ADCs: Other Novel Targets and Pathways

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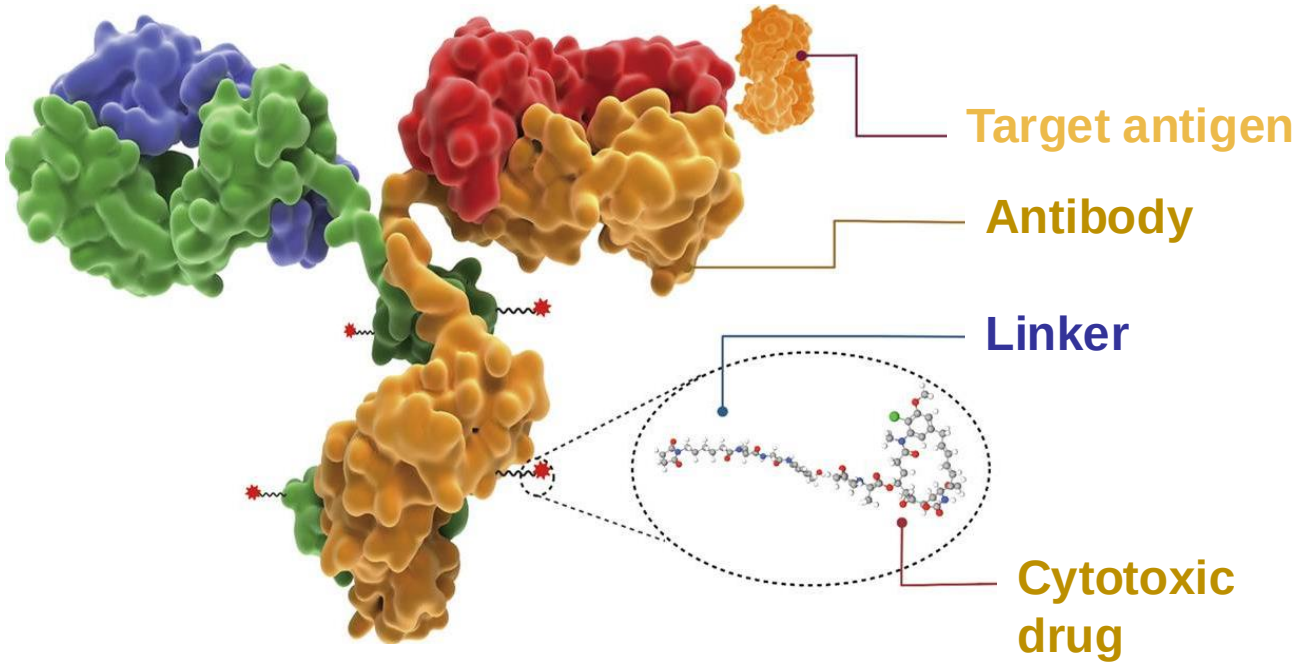
Antibody-drug conjugate (ADC) background



Key Components:

- Tumor-specific mAb
- Linker (Cleavable or non-cleavable)
- Cytotoxic payload

- **Release payload within or near the target cancer cell**
- **Bystander effect for killing surrounding cancer cells**

HER2 and TROP2: most-targeted antigens for Breast ADCs
Topo 1 inhibitor: most common payload

	Trastuzumab Emtansine (T-DM1)	Trastuzumab Deruxtecan (T-DXd)	Sacituzumab Govitecan (SG)	Datopotamab deruxtecan (Dato-DXd)
Target antigen	HER2	HER2	TROP2	TROP2
Linker cleavage	No	Tetrapeptide-based cleavable linker	Acid cleavable hydrolysable linker	Tetrapeptide-based cleavable linker
Membrane-permeable payload	No	Yes	Yes	Yes
Payload MOA	Emtansine (tubulin **inhibitor**)	DXd (Topo 1 inhibitor)	SN-38 (Topo 1 inhibitor)	DXd (Topo 1 inhibitor)
Drug-antibody ratio	3.5:1	8:1	7.6:1	4:1

Sawant et al, Medical Oncology (2024) 41:301

Sacituzumab Tirumotecan (Sac-TMT)

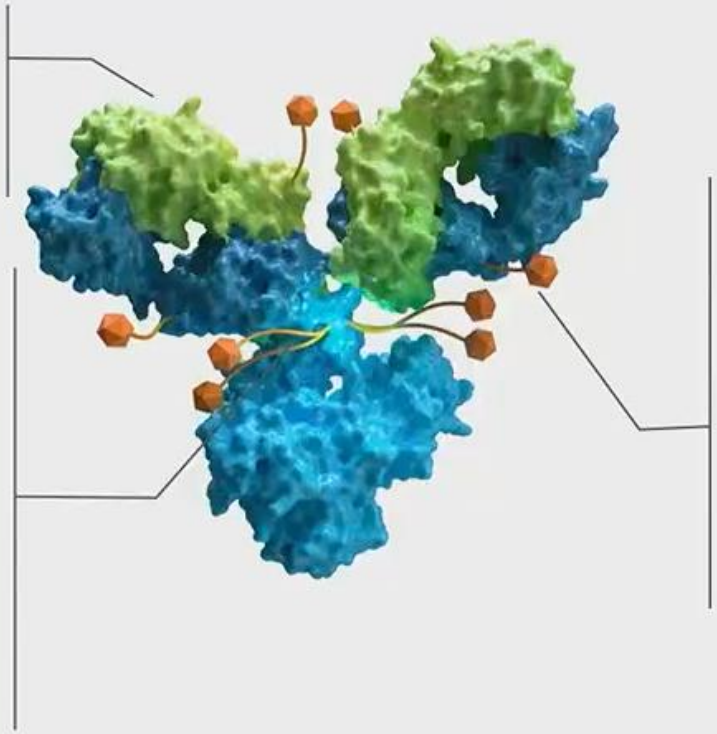
Trop2 targeted ADC with a topo 1 inhibitor payload

