ADC nel carcinoma mammario metastatico

Valentina Guarneri
DiSCOG, Università di padova
Istituto Oncologico Veneto IRCCS

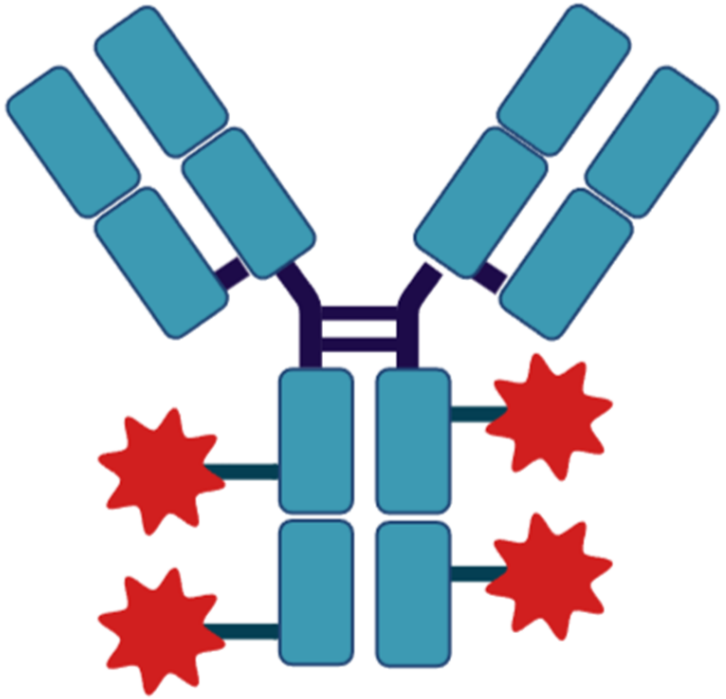
Disclosures

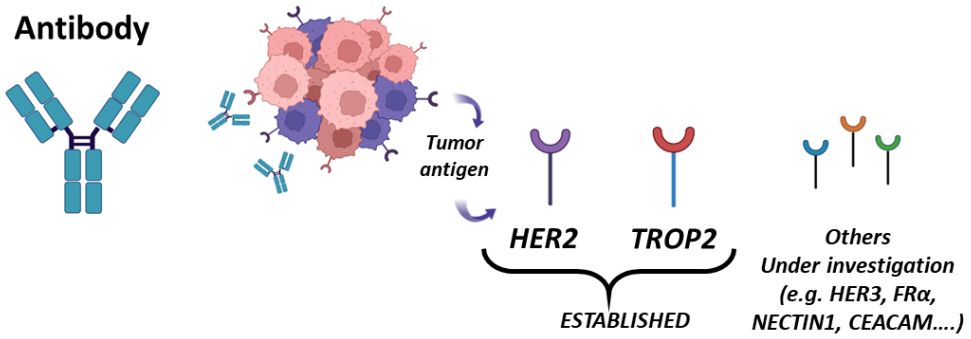
Personal fees for advisory board membership for AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, MSD, Novartis, Pfizer, Olema Oncology, Pierre Fabre, Menarini Stemline, Roche

Personal fees as an invited speaker for AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, GSK, Novartis, Roche, Zentiva, Menarini Stemline

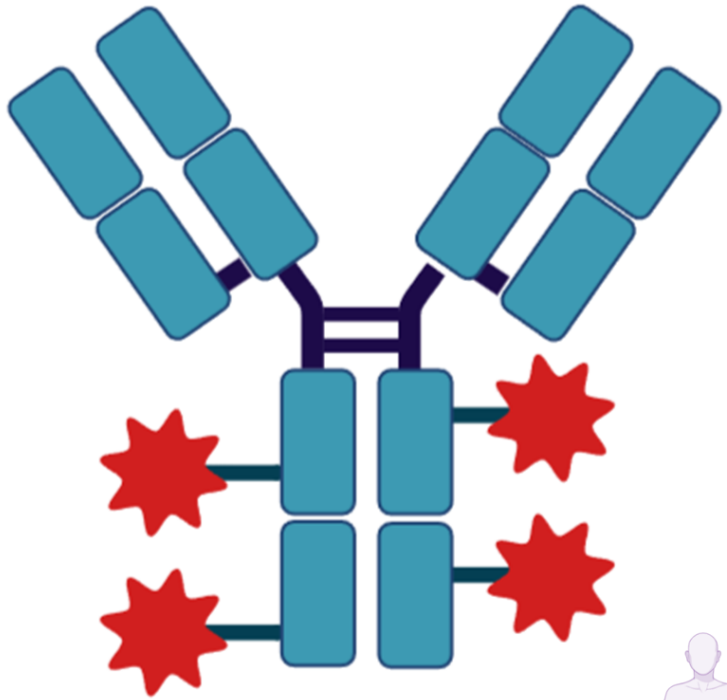
Personal fees for expert testimony for Eli Lilly

ADC

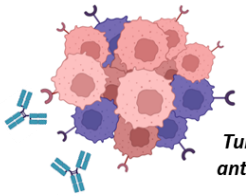



Antibody
Tumor antigen
HER2
TROP2
ESTABLISHED
Others
Under investigation
(e.g. HER3, FRα,
NECTIN1, CEACAM….)

ADC



Antibody



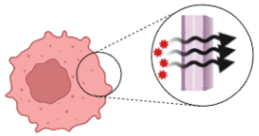
Tumor antigen

HER2 *TROP2*

ESTABLISHED

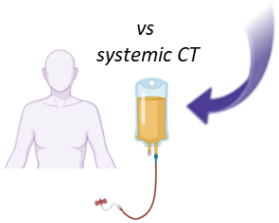
Others Under investigation (e.g. HER3, FRα, NECTIN1, CEACAM….)

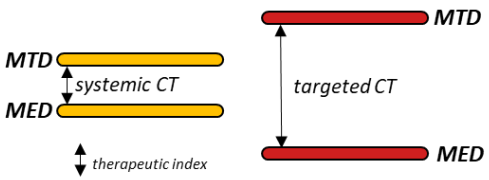
Payload



Membrane permeable

Membrane NON-permeable



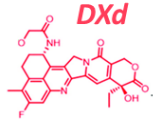


Topoinsomerase inhibitors

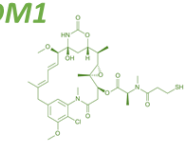
Microtubule inhibitors

DNA alkylating

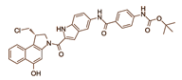
DXd



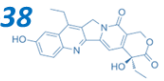
DM1



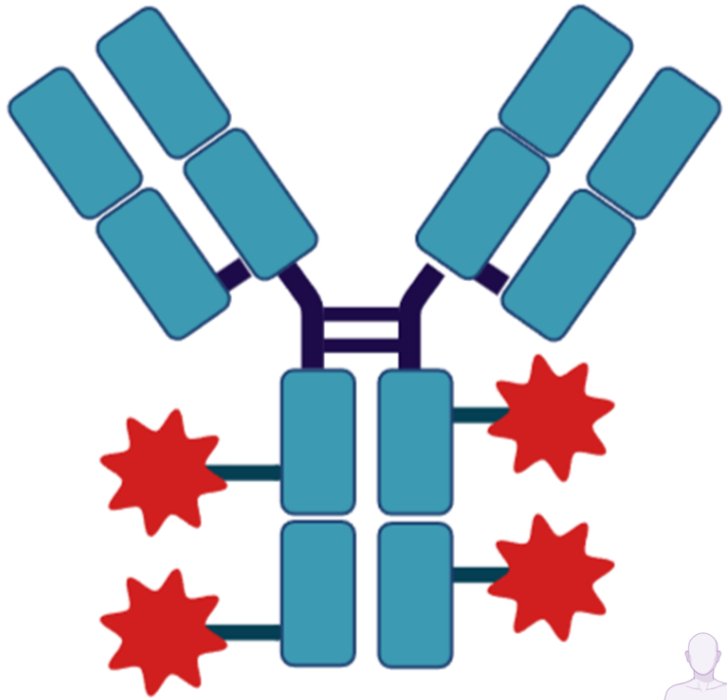
Duocarmycin



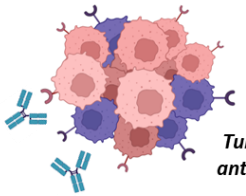
SN-38



ADC



Antibody



Tumor antigen

HER2 *TROP2*

ESTABLISHED

Others Under investigation (e.g. HER3, FRα, NECTIN1, CEACAM….)

