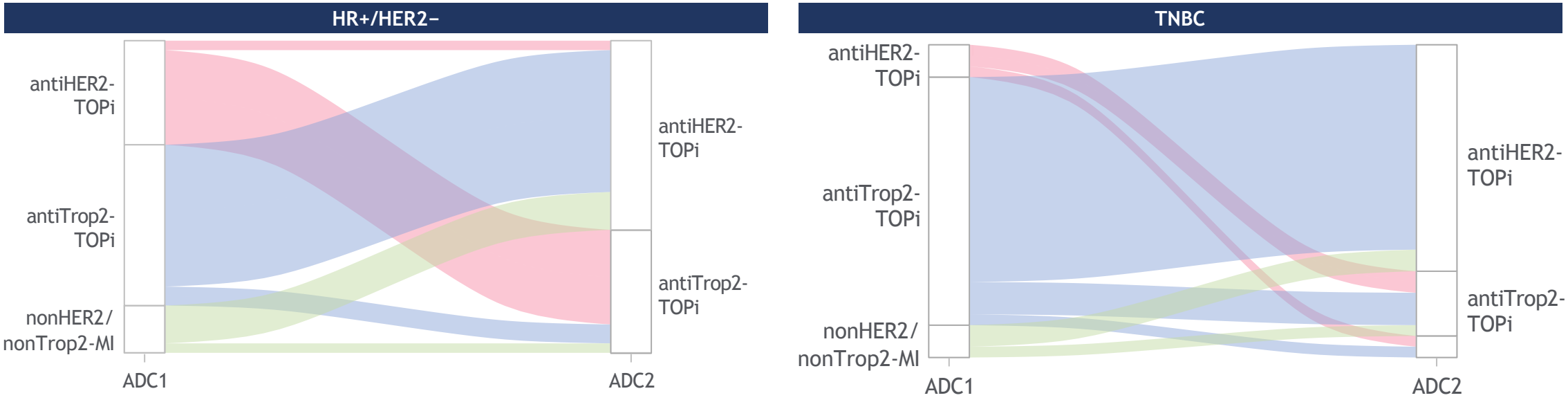
Median follow up was 23.1 (21.7-27.4) months

ADCs, antibody-drug conjugates; CI, confidence interval; HER2, human epidermal growth factor receptor-2; TNTT, time to next treatment.

1. Morganti S, et al. Presented at ESMO BC 2024. Poster #213P.

Dana Farber RWD (N=62 HER2-)

Change in MoAb and/or change in the Payload (or both) can impact on Tx efficacy



*ET/CDK4/6i (1), IO single agent (1), ADC/TT (1)

ADCs, antibody-drug conjugates; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; Mi, microtubule inhibitor; TOPi, topoisomerase inhibitor; Trop2, tumor-associated calcium signal transducer 2.