Antibody

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

Linker

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



Payload

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

Approved in China for TNBC

OptiTROP-Breast01 Phase III trial

Patients with locally recurrent or metastatic TNBC

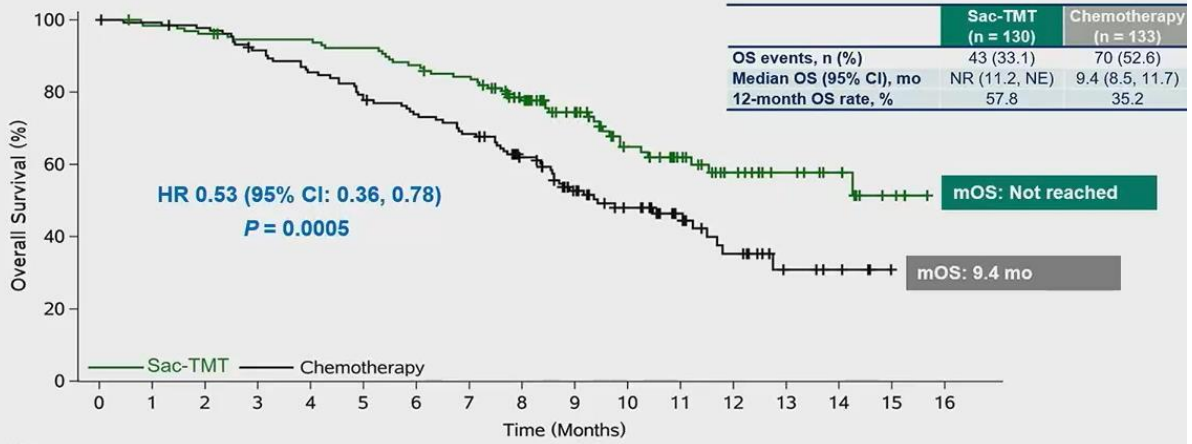
- Relapsed or refractory to 2 or more prior chemotherapy regimens for unresectable, locally advanced or metastatic disease
  - For prior therapy, 1 could be in the (neo)adjuvant setting, provided progression occurred during treatment or within 12 months after treatment discontinuation
- Received taxane(s)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

R 1:1

- **Sac-TMT, 5 mg/kg IV, every 2 weeks**
- **Physician's choice of chemotherapy:** eribulin, capecitabine, gemcitabine, or vinorelbine

Overall Survival (Interim Analysis)

Sac-TMT significantly improved OS over chemotherapy with a 47% lower risk of death.

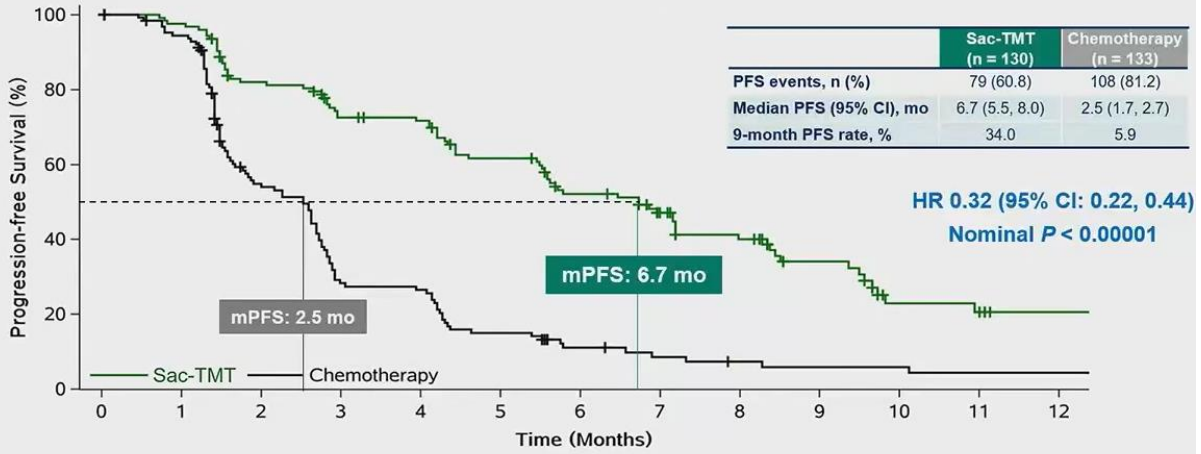


	Sac-TMT (n = 130)	Chemotherapy (n = 133)
OS events, n (%)	43 (33.1)	70 (52.6)
Median OS (95% CI), mo	NR (11.2, NE)	9.4 (8.5, 11.7)
12-month OS rate, %	57.8	35.2

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	

Progression-Free Survival by BICR (Final Analysis)

Sac-TMT significantly improved PFS over chemotherapy with a 68% lower risk of disease progression or death.



	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)
9-month PFS rate, %	34.0	5.9

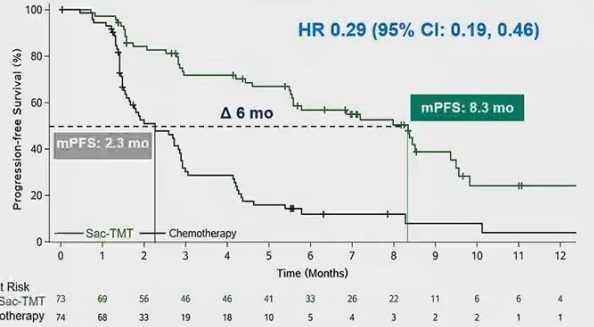
No. at Risk													
Sac-TMT	130	122	97	83	80	67	54	42	33	20	10	9	6
Chemotherapy	133	119	62	32	30	17	10	7	5	4	4	3	3

Progression-Free Survival (per BICR) by TROP2 Expression

PFS benefit was observed with sac-TMT over chemotherapy regardless of TROP2 expression.