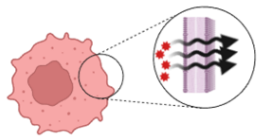
Linker

Non-Cleavable

Cleavable

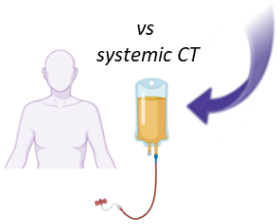
BYSTANDER EFFECT

Payload

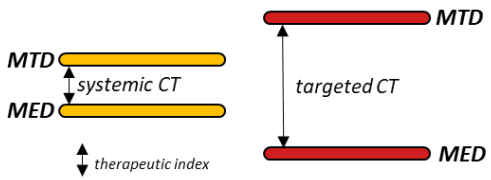


Membrane permeable

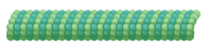
Membrane NON-permeable



vs systemic CT



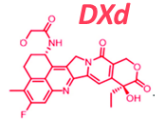
Topoinsomerase inhibitors



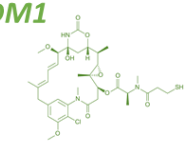
Microtubule inhibitors

DNA alkylating

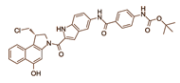
DXd



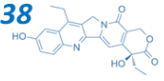
DM1

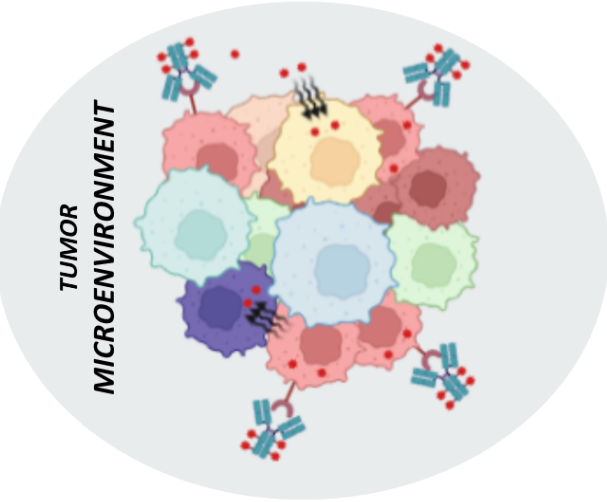


Duocarmycin



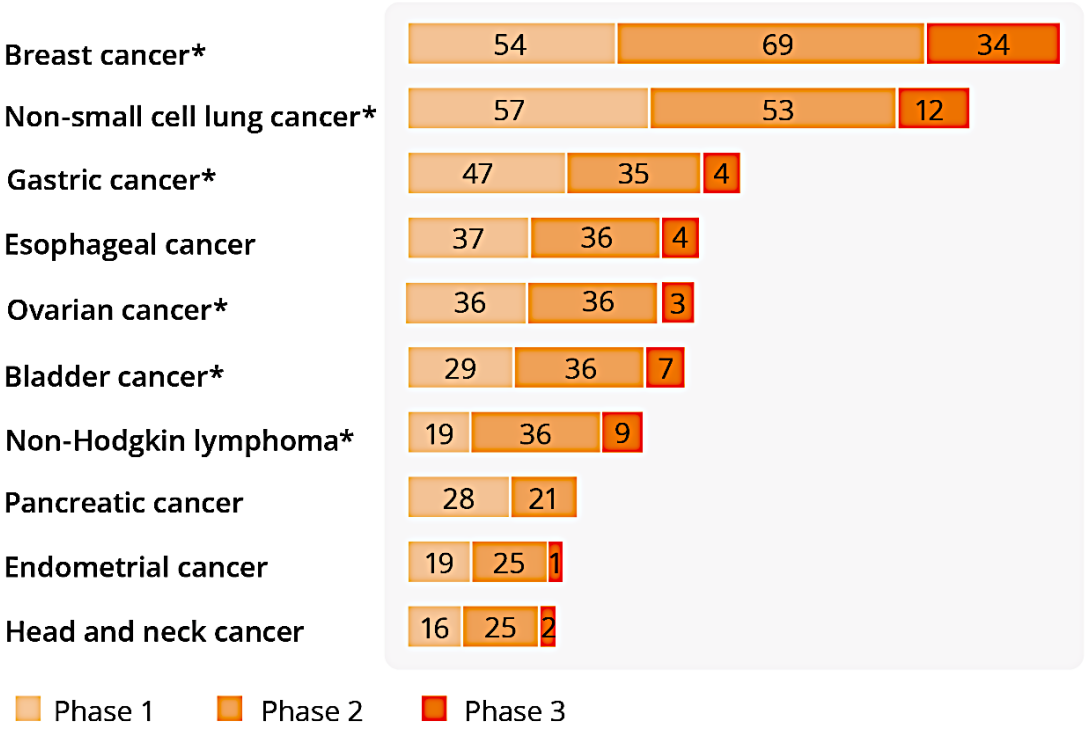
SN-38



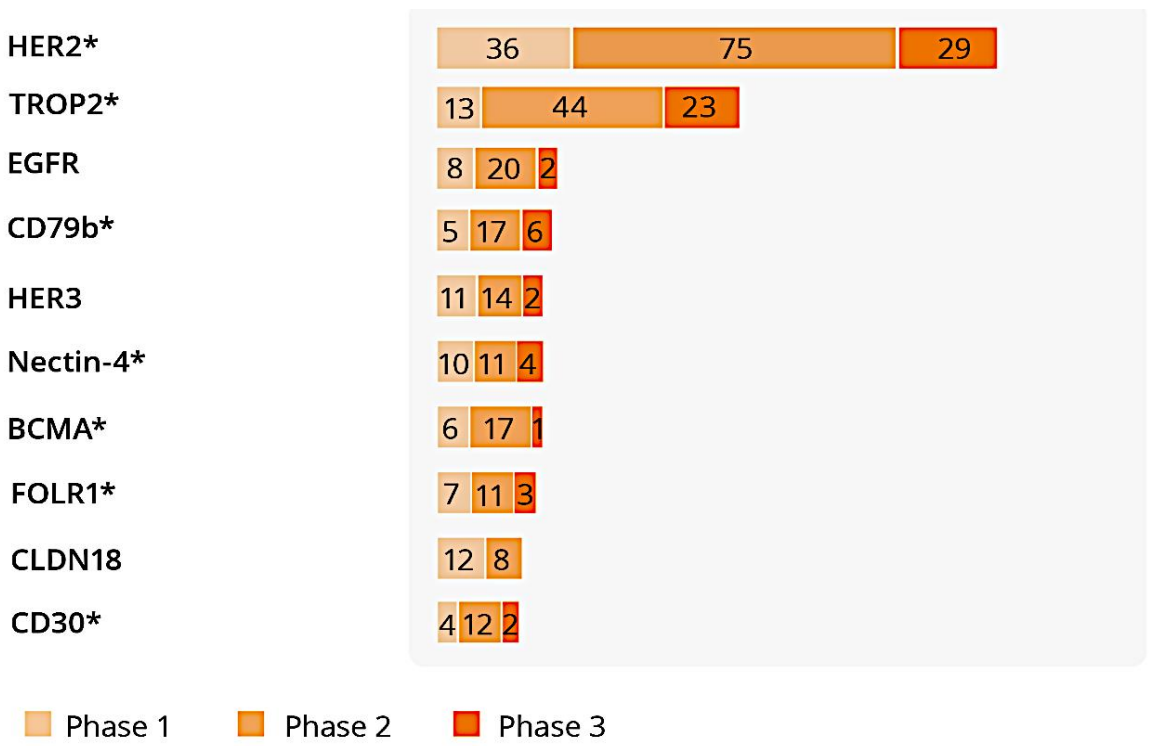


ADCs trials by Phase, Tumor type and Target

ADCs Trials by Phase and Tumor Type



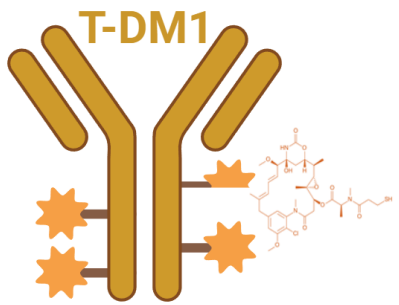
ADCs Trials by Phase and Target



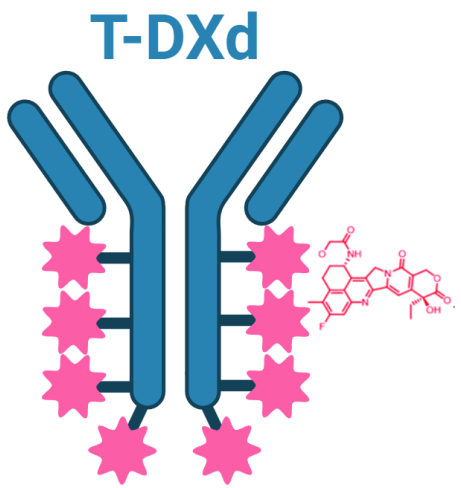
- **More than 140 ADCs are reported in clinical development**
- **22 novel ADCs were presented at ESMO 2024**

https://www.zs.com/insights/oncology-antibody-drug-conjugates-revolution

ANTI-HER2 ADC IN HER2+ BC: EVOLUTION OF AN OLD CONCEPT



PAYLOAD	MICROTUBULE INH.	TOPOISOMERASE I INH.
DRUG/mAB RATIO	3.5	7.7
LINKER	NOT CLEAVABLE	CLEAVABLE
BYSTANDER EFFECT	NO	YES



DB-03

HER2+ LABC or MBC

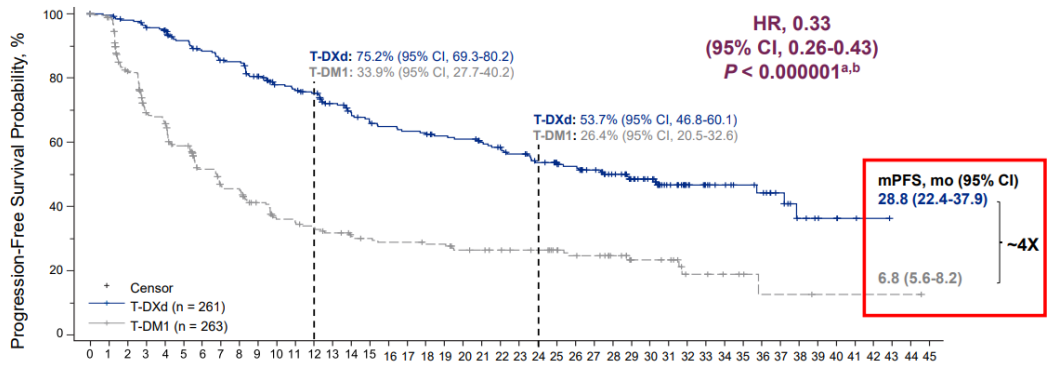
- Prior taxane and trastuzumab in advanced/metastatic setting
- Could have clinically stable, treated BMs

N=524

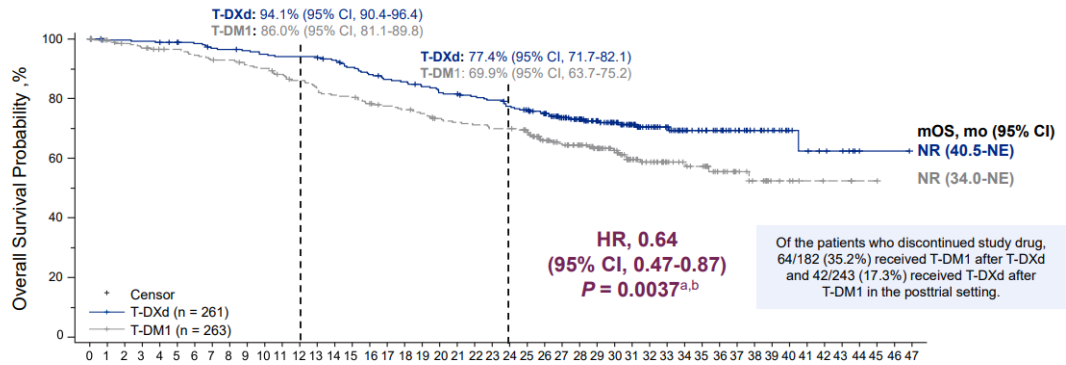
R

T-DXd

T-DM1



PFS (update)

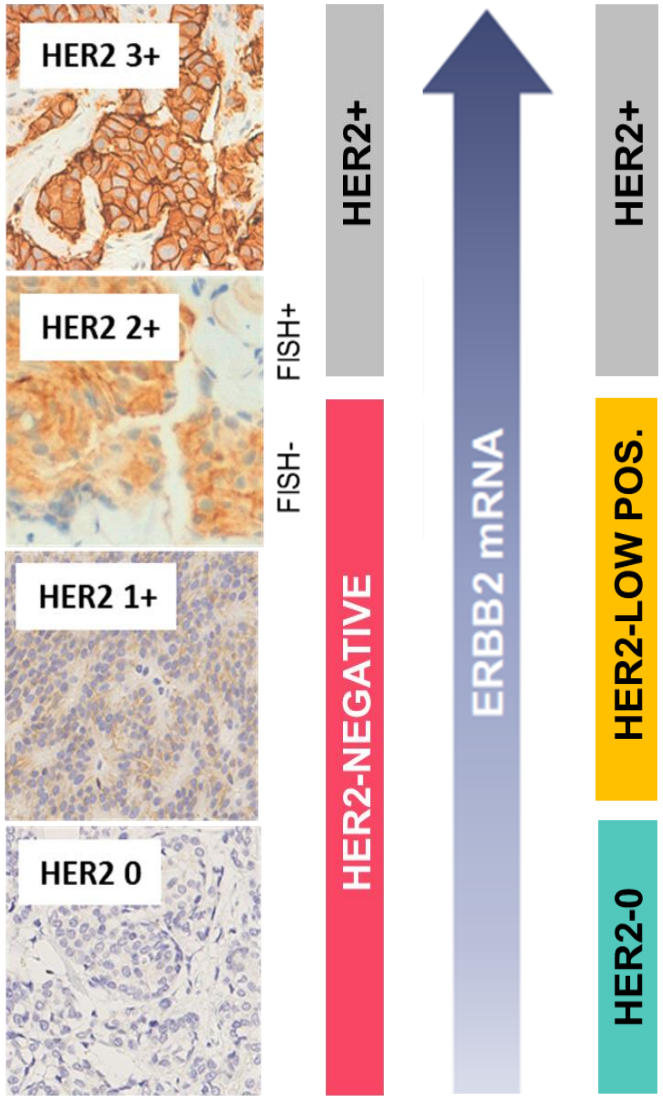


OS (update)

Enhertu RCP, https://www.ema.europa.eu/ last access aug 27 2024;

Cortes J et al, ESMO 2021, NEJM 2022; Hurvitz Lancet Oncol 2023

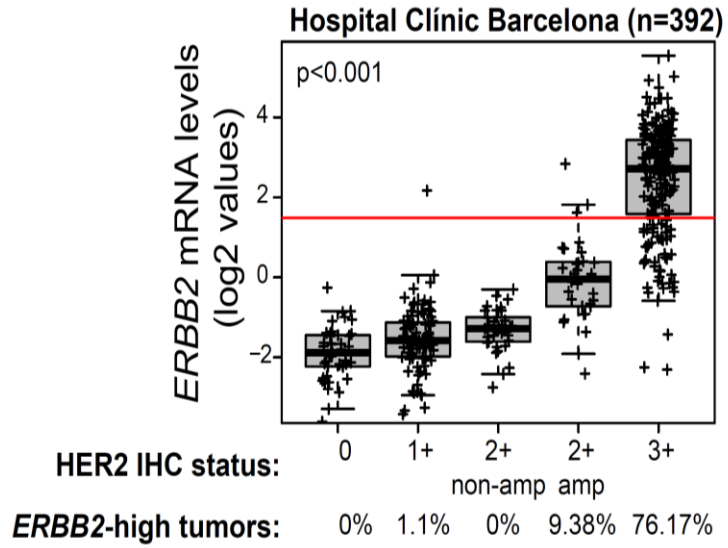
ANTI-HER2 ADC IN HER2- BC: CHANING THE PARADIGM