1. Morganti S, et al. Presented at ESMO BC 2024. Poster #213P.

Tentative take home message #2

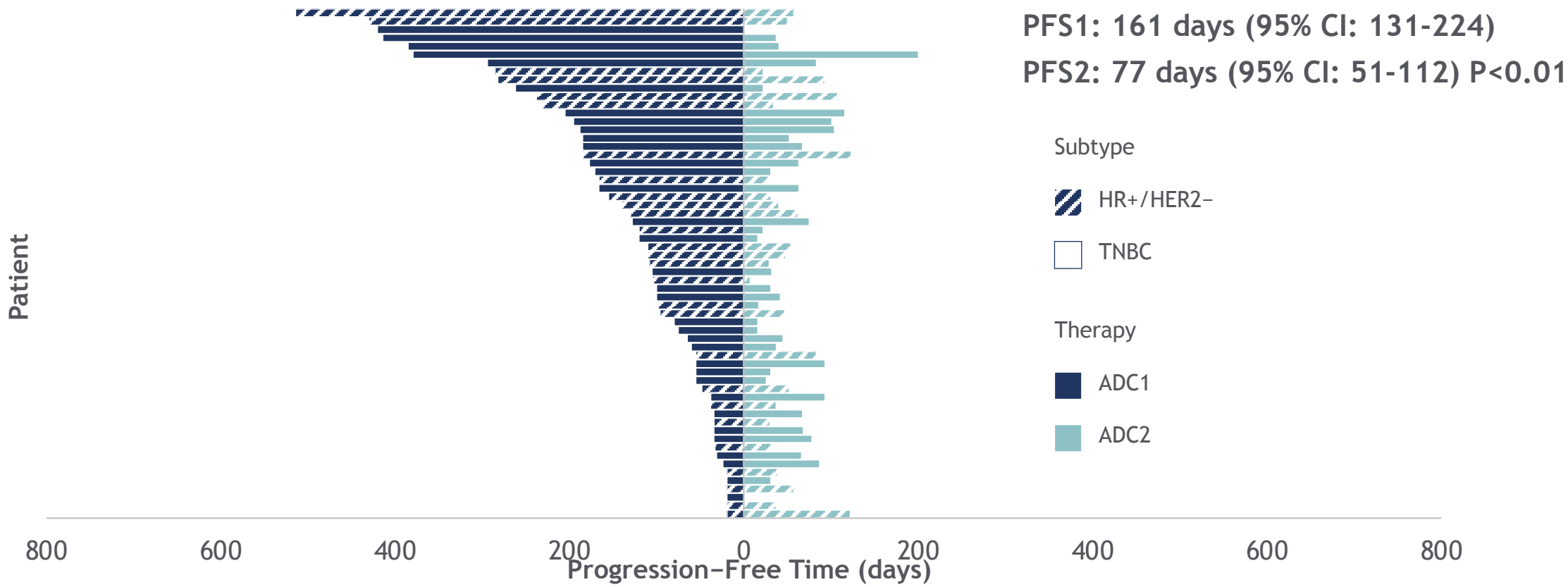
The performance of ADC2 is expected to be inferior than ADC1, with exceptions

Sequencing of ADCs with a similar payload results in modest outcomes in pretreated pts. However, a non-negligible subset of pts exhibits an increased responses to ADC2 vs ADC1.

To prioritize ADC sequence, we should consider more granular data of patients and tumor characteristics, including TROP-2 and HER2 antigen expression

MassGen Hospital (A3 study, N=68 HR+=30)