High TROP2 expression (H-Score >200)

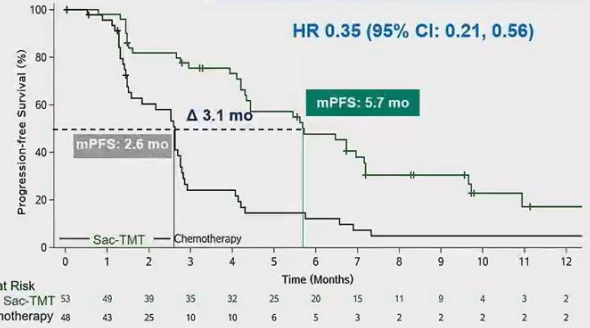
	Sac-TMT (n = 73)	Chemotherapy (n = 74)
PFS events, n (%)	41 (56.2)	59 (79.7)
Median PFS (95% CI), mo	8.3 (5.6, 9.4)	2.3 (1.6, 2.9)



No. at Risk												
Sac-TMT	73	69	56	46	46	41	33	26	22	11	6	6	4
Chemotherapy	74	68	33	19	18	10	5	4	3	2	2	1	1

Low/medium TROP2 expression (H-Score ≤200)

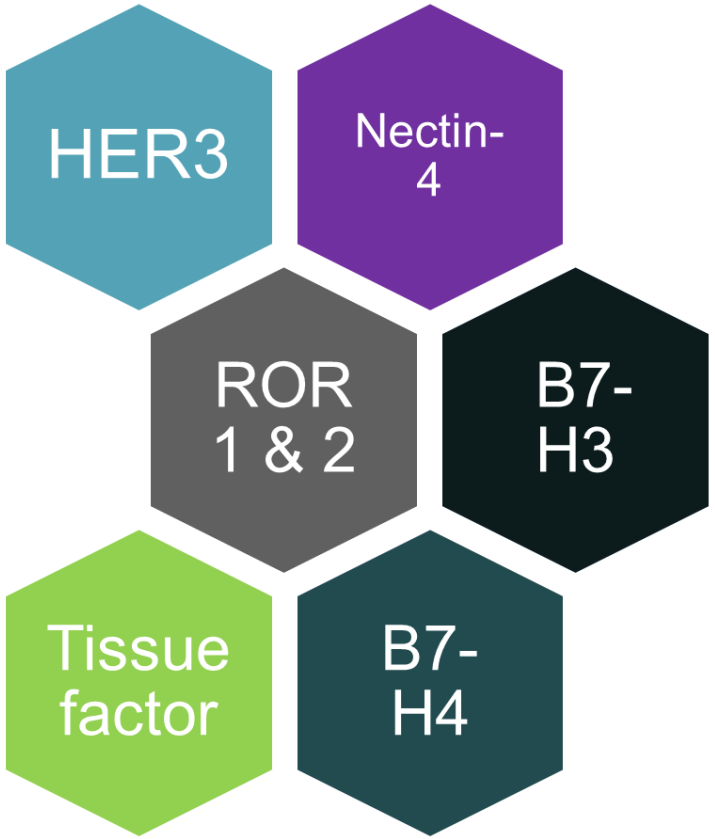
	Sac-TMT (n = 53)	Chemotherapy (n = 48)
PFS events, n (%)	34 (64.2)	40 (83.3)
Median PFS (95% CI), mo	5.7 (4.3, 7.2)	2.6 (1.5, 2.8)



No. at Risk												
Sac-TMT	53	49	39	35	32	25	20	15	11	9	4	3	2
Chemotherapy	48	43	25	10	10	6	5	3	2	2	2	2	2

Data cutoff: Nov 30, 2023; the protocol-specified final analysis of PFS.
BICR, blinded independent central review; Chemo, chemotherapy; CI, confidential interval; HR, hazard ratio; mPFS, median progression-free survival; TROP2, trophoblast cell surface antigen 2.