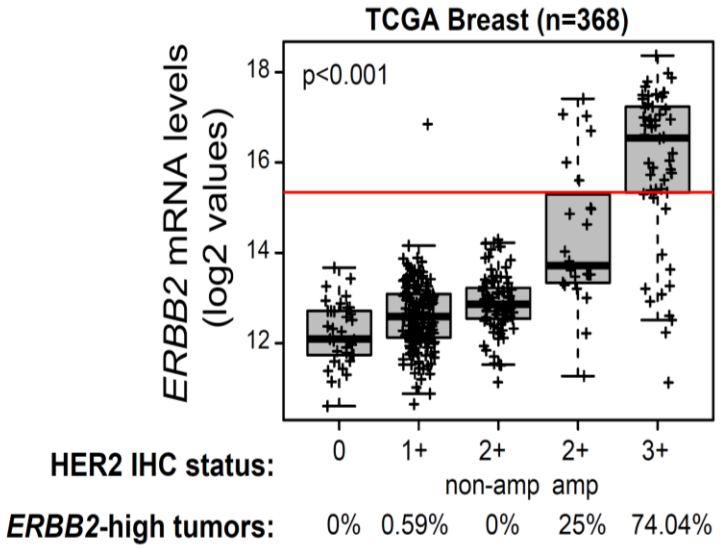


HER2 expression is a continuum

HER2 dichotomization in positive vs negative is intrinsically anchored to the predictive value of HER2 in terms of trastuzumab benefit

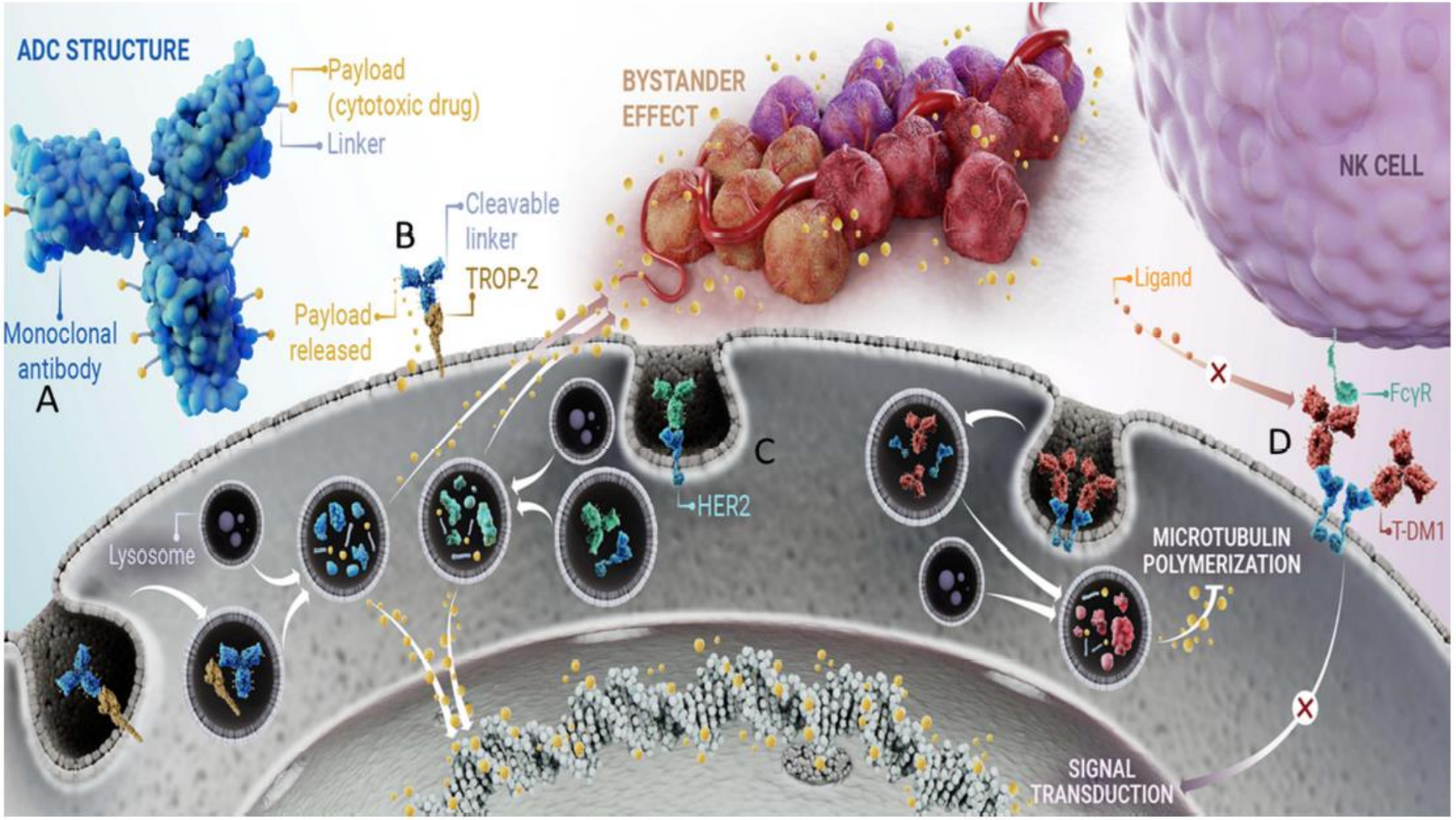
Levels of ERBB2 mRNA progressively increase across samples classified as: IHC score 0 **>** IHC score 1+ **>** IHC score 2+/ISH non-amplified **>** IHC score 2+/ISH amplified **>** IHC score 3+.





Griguolo et al, Cancers 2020

ANTI-HER2 ADC IN HER2-LOW BC: THE REVOLUTION
Novel anti-HER2 ADCs - The crux of the matter is the bystander effect



Ribeiro Monteiro et al, Dove Press 2024

2022 ASCO ANNUAL MEETING

DESTINY-Breast04

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, NY, USA

June 5, 2022

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

R 2:1

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

HR+ ≈ 480
HR− ≈ 60

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

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

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

Efficacy in All Patients (HR+ and HR−)

Progression-Free Survival

Hazard ratio: **0.50, *P* < 0.0001**

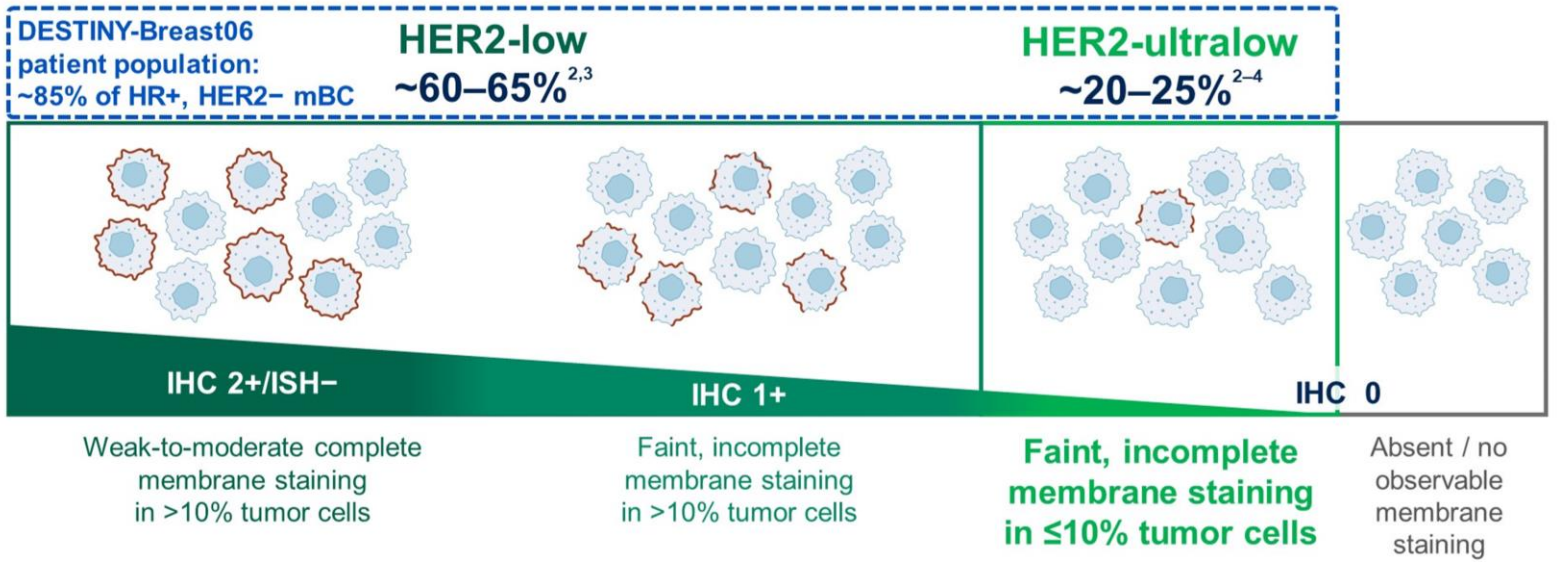
Overall Survival

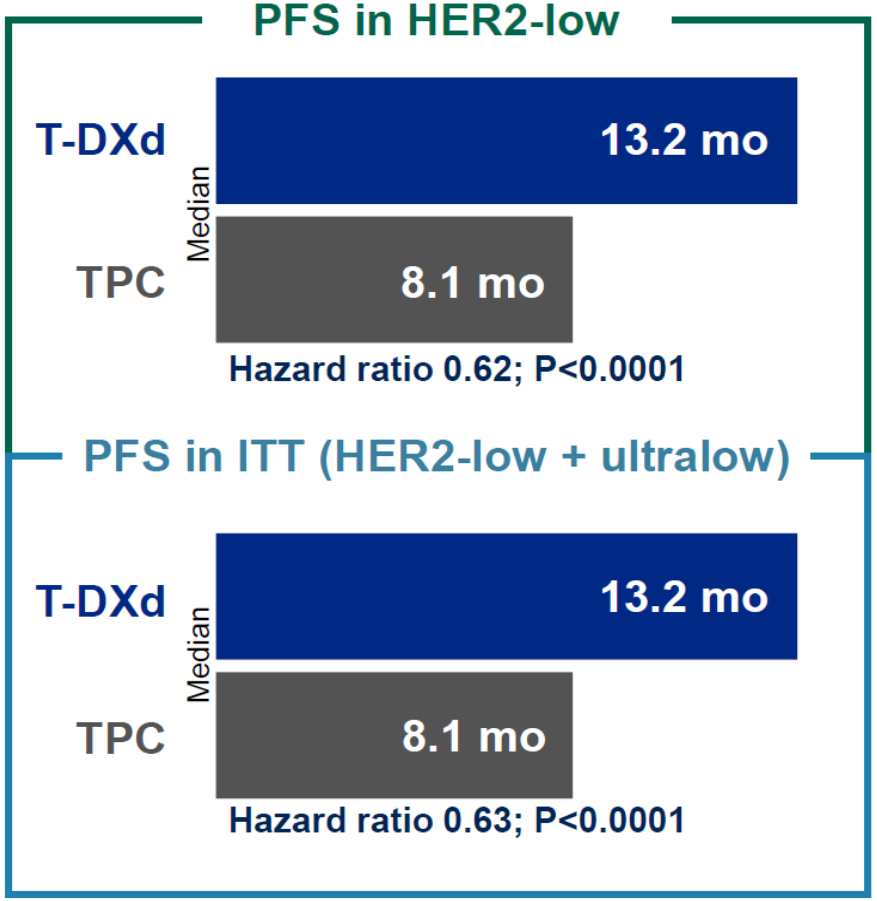
Hazard ratio: **0.64, *P* = 0.001**

2024 ASCO ANNUAL MEETING

DESTINY BREAST06

Trastuzumab deruxtecan vs physician's choice of chemotherapy in patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–low or HER2-ultralow metastatic breast cancer with prior endocrine therapy: primary results from DESTINY-Breast06