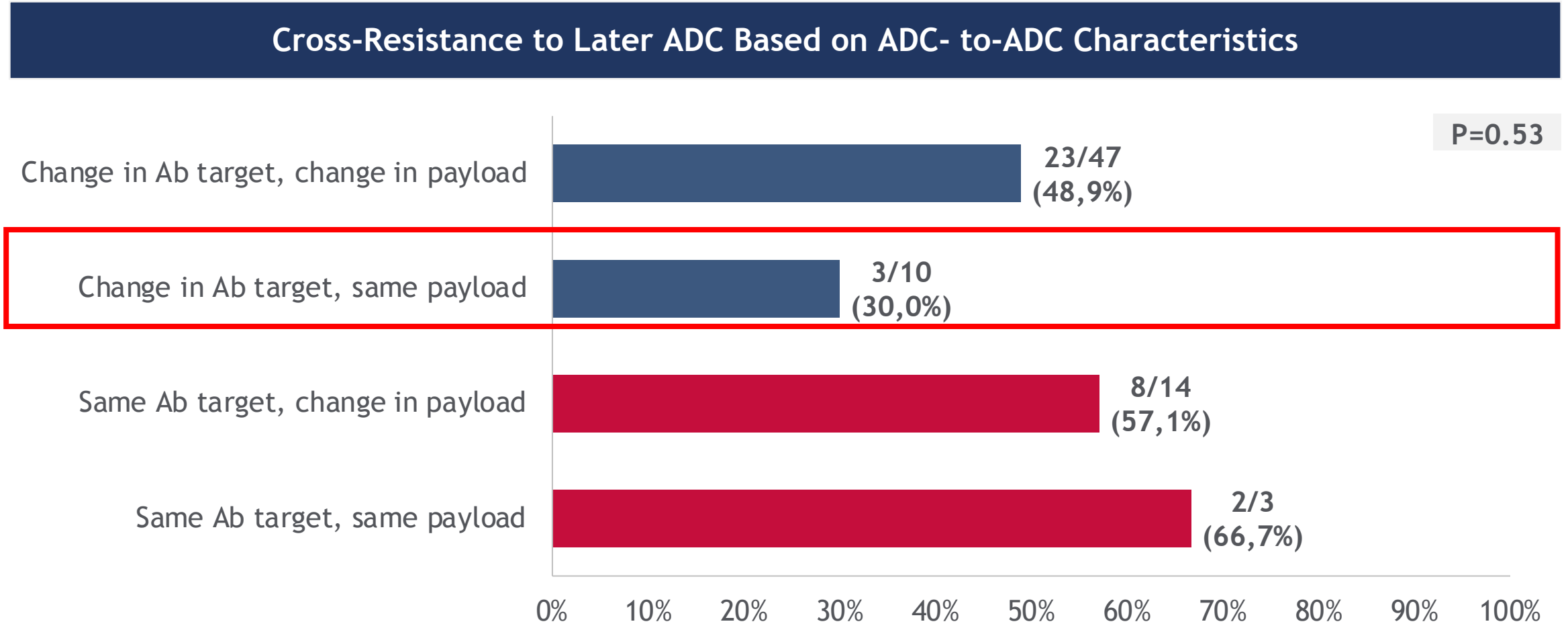
Time To Progression ADC1 vs. ADC2



ADC, antibody drug conjugate; CI, confidence interval; HER2, human epidermal growth factor receptor; PFS, progression free survival; TNBC, triple-negative breast cancer.

1. Abelman R, et al. Presented at SABCS 2023. Poster #PS08-03.

MassGen Hospital (A3 study, N=68 HR+=30)



ADC, antibody drug conjugate; CI, confidence interval; HER2, human epidermal growth factor receptor; PFS, progression free survival; TNBC, triple-negative breast cancer.

1. Abelman R, et al. Presented at SABCS 2023. Poster #PS08-03.

Tentative take home message #3

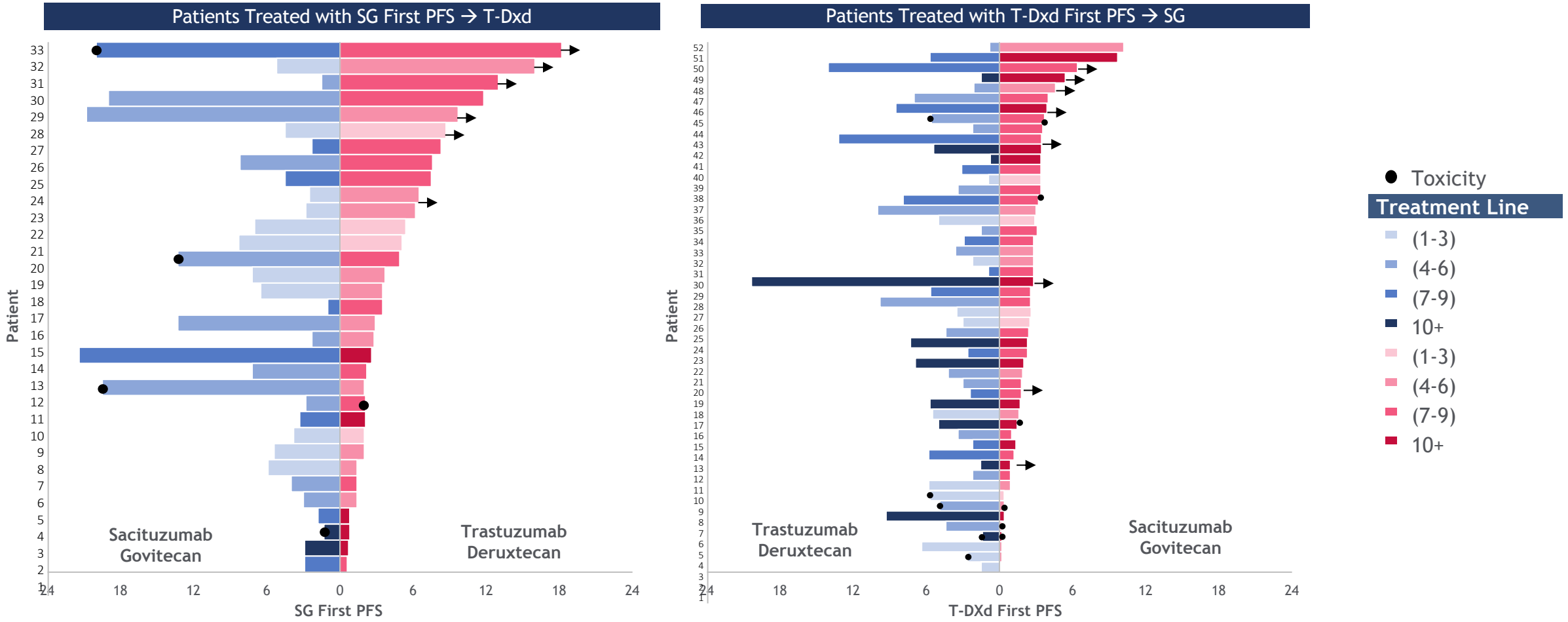
The performance of ADC2 is expected to be inferior than ADC1, with exceptions