Other ADC targets under evaluation in breast cancer



HER3 Targeted ADCs

HER3 Signaling in breast cancer

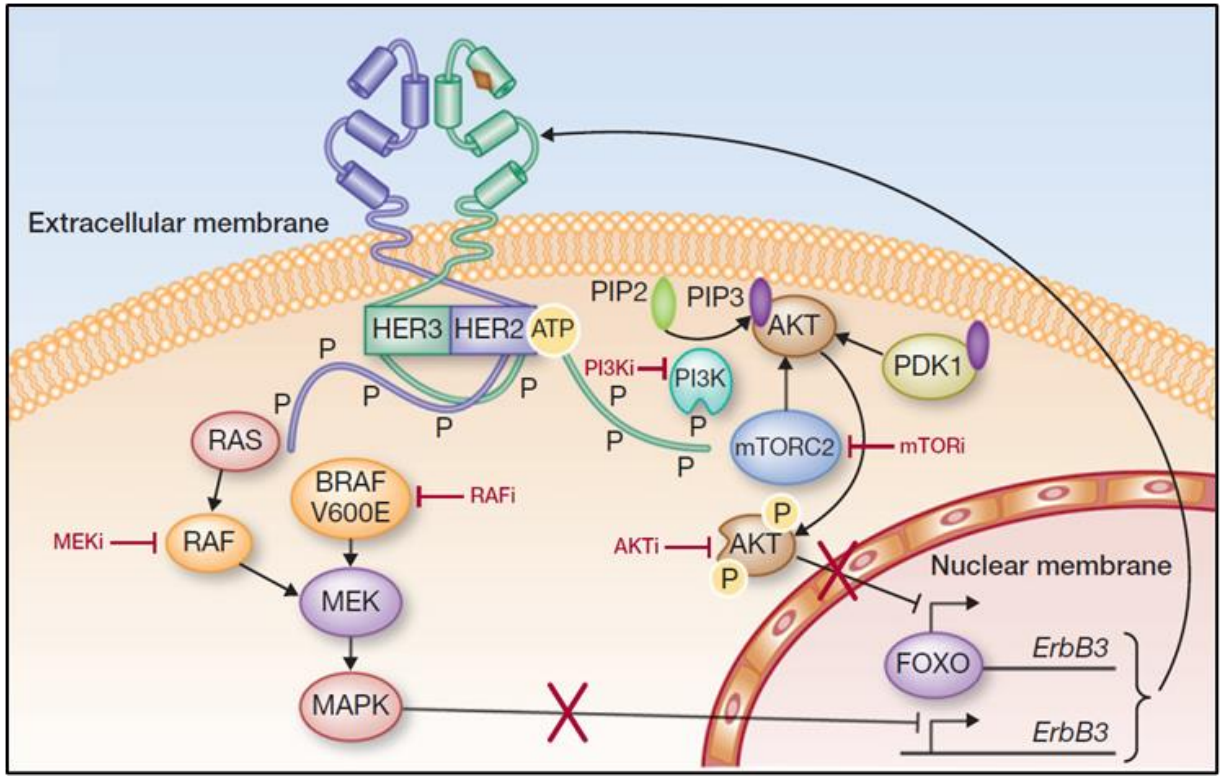
HER3 Structure

- Ligand-binding extracellular domain
- Transmembrane domain
- Intracellular domain
- C-terminal tail

HER3 receptor dimerization with EGFR or HER2 leads to activation of downstream signaling pathways

Increased HER3 expression in MBC compared with primary breast tumors

HER3 overexpression in BC associated with higher risk for death at 5 years (OR 2.89)



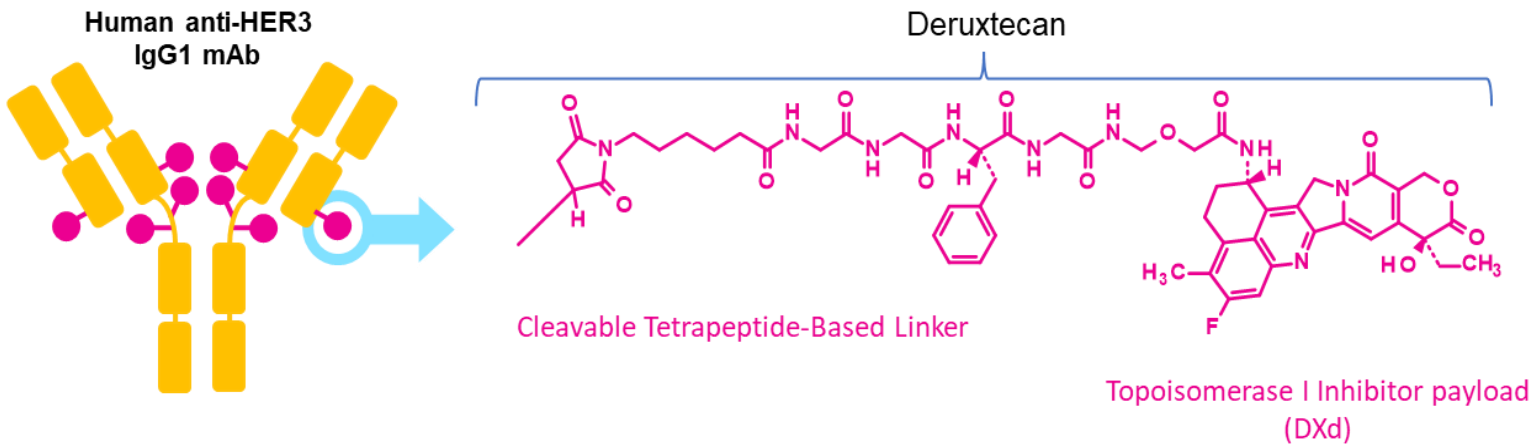
Gala and Chandarlapaty, *Clin Cancer Res* 2014; 20(6)

Li Q *et al*. Oncotarget 2017; Ocana A *et al*., JNCI 2013.

PATRITUMAB DERUXTECAN (HER3-DXd)

HER3-DXd is an ADC comprised of

- Fully human anti-HER3 IgG1 monoclonal antibody (patritumab)
- Tetrapeptide-based cleavable linker
- Topoisomerase I inhibitor payload, an exatecan derivative (DXd)



Key attributes of HER3-DXd
Topoisomerase I inhibitor payload
High payload potency
High drug to antibody ratio (8)
DXd has short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Bystander antitumor effect