Curigliano et al, ASCO 2024; Bardia et al, NEJM 2024

ANTI-HER2 ADC: CONSIDERATIONS

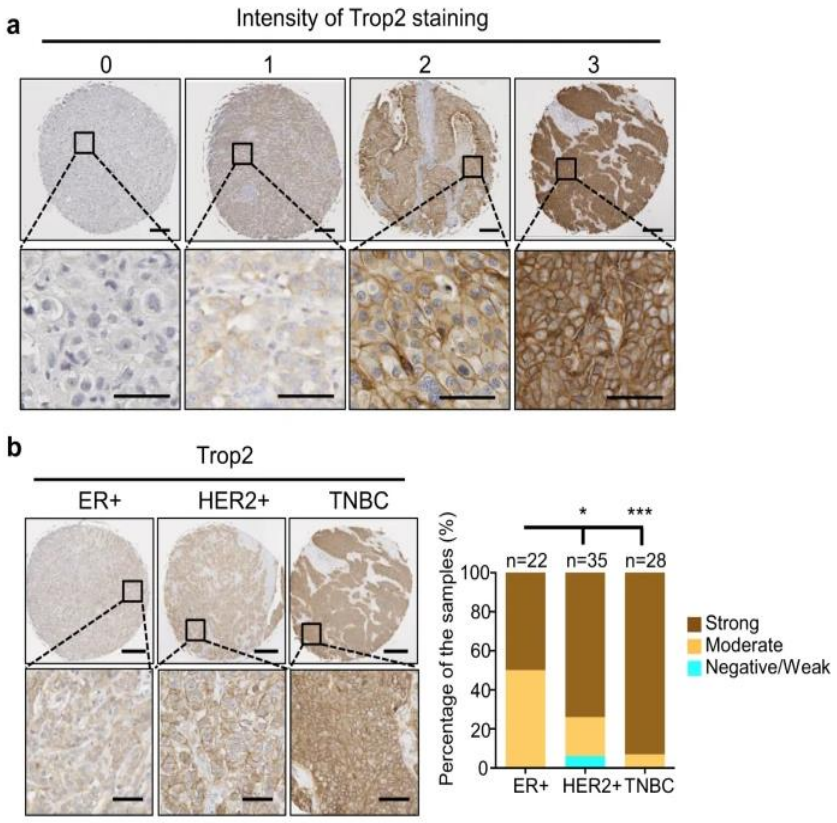
- **HER2 presents a dual role in breast cancer**:
  - Oncogene driver when overexpressed or amplified
  - Selection criterion for T-DXd in the metastatic setting when HER2 is negative but not entirely absent.

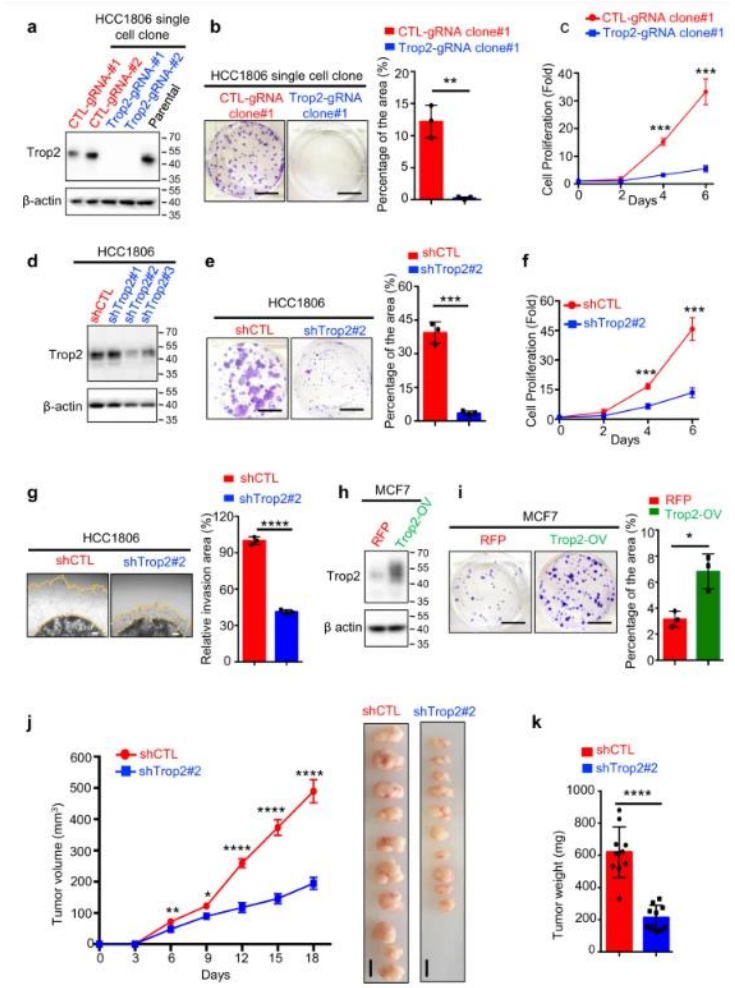
- **Currently, we are able to address around 90% of patients with hormone receptor-positive disease and 30-40% of triple-negative BC patients**
  - This marks significant progress in therapeutic options.

- **May have we missed an opportunity?**
  - The current landscape is extremely challenging in terms of HER2 detection and the introduction of the HER2 ultralow category adds a further layer of complexity.
  - This gap must be addressed during the time leading up to regulatory approval of T-DXd for HER2ultra low pts. It is crucial that we use this period to educate pathologists and clinicians.
    - Importance of analytical validation, central confirmation, as well as training of pathologists.

- **Future studies should focus on improving selection to enhance patients' prognosis**

ANTI-TROP2 ADC: RATIONAL FOR TARGETING TROP2 IN BC





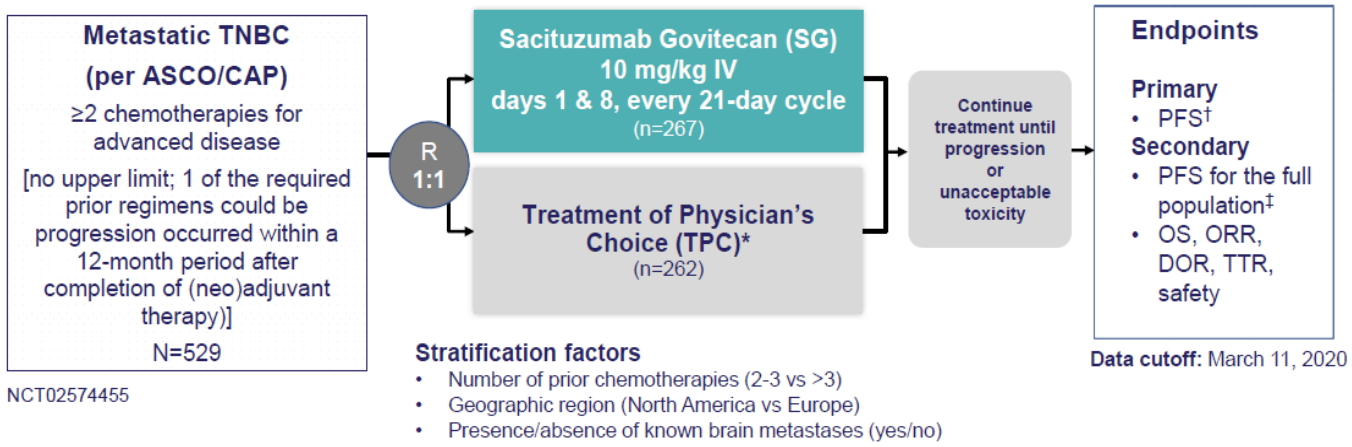
Trop2 is highly expressed in BC (>85-90%)

Trop2 regulates TNBC cell and tumor growth in vitro and in vivo

Unconclusive data regarding the prognostic impact of TROP2

Aslan et al, NPJ BC 2021

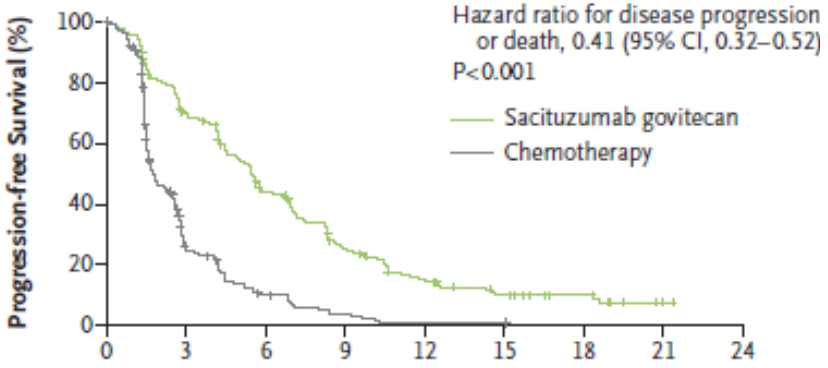
ANTI-TROP2 ADC IN TNBC: ASCENT TRIAL



- TNBC at initial diagnosis ≈70%
- Median anticancer regimens: 4 (2-17)
- 29-26% previously treated with PD-1/PD-L1 inhibitors
- 17-18% previously treated with PARP inhibitors

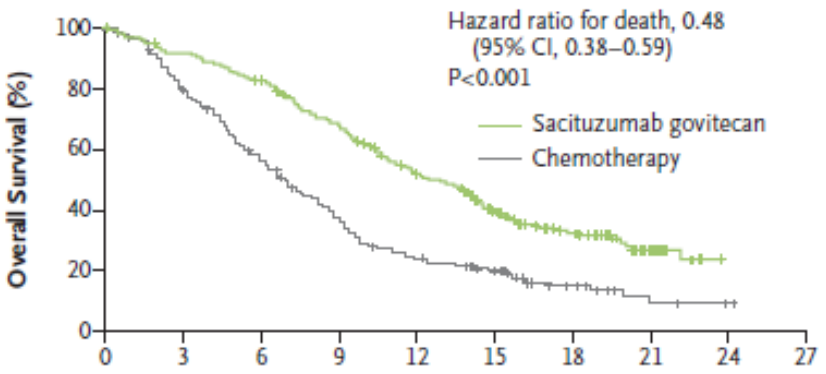
Without BMs

	No. of Patients	No. of Events	Median Progression-free Survival
			mo (95% CI)
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)



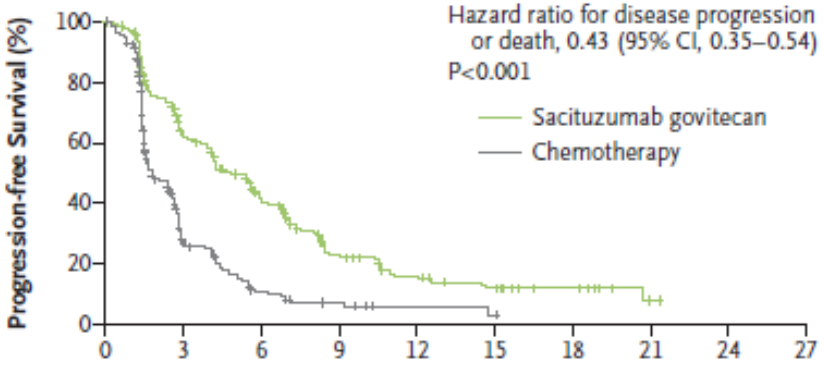
Without BMs

	No. of Patients	No. of Events	Median Overall Survival
			mo (95% CI)
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)