Sequencing of ADCs with a similar payload results in modest outcomes in pretreated pts. However, a non-negligible subset of pts exhibits an increased responses to ADC2 vs ADC1.

To prioritize ADC sequence, we should consider more granular data of patients and tumor characteristics, including TROP-2 and HER2 antigen expression

To reduce the risk of cross-resistance in ADC sequencing, the MoAb change in ADC2 might be more relevant than the payload change

MSKCC RWD (N=85, TNBC=52)



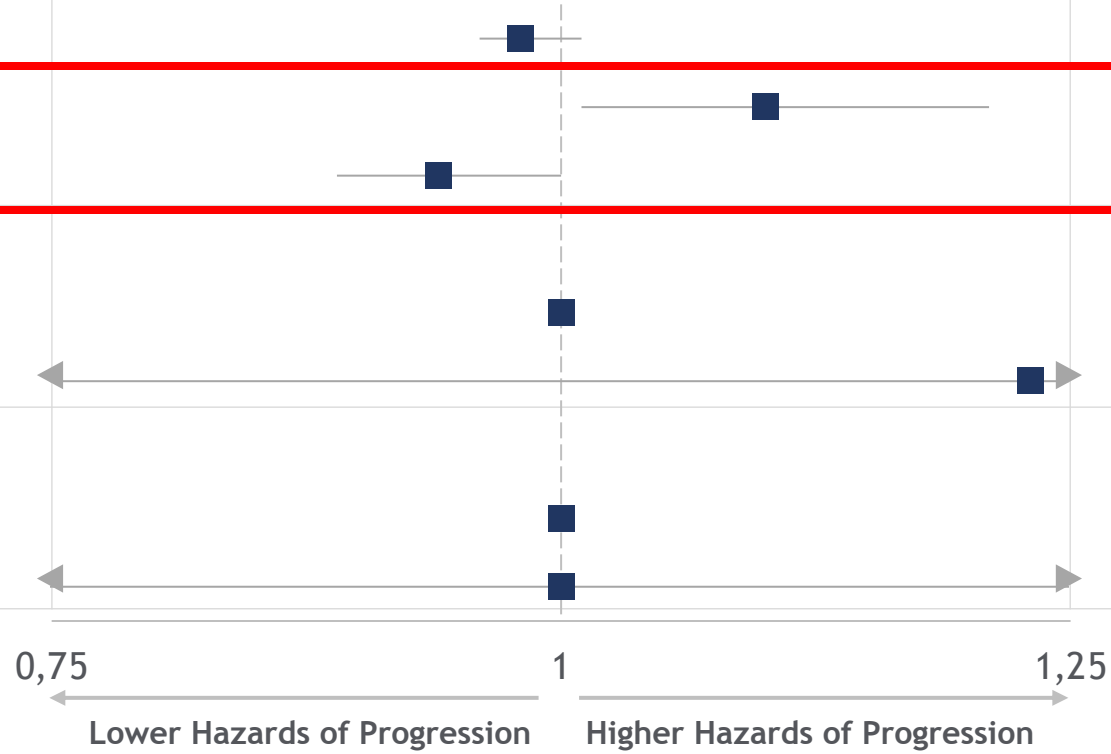
In 75% of patients, the PFS of ADC2 was shorter than ADC1 by a pseudo median of 2 months (95% CI -2.85-1.13, p=<001)

1. Mai N, et al. Presented at ASCO 2024. Poster #63.

MSKCC RWD (N=85, TNBC=52)