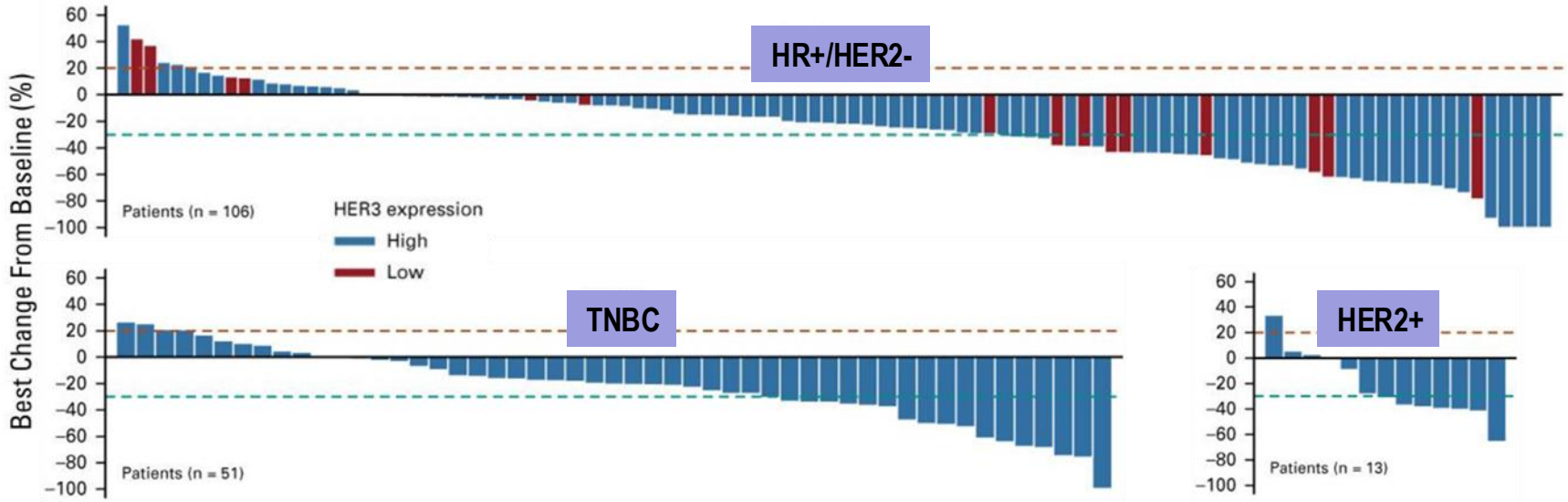
Krop IE *et al*., ASCO 2022.

Ph I/II: Patritumab Deruxtecan (HER3 DXd) in mBC

Dose escalation trial in MBC
- included all 3 subtypes
- median priors for MBC: 5 (3 prior chemos)

Outcome (BICR per RECIST v1.1)	HR+/HER2- (n=113)	TNBC (n=53)	HER2+ (n=14)
Confirmed ORR	30.1%	22.6%	42.9%
Median PFS	7.4 months	5.5 months	11.0 months
Median OS	14.6 months	14.6 months	19.5 months

HER3-DXd demonstrated clinically meaningful and durable activity across all subtypes.



Krop IE *et al*., *J Clin Oncol* 2023; 41(36): 5550-5560.

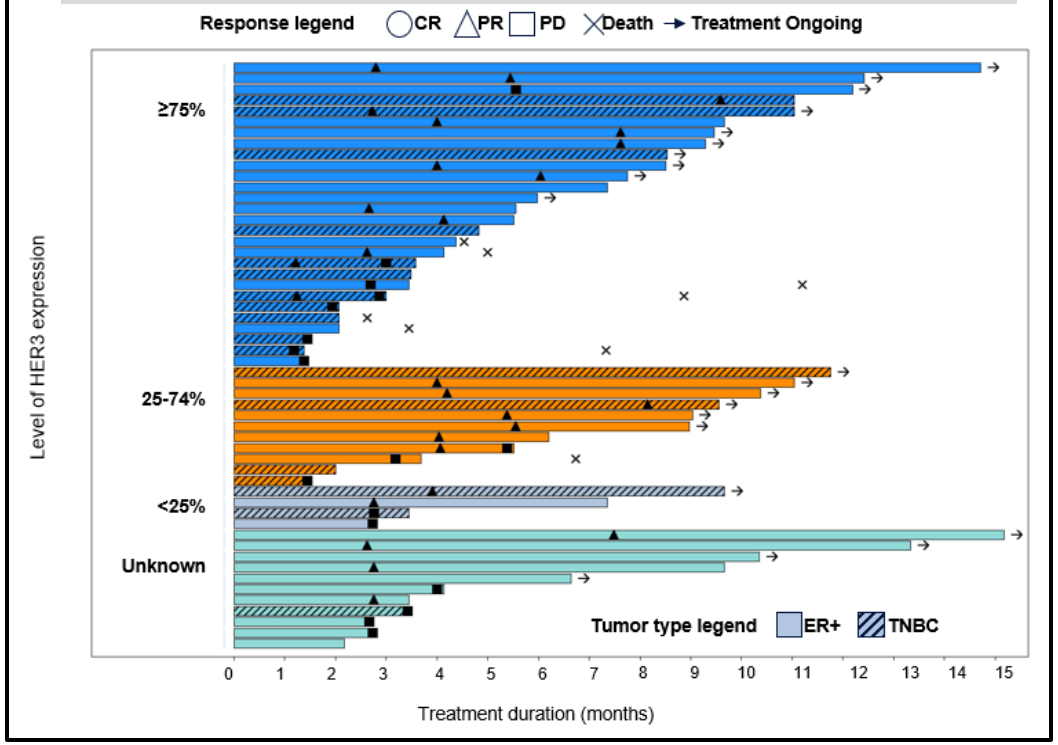
NCT02980341

HER3-Dxd: phase II study in TNBC and ER+ MBC

N=60; 40% TNBC

- Median priors for MBC: 3
- Prior chemotherapy: 90%
- Prior IO: 20%

Duration of study treatment by HER3 membrane expression



	Membrane HER3 ≥75% (N=30)	Membrane HER3 25-74% (N=13)	Membrane HER3 <25% (N=4)	Unknown HER3 Expression (N=13)	Total (N=60) N (%)
Partial Response	10 (33.3)	6 (46.2)	2 (50.0)	3 (23.1)	21 (35.0)
ORR, n (%)	10 (33.3)	6 (46.2)	2 (50.0)	3 (23.1)	21 (35.0)
CBR, n (%)	12 (40.0)	7 (53.8)	2 (50.0)	5 (38.5)	26 (43.3)

Among patients with heavily pretreated BC:

ORR was 35%,

CBR was 43%, and

DoR was at least 6 months in nearly half of responders

Responses were independent of HER-3 expression!