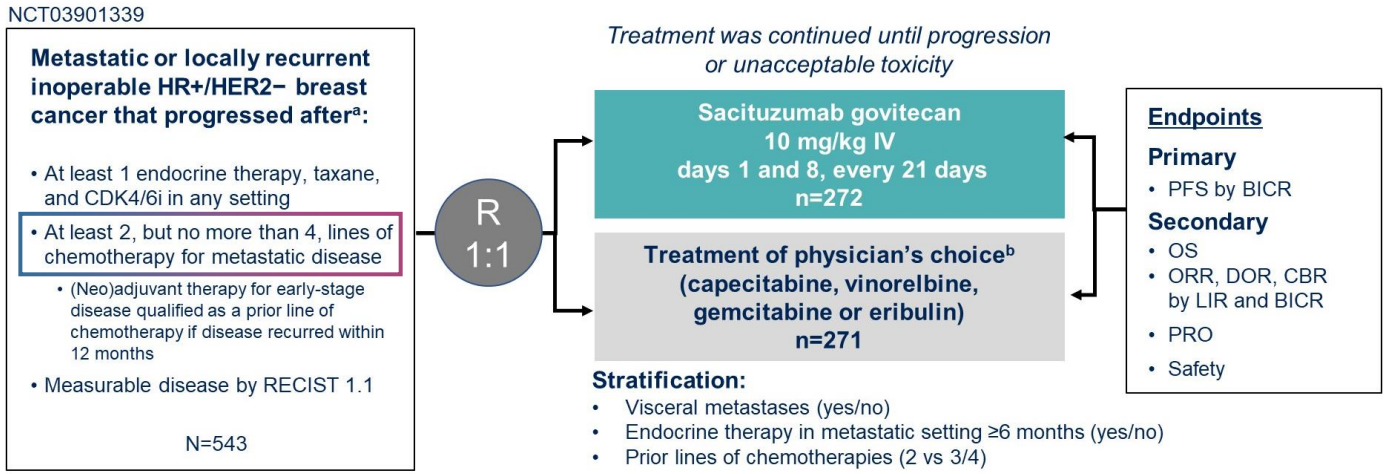


Full population

	No. of Patients	No. of Events	Median Progression-free Survival
			mo (95% CI)
Sacituzumab Govitecan	267	190	4.8 (4.1–5.8)
Chemotherapy	262	171	1.7 (1.5–2.5)

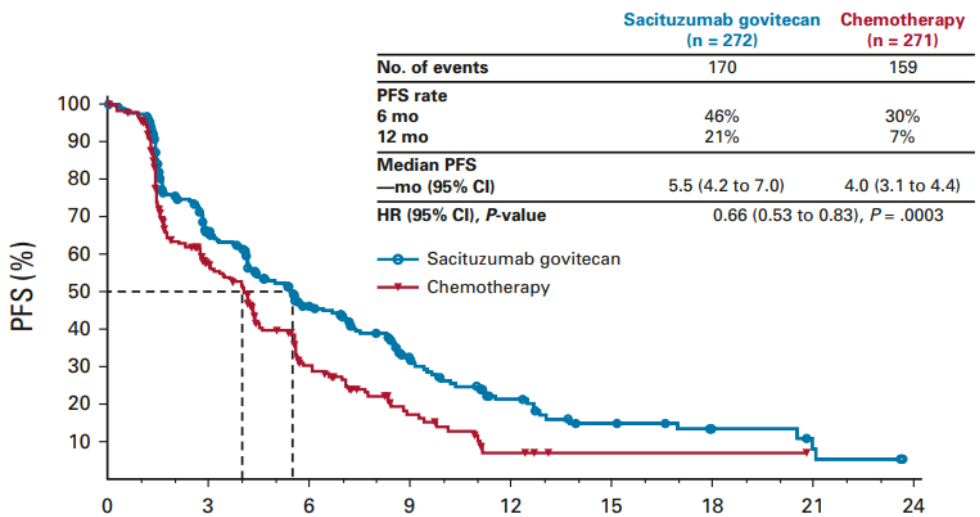


ANTI-TROP2 ADC IN HR+/HER2-: TROPICS-02 TRIAL

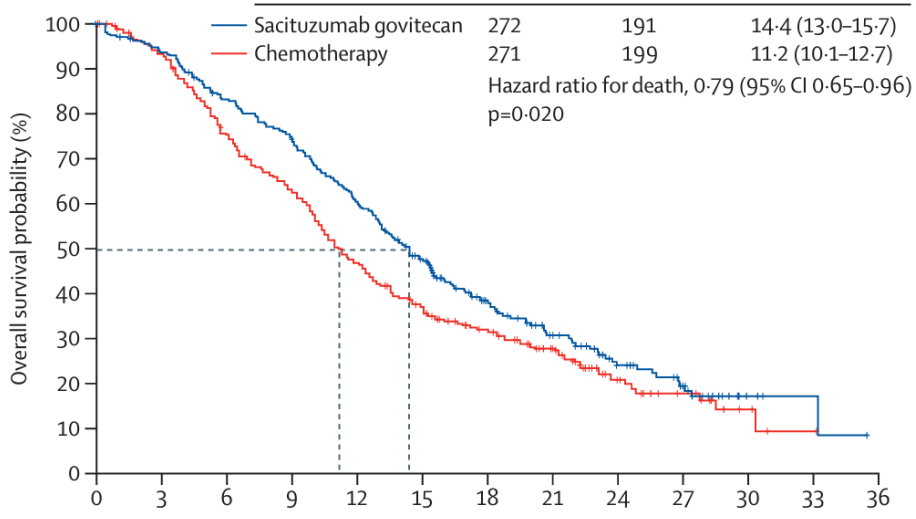


SG arm:

- Median **prior tx lines**: 3 (2, 38%; ≥3, 58%)
- **Prior CDK 4/6i use**: ≤12 mos 58%



	Sacituzumab govitecan (n = 272)	Chemotherapy (n = 271)
No. of events	170	159
PFS rate		
6 mo	46%	30%
12 mo	21%	7%
Median PFS —mo (95% CI)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)
HR (95% CI), *P*-value	0.66 (0.53 to 0.83), *P* = .0003	



	Number of patients	Number of events	Median overall survival, months (95% CI)
Sacituzumab govitecan	272	191	14·4 (13·0–15·7)
Chemotherapy	271	199	11·2 (10·1–12·7)

Hazard ratio for death, 0·79 (95% CI 0·65–0·96)
p=0·020

TROPIC02 trial: more heavily pre-treated population compared to DB04 trial.

SG efficacy confirmed regardless of HER2 IHC groups → confirmed also in HER2-low BC

Rugo et al, JCO 2022;
Rugo et al, Lancet Oncol 2023; Rugo et al, ESMO 2022

ANTI-TROP2 ADC IN HR+/HER2-: THE STORY IS NOT OVER
A new kid on the block - TROPION-BREAST01 TRIAL

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

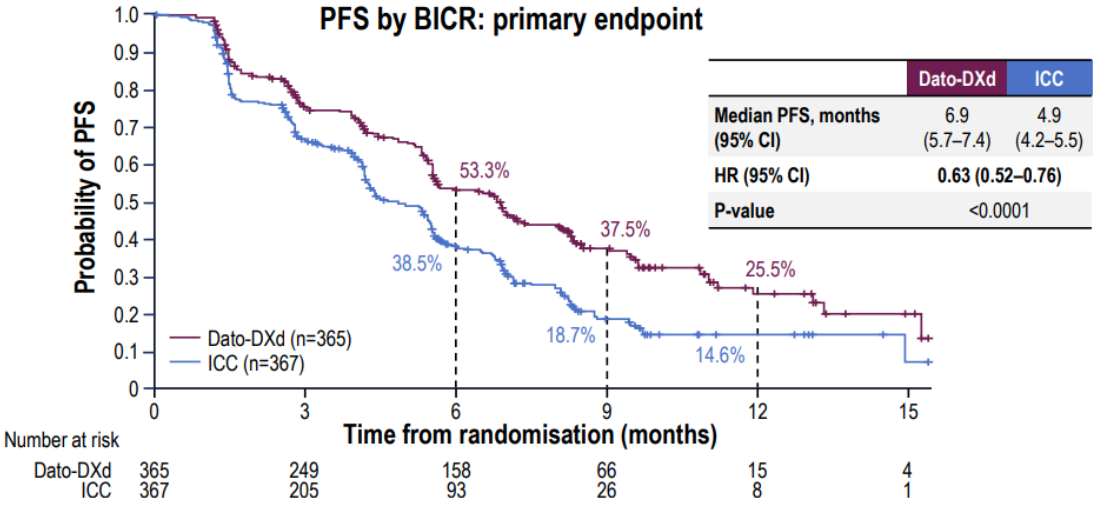
1:1

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

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

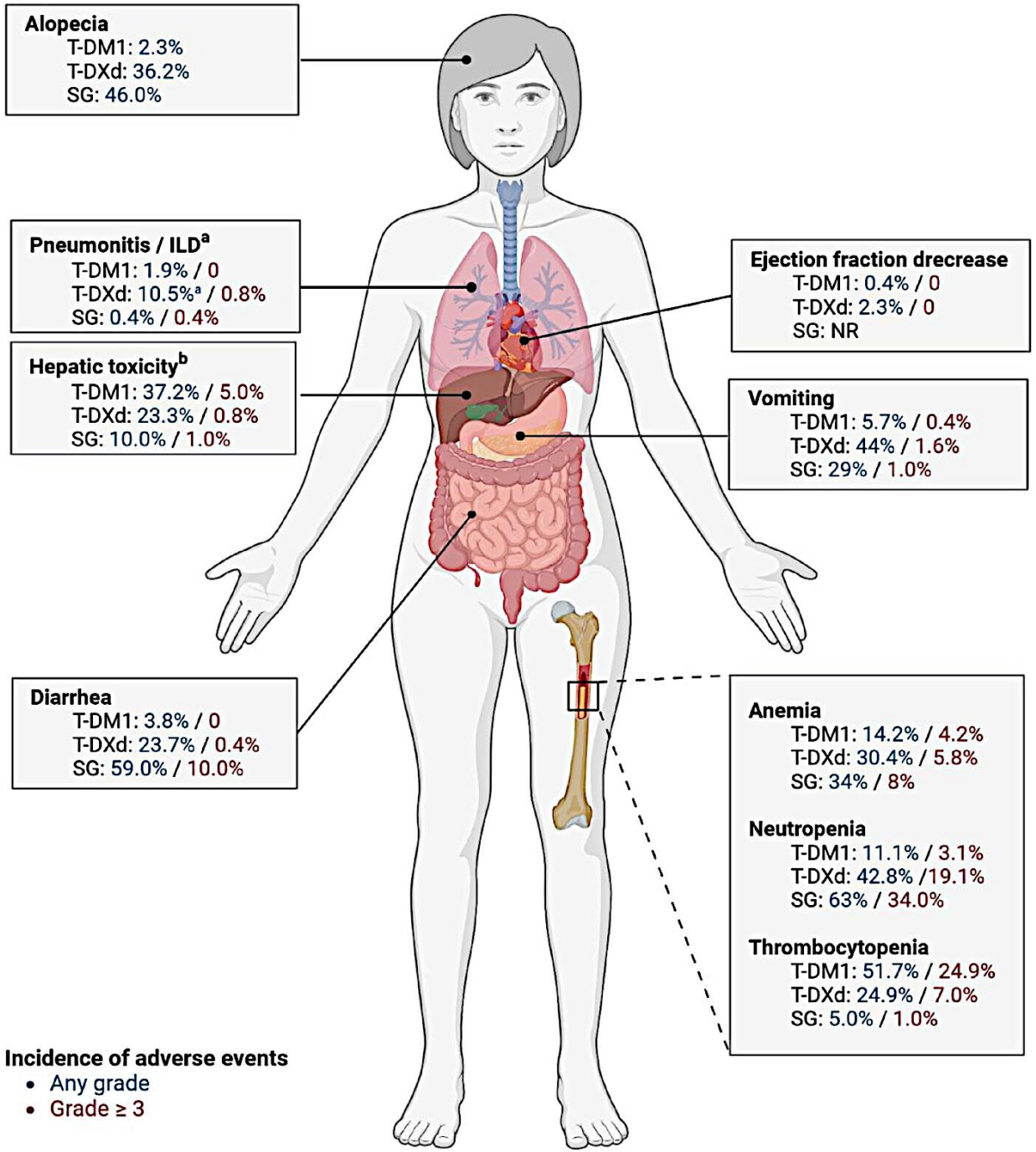
PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system				
Anaemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

Bardia ESMO 2024

Potential Mechanisms of Action and Toxicity of ADCs

- Bystander effect
- Antibody - Targeted delivery of the payload
- Antibody - Target biological interaction
- Immune response to the Antibody
- Sustained and prolonged very low dose of free-payload in the circulation
- Albumin transfer of the payload
- Combination of multiple mechanisms



ADCs may cause toxicities through different mechanisms, depending on the chemical properties of the payload (i.e., hydrophilic), the drug-to antibody ratio (DAR), as well as the stability of the linker (cleavable or not) and the expression of the target in non-cancer tissues.