Clinical Variables Associated with Longer ADC2 PFS

Variable	Hazard Ratio (95% CI)	p-value
Baseline Clinical Data		
Age	0.98 (0.96-1.01)	0.2
Treatment Lines Preceding ADC2	1.10 (1.01-1.21)	0.034*
ADC1 Time to Treatment Failure	0.94 (0.89-1.00)	0.044*
First ADC		
SG		
T-DXd	1.23 (0.68-2.24)	0.5
ER Status		
ER+		
TNBC	1.0 (0.52-1.90)	0.99



1. Mai N, et al. Presented at ASCO 2024. Poster #63.

Tentative take home message #4

The performance of ADC2 is expected to be inferior than ADC1, with exceptions

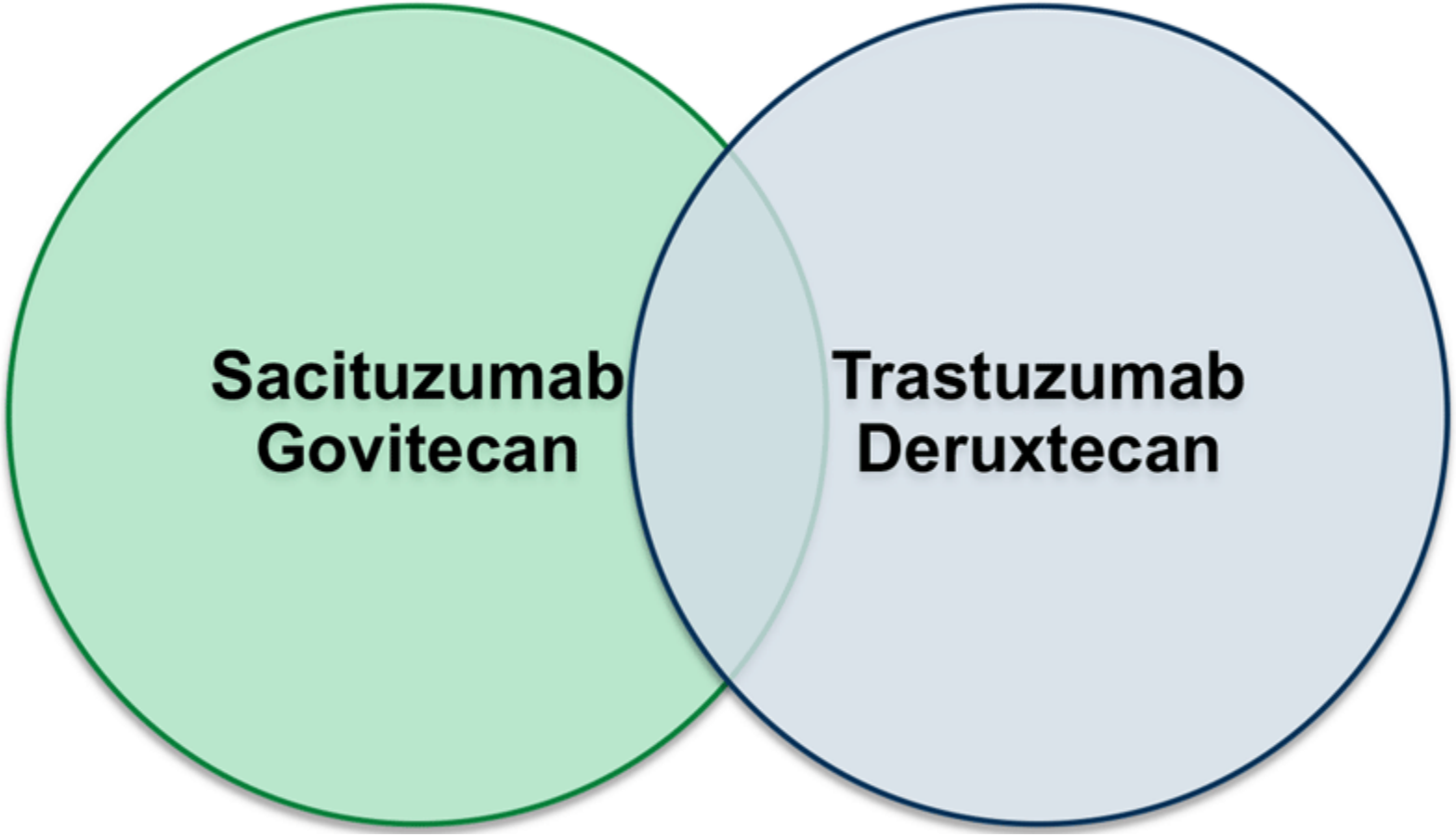
Sequencing of ADCs with a similar payload results in modest outcomes in pretreated pts. However, a non-negligible subset of pts exhibits an increased responses to ADC2 vs ADC1.