Hamilton E et al. ASCO 2023

NCT046996

ICARUS-Breast01: Patritumab-DXd in 2L HR+/HER2- MBC

Single arm study with patritumab deruxtecan (5.6mg/kg q3w)

- HR+/HER2- or HER2low
- Progression on CDK4/6 inhibitors + ET
- Progression on 1 prior line of MBC chemotherapy

Tumor response at 3 months from treatment initiation, n (%)	
Partial response	16 (28.6)
Stable Disease	30 (53.3)
Progressive Disease	10 (17.9)

Most common AEs were fatigue and GI toxicity

Grade ≥3 neutropenia in 10% and Grade ≥3 thrombocytopenia in 4% of patients

Further efficacy and biomarker analysis from ICARUS-Breast01 ongoing

Pistilli B *et al*., Abstract 189O ESMO Breast 2023.

NCT04965766

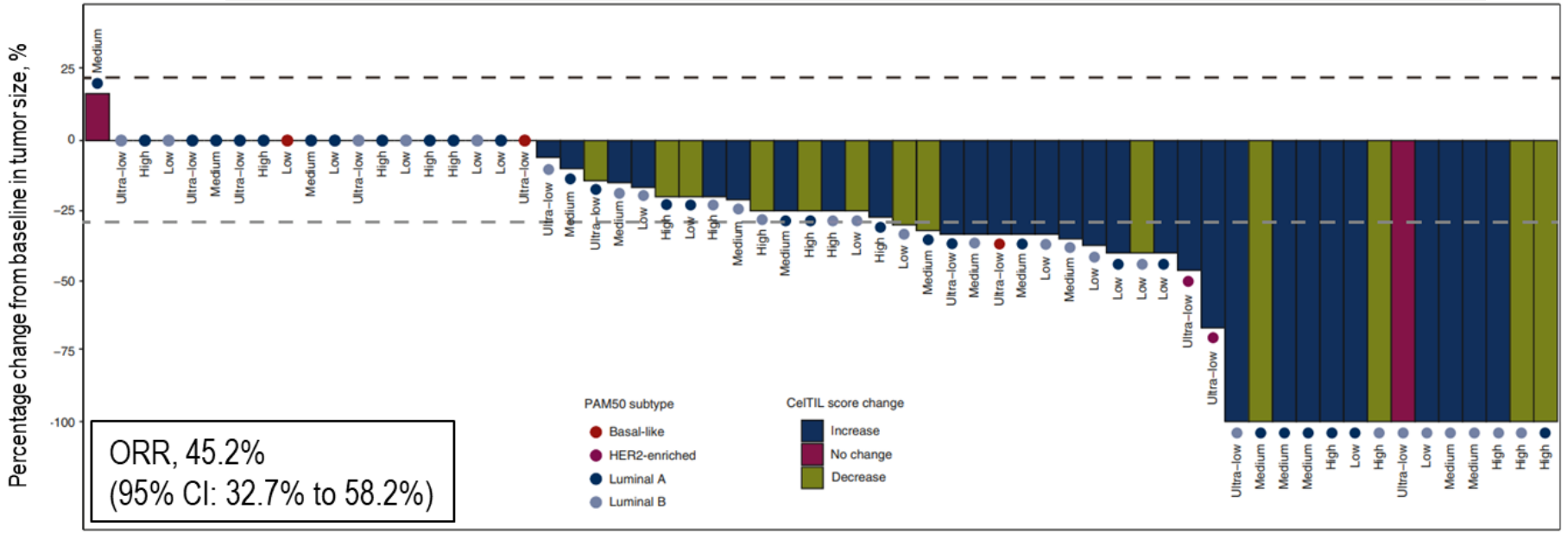
Solti-TOT-HER3: Neoadj single dose patritumab-DXd in HER2- BC

Two-part window of opportunity study in treatment-naïve patients with single dose of patritumab deruxtecan

Part A: HR+/HER2- (N=78) 6.4 mg/kg

Part B: HR+/HER2- (N=20) or TNBC (N=17) 5.6 mg/kg

Part A results: ORR 45.2% independent of HER3 expression



- **ORR for Part B was 32%**
- **Lower incidence of hematological and hepatic toxicity observed with lower dose**

Oliveira M *et al*., *Ann Oncol* 2023; 34(8):670-680. Oliveira M *et al*., ASCO 2023