Evidence suggests that most of the off-targeted ADC toxicity relates to off-target delivery of the cytotoxic payload, and that this is the critical driver for the tolerability of these drugs and, ultimately, the recommended dose used in patients

Nader-Marta G, et al. Therapeutic Advances in Medical Oncology. 2023;15.
doi:10.1177/17588359231183679

THE EVOLVING LANDSCAPE
The expansion of the treatment arsenal calls for strategic sequencing

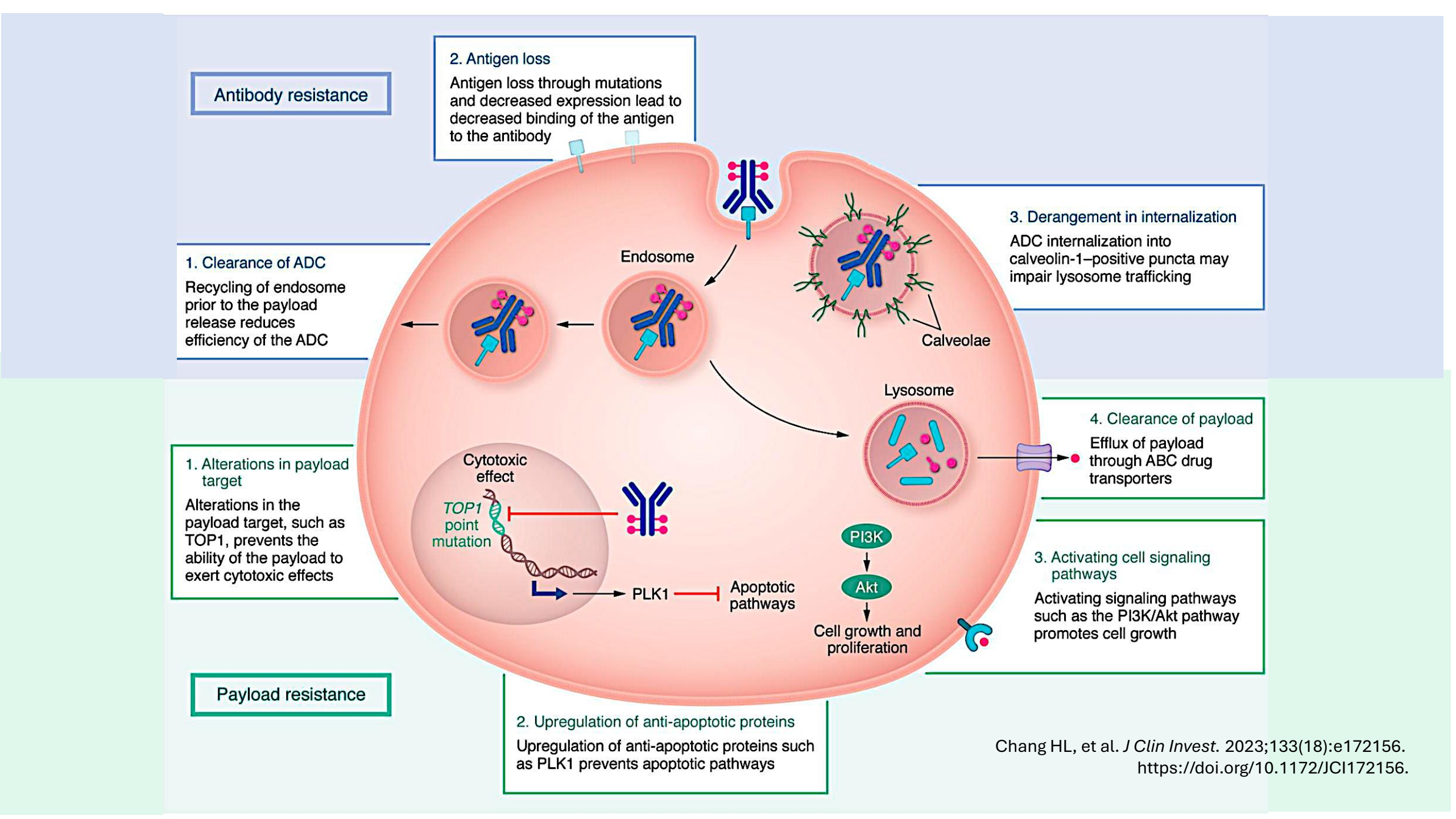
	Population	ADC 1	ADC	
Abelman	**n=68** HR+: 44%, TNBC: 56% Prior lines of treatment: 3-7	mTTP: 5.4mo	mTTP:2.5mo	Trop1 variant may drive resistance
Raghavendra	**n=33** Subtype data not available	PFS: SG: 4.6 mo. PFS: TDXd: 7.6 mo	PFS SG→ TDXd: 5.5mo PFS TDXd→ SG: 2.4 mo	Suggest superiority of T-DXd but unknown HR status
Huppert	**n=84** HR+/HER2-low: 67% HR-/HER2-low: 33% Prior lines of treatment: 2-4.5	TTNT SG→TDXd: HR+ 8 mo HR- 7.8 mo TTNT TDXd → SG: HR+ 5.5 mo HR- undetermined	TTNT SG→TDXd: HR+ 3.7 mo HR:- 2.8 mo TTNT TDXd → SG: HR+ 2.7mo HR- undetermined	All HER2-low expressing Longer PFS with ADC1 than ADC2
Poumeaud	**n= 179** HR+/HER2-low: 69% HR-/HER2-low: 31% Prior lines of treatment: 3-5 Prior ADC use: 64% received SG as ADC1	mPFS: 4.5 mo. mPFS HR+/HE2-low: 2.7 mo. (T-DXd) mPFS HR-/HE2-low: 4.9 mo. (SG)	. SG-T-DXd- PFS2: 3.1mo. T-DXd-GG: 2.2 mo.	In MV analysis **SG -->T-DXd was associated with improved outcomes** 50% primary resistance to ADC2

- Current evidence limited by the **retrospective nature**

(heterogeneous population in terms of composition and tx line, not necessarily immediate sequencing)

- Current data suggest that **ADC#2 may have shorter PFS that ADC#1**

Chavez SABCS 2023



Chang HL, et al. *J Clin Invest*. 2023;133(18):e172156. https://doi.org/10.1172/JCI172156.

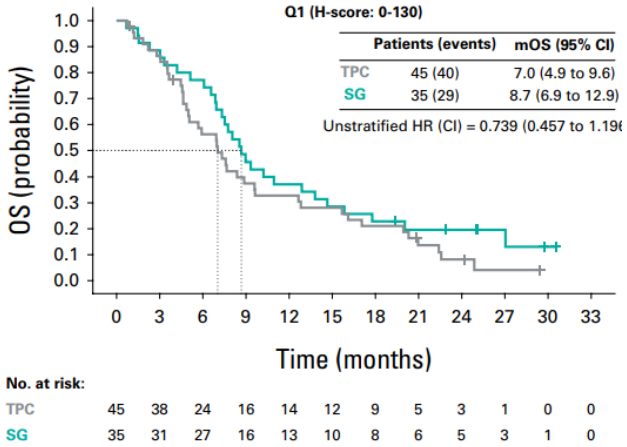
THE EVOLVING LANDSCAPE
The expansion of the treatment arsenal calls for strategic sequencing

Biomarkers of resistance

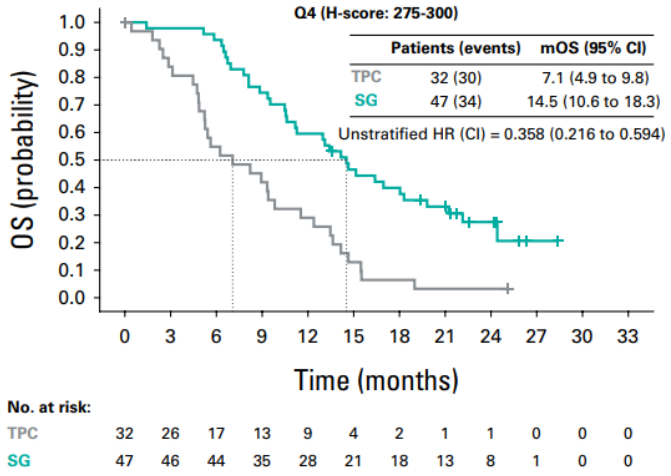
Biomarker analysis from the ASCENT trial

0 ——— **300**

LOWEST H score category

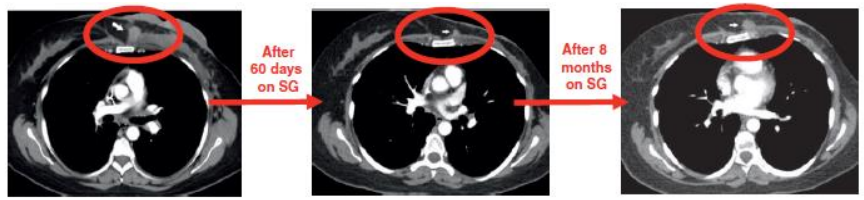


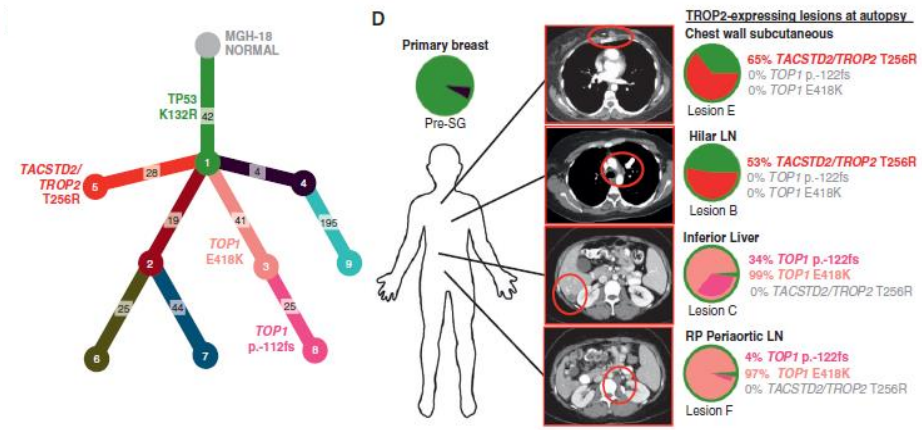
HIGHEST H score category



a trend was observed for improved OS across quartiles

Major phylogenetic branches of resistance (mutually-exclusive)





Mutations in TROP2 and TOP1 genes associated with acquired (secondary) resistance to SG

Bardia et al, JCO 2024

THE EVOLVING LANDSCAPE
The expansion of the treatment arsenal calls for strategic sequencing