To prioritize ADC sequence, we should consider more granular data of patients and tumor characteristics, including TROP-2 and HER2 antigen expression

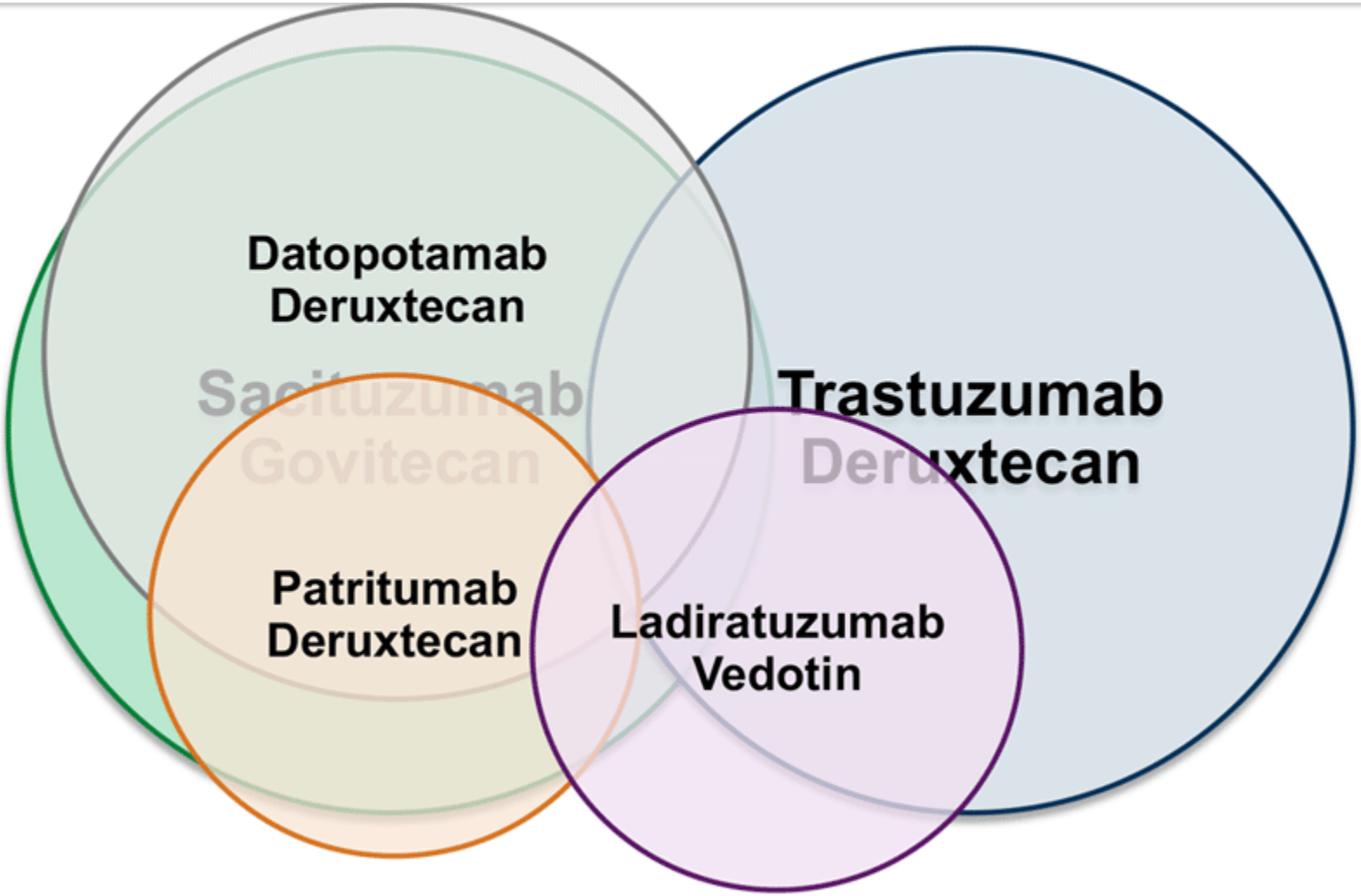
To reduce the risk of cross-resistance in ADC sequencing, the MoAb change in ADC2 might be more relevant than the payload change