NCT04610528

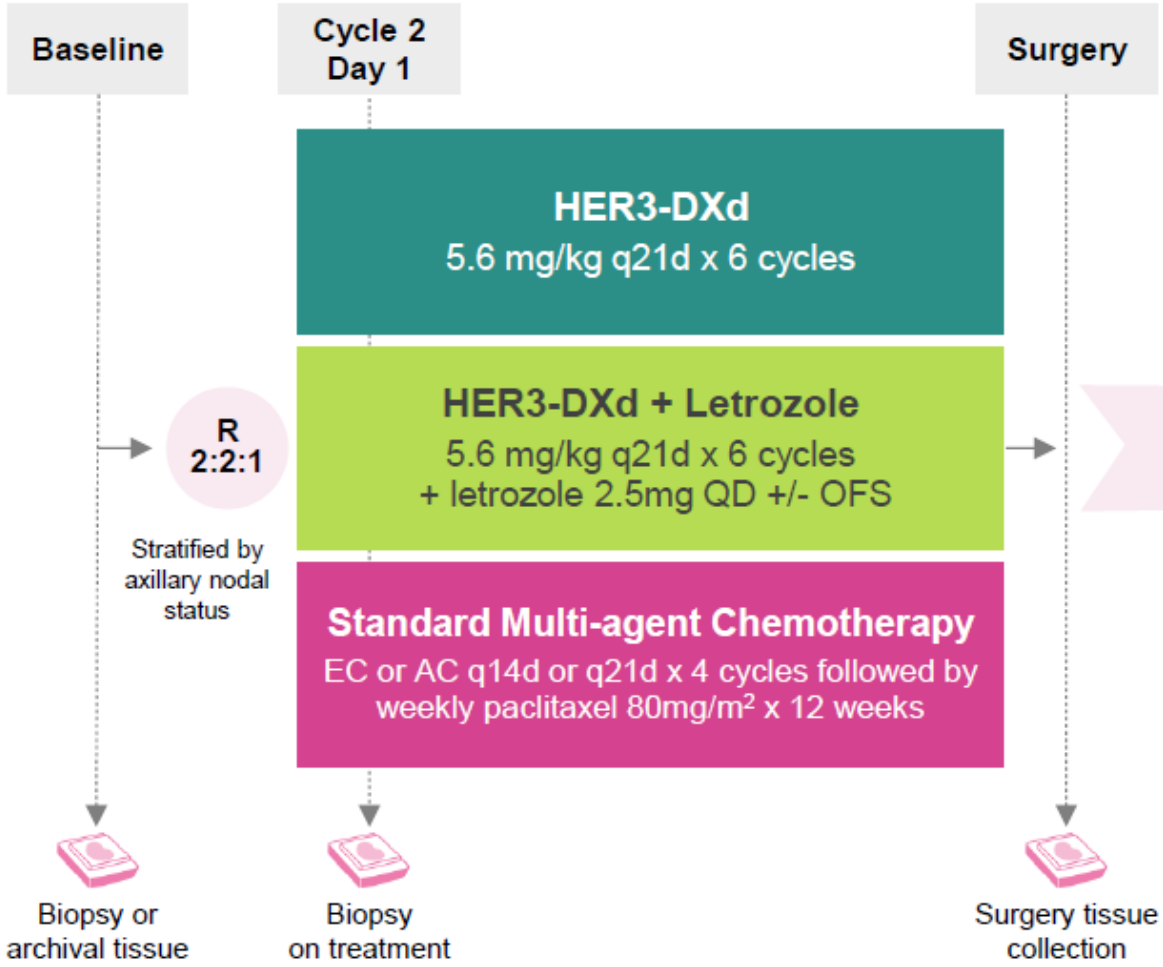
Parallel, randomized, non-comparative, open-label, phase II trial (NCT05569811)

N=120

Key eligibility criteria:

- Pre- and post-menopausal women, or men
- Primary operable breast cancer ≥1 cm by MRI
- HR+/HER2-negative[a]
- Ki67 ≥20%[a] and/or high genomic risk (gene signature)
- No prior treatment for the current breast cancer
- Available pre-treatment FFPE core-needle biopsy

[a]HR, HER2, and Ki67 determined by local assessment.



pCR → Follow up 5 years

Primary Endpoint:

- Rate of pCR (ypT0/is ypN0) at surgery

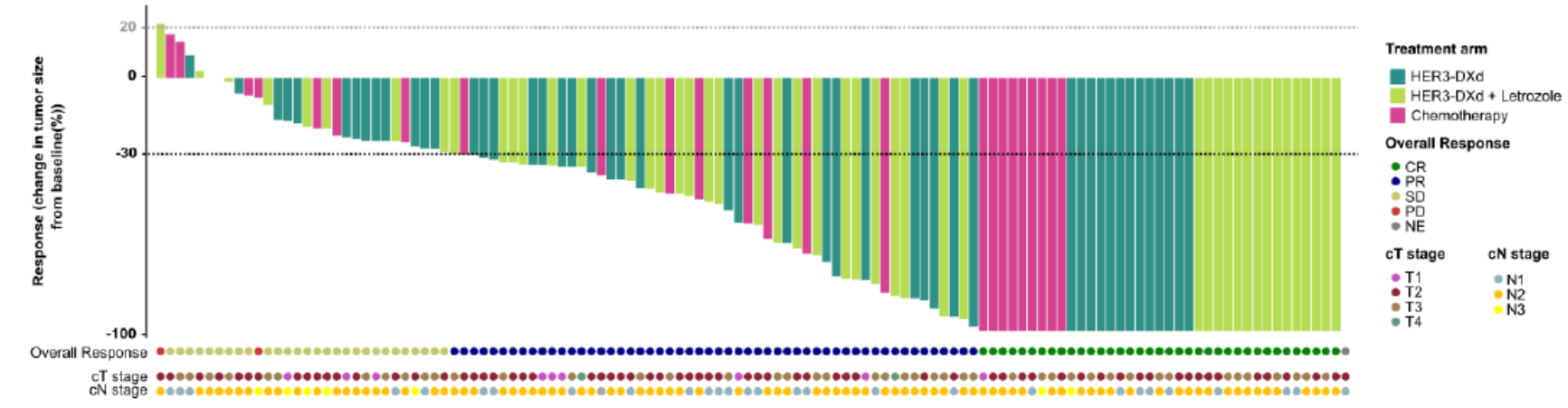
Secondary Endpoints:

- ORR
- CelTIL score change, Ki67 drop, PAM50, ROR
- Safety
- iDFS

Oliveira M et al, SABCS 2024

HER3-DXd showed pCR and ORR rates similar to multi-agent chemotherapy

	HER3-DXd N=50	HER3-DXd + LET N=48	Chemotherapy N=24	Overall N=122
pCR rate				
N	2	1	1	4
% (95%CI[a])	4.0% (0.5-13.7)	2.1% (0.1-11.1)	4.2% (0.1-21.1)	3.3% (0.9-8.2)
ORR				
N	35	39	17	91
% (95%CI[a])	70.0% (55.4-82.1)	81.3% (67.4-91.1)	70.8% (48.9-87.4)	74.6% (65.9-82.0)
PD				
N (%)	0	1 (2.1%)	1 (4.2%)	2 (1.6%)



- Treatment response correlated with decrease in Ki67, switch to less proliferative PAM50 subtype, decrease in ROR, and increase in CelTIL score.
- HER3-DXd led to a lower incidence of G3+ AE, dose reduction, treatment discontinuation.