SAME TARGET - HER2+ disease
T-DXd after T-DM1

DESTINY-Breast02
Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

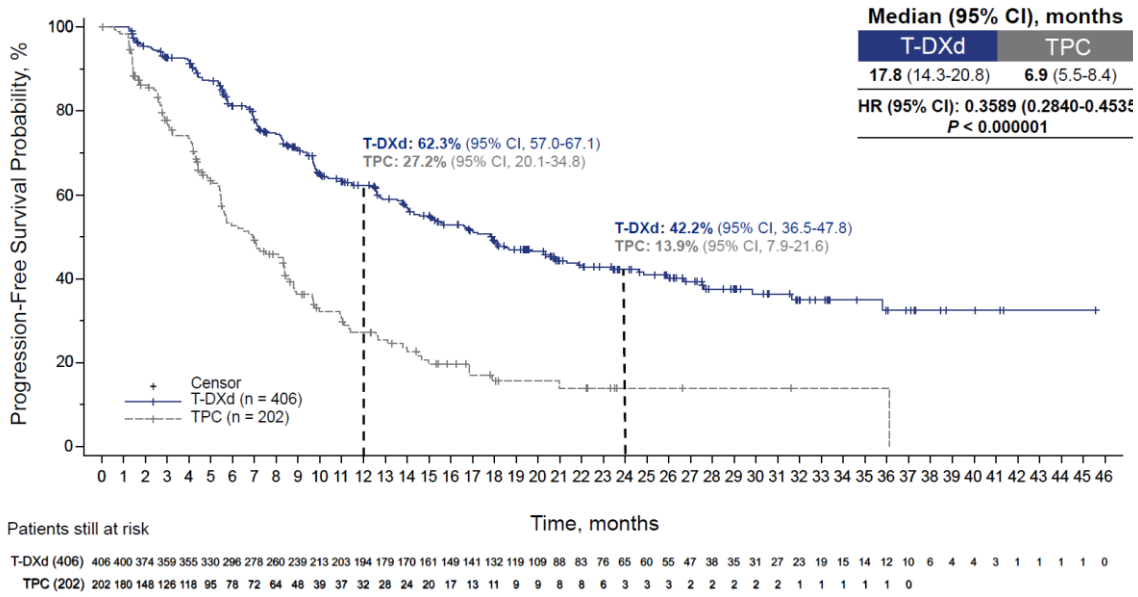
Key secondary endpoint
- OS

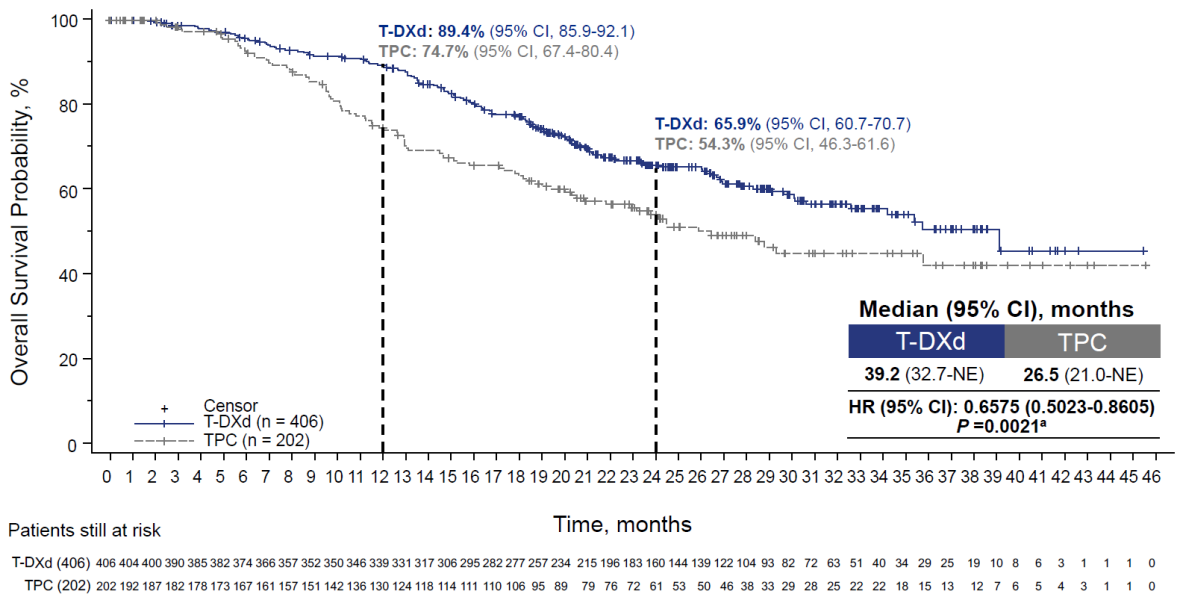
Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm





Krop et al, SABCS 2022; André et al, Lancet Oncol 2023

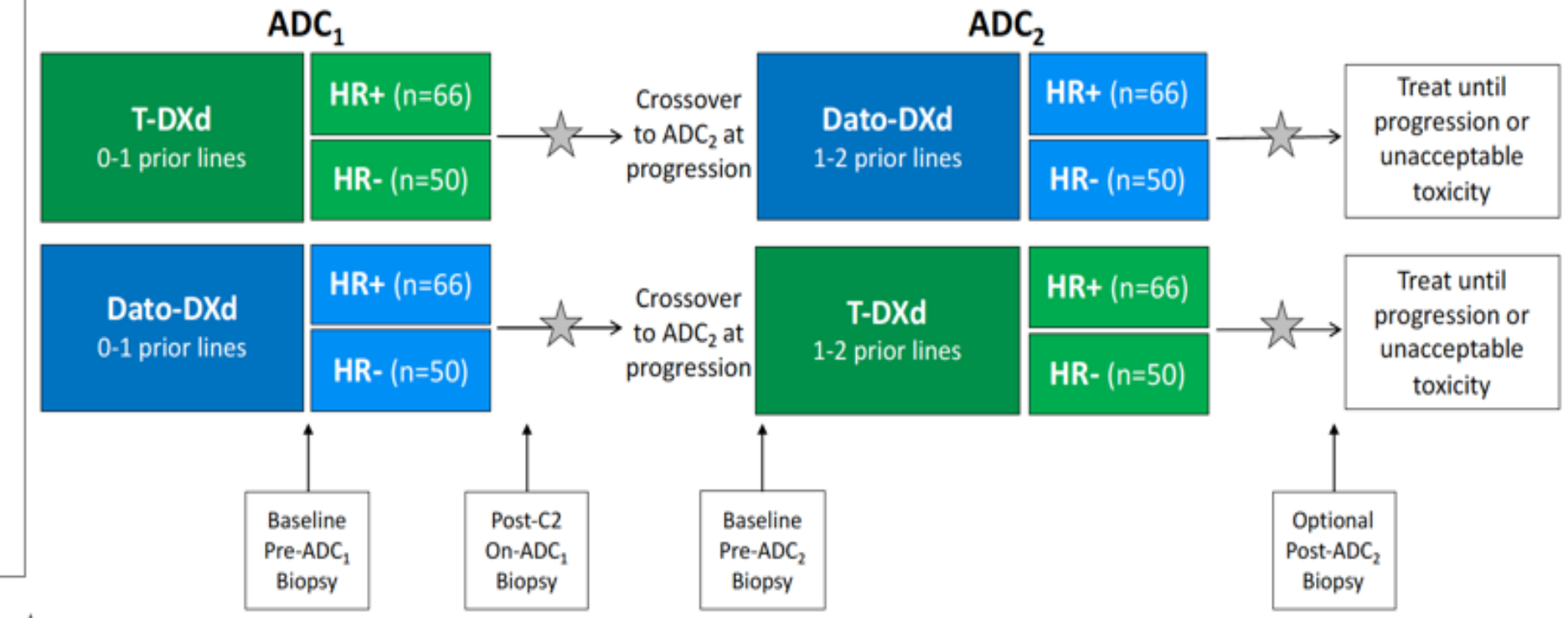
TBCRC-064: TRADE DXd
Treatment of refractory BC with Dato-DXd or T-DXd

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



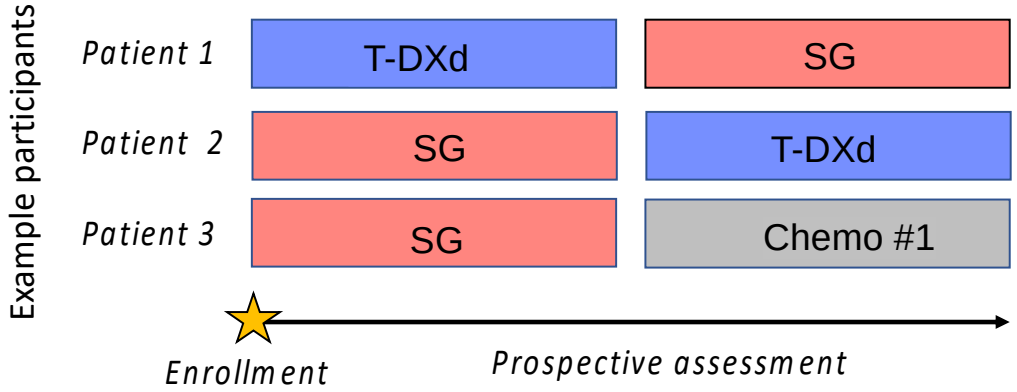
Tumor assessments + Blood collection q9w

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

Garrido-Castro A, et al. DFCI

Registry Sequencing Study

Cohorts 1 & 2: Enrollment Prior to ADC #1



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

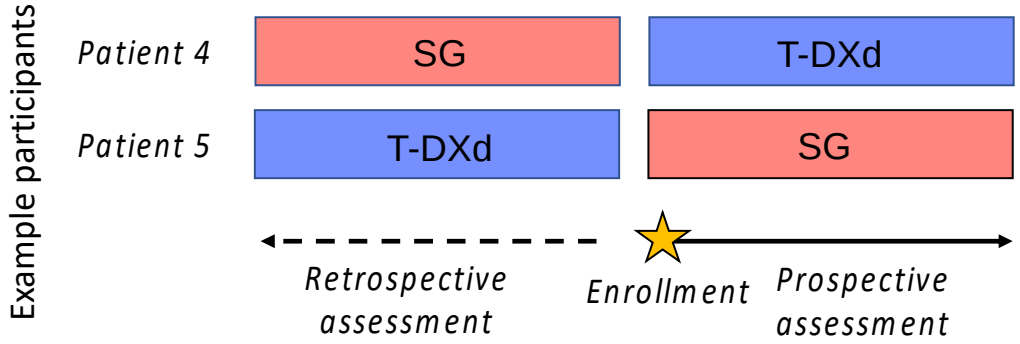
Cohort 2: TNBC, HER2 low
~25 patients

- 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

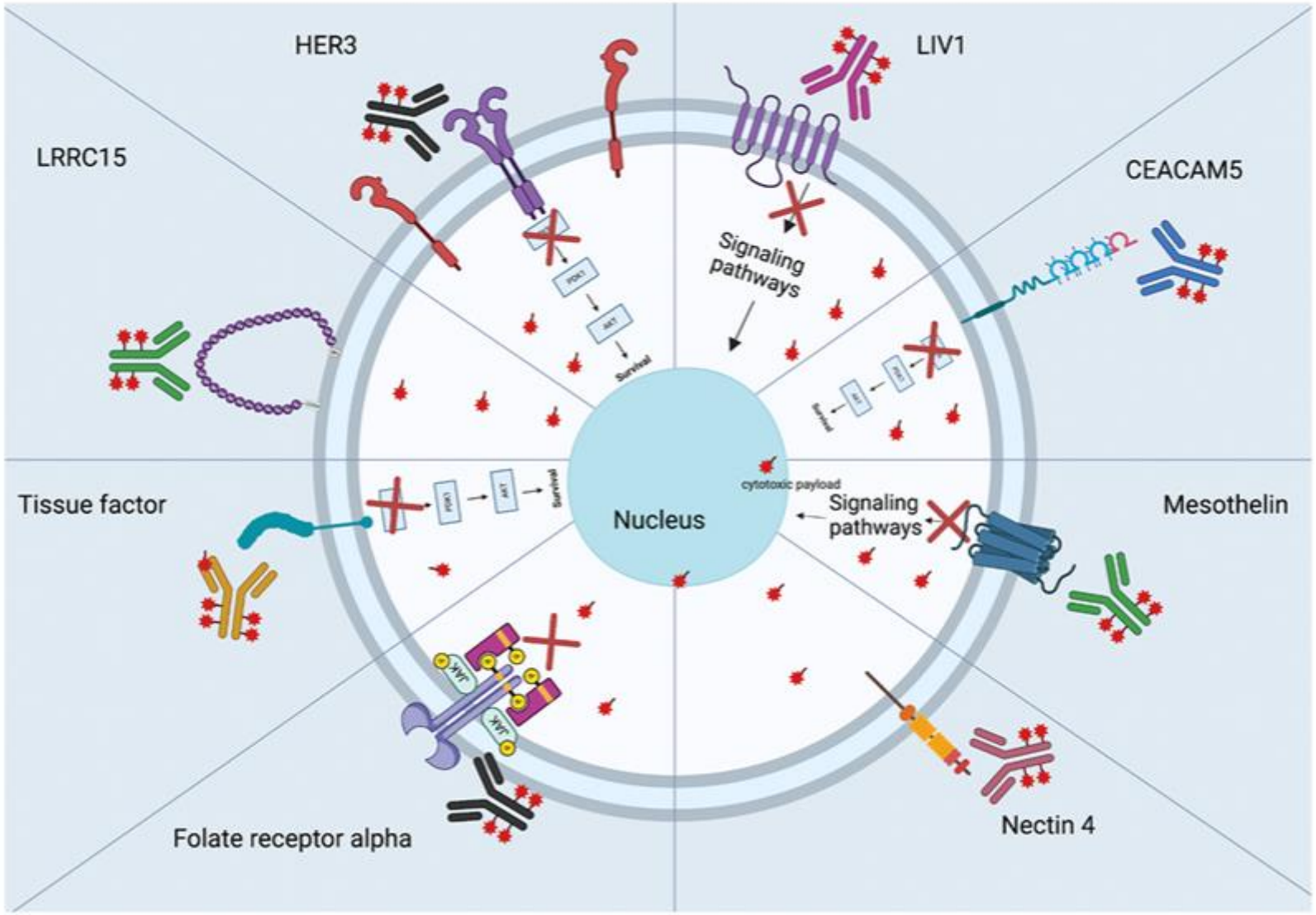
- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

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

Huppert L, et al. UCSF.