Intervening chemotherapy bw ADC1 and ADC2 and/or other treatment lines before ADC2 appear to have a unfavorable impact on ADC sequence

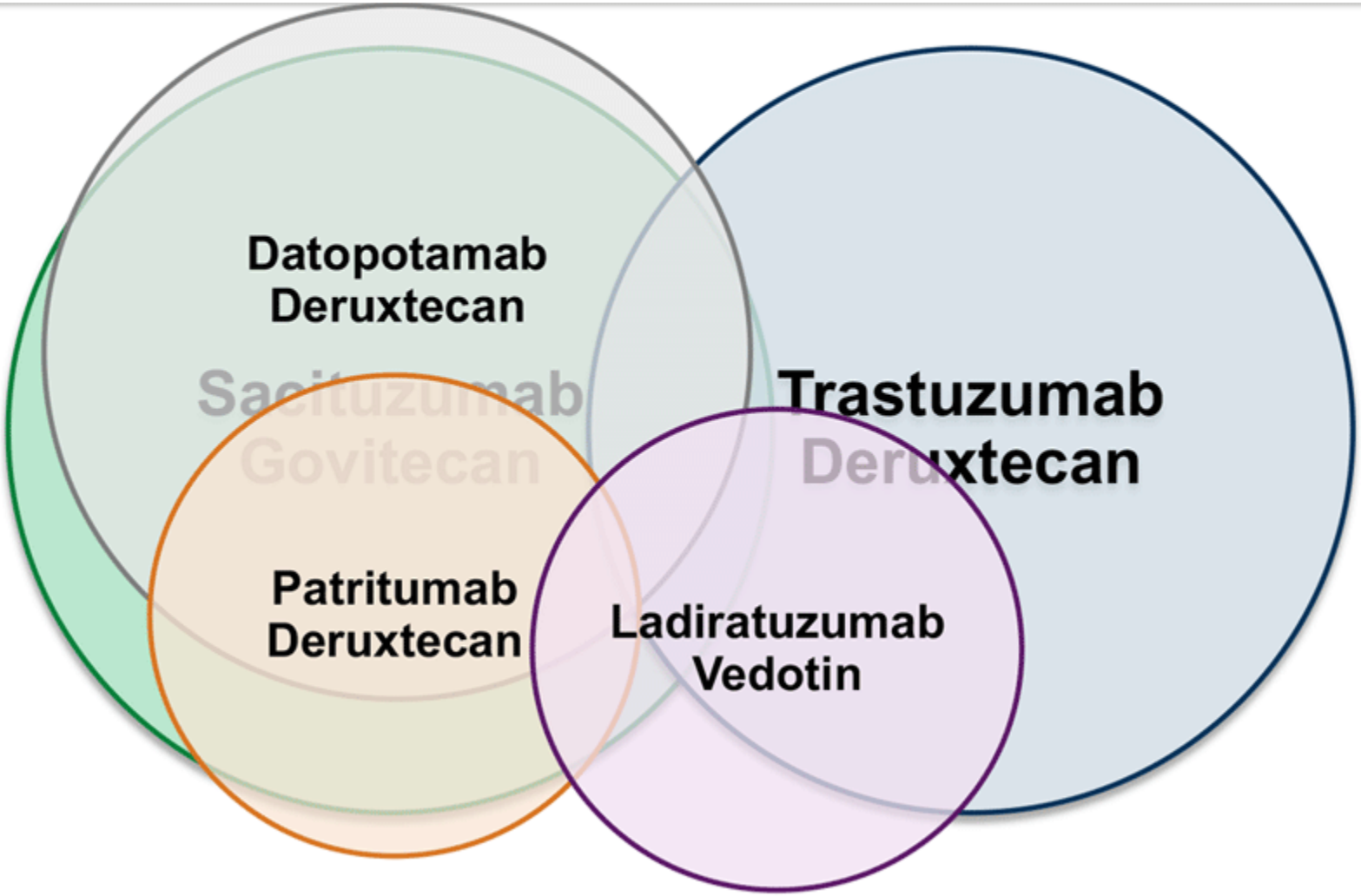
The Emerging Challenge of Sequencing



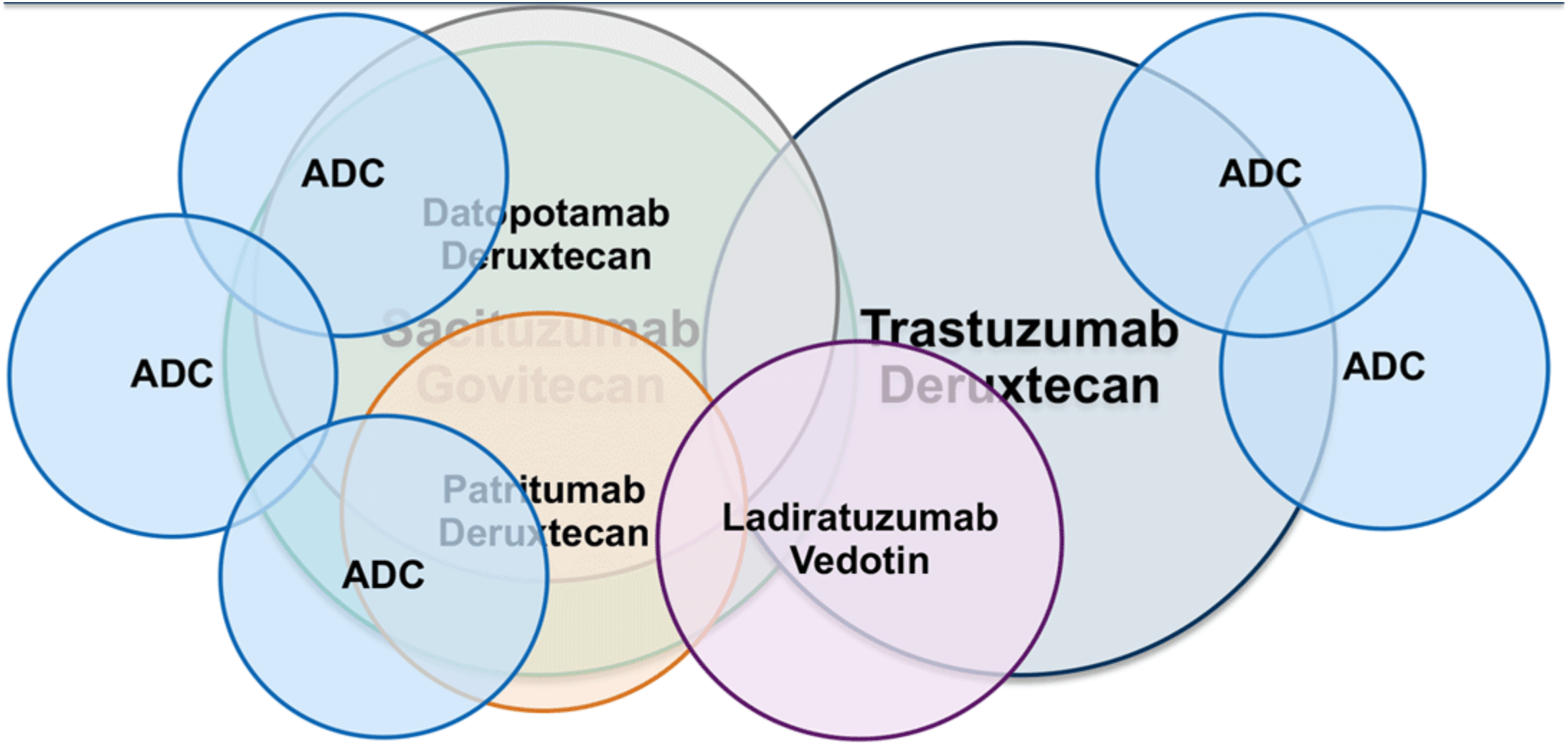
The Emerging Challenge of Sequencing



The Emerging Challenge of Sequencing



The Emerging Challenge of Sequencing



The Emerging Challenge of Sequencing

Need additional biomarkers to aid treatment selection

Need sequencing studies

Need of understanding of MoR