THE EVOLVING LANDSCAPE: NEW TARGETS

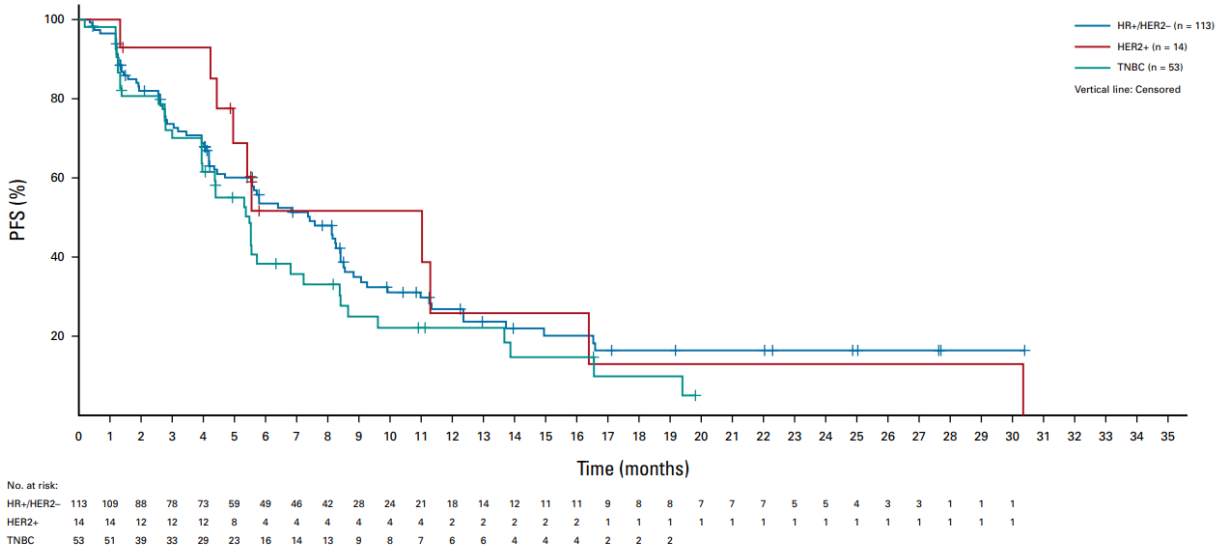


Schlam et al, Critical reviews in Oncology

THE EVOLVING LANDSCAPE: NEW TARGETS

HER3
Patritumab Deruxtecan

Outcome (BICR per RECIST 1.1)	HR+/HER2− (n = 113) HER3-High[a] and HER3-Low	TNBC (n = 53) HER3-High[a]	HER2+ (n = 14) HER3-High[a]
Confirmed ORR (95% CI), %[b]	30.1 (21.8 to 39.4)	22.6 (12.3 to 36.2)	42.9 (17.7 to 71.1)
Best overall response, %[c]			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0
DCR (95% CI), %	80.5 (72.0 to 87.4)	79.2 (65.9 to 89.2)	92.9 (66.1 to 99.8)
CBR (95% CI), %	43.4 (34.1 to 53.0)	35.8 (23.1 to 50.2)	50.0 (23.0 to 77.0)
DOR, median (95% CI), months	7.2 (5.3 to NE)	5.9 (3.0 to 8.4)	8.3 (2.8 to 26.4)
PFS, median (95% CI), months	7.4 (4.7 to 8.4)	5.5 (3.9 to 6.8)	11.0 (4.4 to 16.4)
Six-month PFS rate (95% CI), %	53.5 (43.4 to 62.6)	38.2 (24.2 to 52.0)	51.6 (22.1 to 74.8)
OS, median (95% CI), months	14.6 (11.3 to 19.5)	14.6 (11.2 to 17.2)	19.5 (12.2 to NE)



Krop et al, JCO 2023

ICARUS BREAST01: Study Design

Multi-center, single-arm, phase 2 study (NCT04965766)

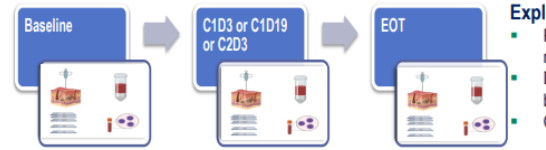
KEY ELIGIBILITY CRITERIA*:
-unresectable locally advanced/metastatic BC
-HR+/HER2-neg[a]
-progression on CDK4/6inh + ET
-progression on 1 prior chemotherapy for ABC
-prior PI3K/AKT/mTORinh allowed
-no prior T-DXd

HER3-DXd 5.6 mg/kg every 3 weeks until PD or unacceptable toxicity

Primary Endpoint:
- Investigator-assessed confirmed ORR

Secondary Endpoints:
- DOR, PFS, CBR, OS
- Safety and tolerability

Mandatory:
-tumor biopsy (1 frozen + 3 FFPE)
-blood (whole blood + serum)



Exploratory Endpoints:
- Predictors of response/resistance
- Dynamics of HER3 expression before and after treatment
- CTCs levels during treatment

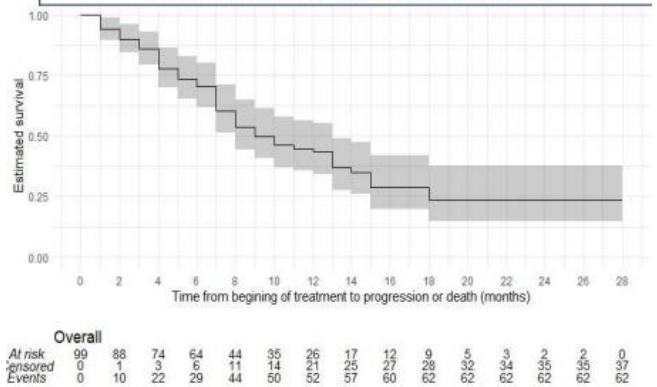
***HER3-expression prescreening (75% of membrane positivity at 10x) was removed by amendment on April 21st 2022[b]**

N=99	n	% [95%CI][a]
Confirmed ORR[b]	**53**	**53.5** [43.2; 63.6]
CR	2	2.0 [0.2;7.1]
PR	51	51.5 [41.3; 61.7]
SD	37	37.4 [27.8; 47.7]
PD	7	7.1 [2.9; 14.0]
NE[c]	2	2.0 [0.2;7.1]
CBR[d]	**62**	**62.6** [52.3;72.1]

No significant association between HER2 expression and ORR (*p-value 0.8*)[e]

PFS

Median, months [95% CI] **9.4** [8.1; 13.4]



Pistilli et al, ESMO 2024

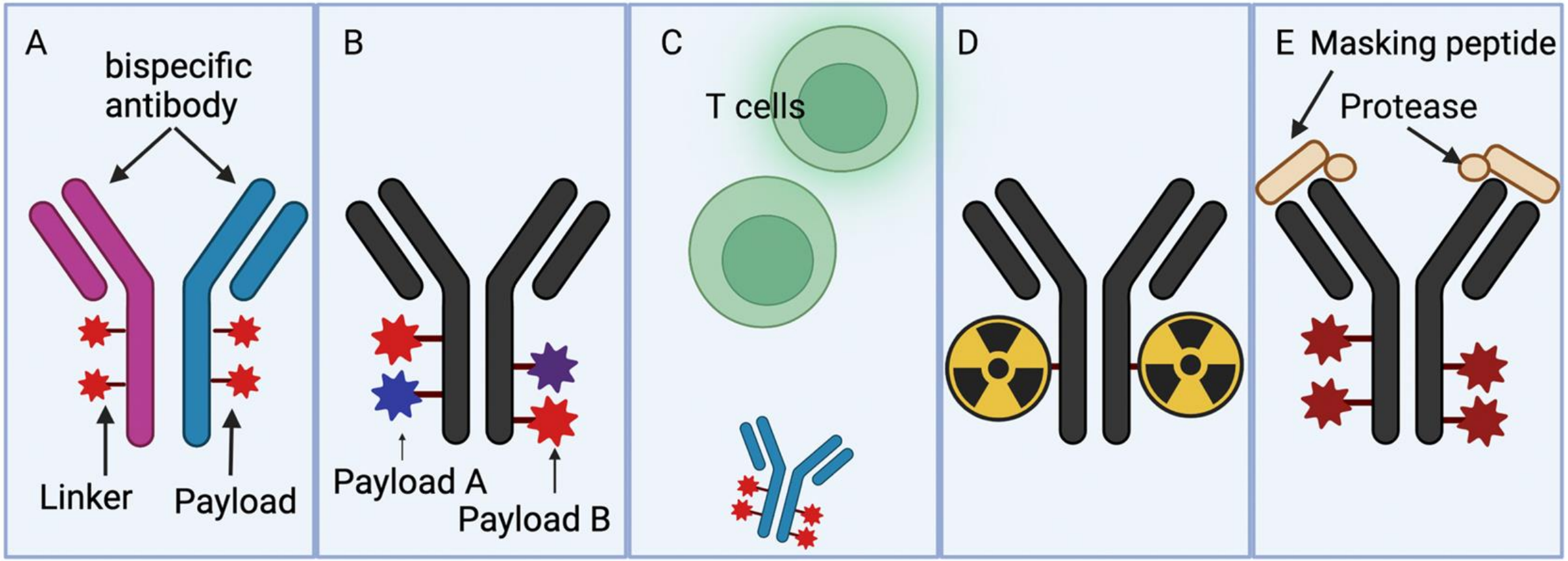
THE EVOLVING LANDSCAPE
New generation-ADC

Bispecific ADC

ADC with dual payload

Immune-modulating ADC

Radionuclide drug conjugate



E.g. ***zanidatamab zovodotin*** *targeting trastuzumab and pertuzumab HER2 binding domains*

E.g. HER2-directed mAB with ***DNA cross-linking*** *(PNU 159682)+* ***tubulin polymerization inhibitor*** *(MMFA)* ***payloads***

E.g. PD-L1 inhibitor + D18 immunomodulator; HER2-targeted mAB conjugated with a toll-like receptor 7 agonist

E.g. HER2-directed mAB with ***DNA cross-linking*** *(PNU 159682)+* ***tubulin polymerization inhibitor*** *(MMFA)* ***payloads***

Modified from Schlam et al, Critical Reviews in Oncology 2023

CONCLUSIONS

- **ADCs have reshaped the treatment of metastatic breast cancer, across all subtypes**
- **Anti-HER2 and TROP2 ADCs dominate the current landscape**
- **Several ADC with novel targets are advancing in the experimental scenario**
- **New generation ADCs with innovative mechanisms are also emerging**