Oliveira M et al, SABCS 2024

Ongoing trials for patritumab-DXd

- TUXEDO-3 Trial NCT05865990
  - Phase II single-arm study of patritumab-DXd in patients with active brain metastases from BC and NSCLC

- Patritumab deruxtecan in patients with MBC NCT04699630
  - Phase II three-part study evaluating Patritumab-DXd in patients with MBC
  - HR+/HER2- or TNBC post other ADCs

HER3-targeted ADCs in development

DB-1310[1]

- Duality Biologics
- Topo I inhibitor payload
- DAR ~8
- Preclinical efficacy in breast & NSCLC models

BL-B01D1[2]

- SystImmune & BMS
- EGFR-HER3 bispecific antibody with Topo I inhibitor payload
- DAR ~8
- Phase I BC study, ORR 45.5%

SHR-A2009[3]

- Jiangsu Hengrui
- Topo I inhibitor payload
- adv solid tumors (median 3L prior) ORR 25.0%, mDoR 7.0 months

YL202[4]

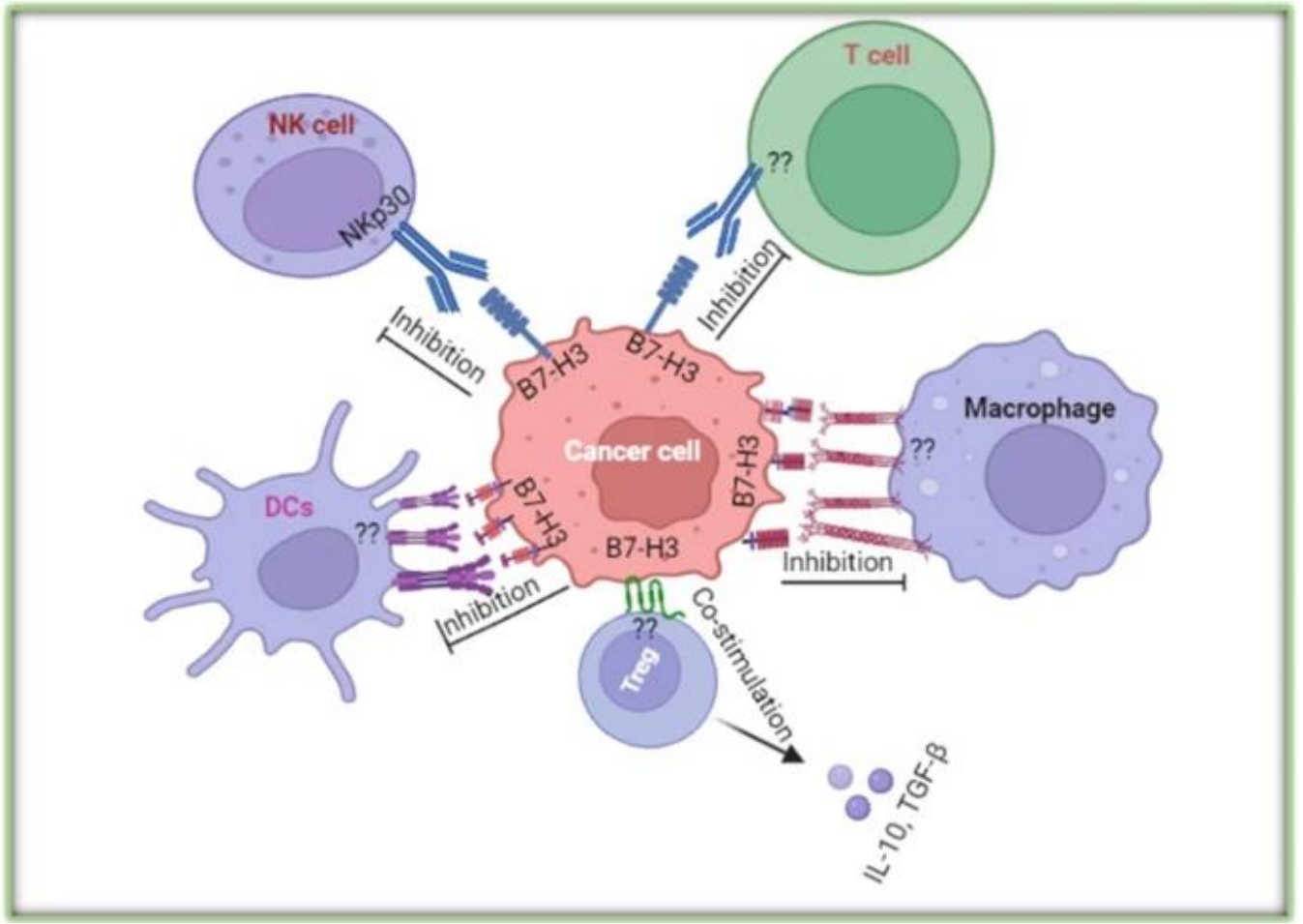
- Suzhou Medilink
- Topo I inhibitor payload

1. Xi L *et al*. Abstract 1884 AACR 2023. 2. Zhang J *et al*., Abstract PS08-07 SABCS 2023. 3. Zhou Q *et al*., Abstract 658MO ESMO 2023. 4. Xu J *et al*., Abstract 563 AACR 2023.

B7-H3

B7-H3 (CD276) an IMMUNE CHECKPOINT molecule

- B7H3 is an immune checkpoint molecule in B7 family that promotes tumorigenesis by suppressing anti-tumor immunity
- B7H3 inhibits proliferation of CD4+ and CD8+ T cells and inhibits release of interferon γ release via the mTOR pathway
- Overexpressed in multiple tumor types and correlates with poor prognosis[1]
- Regulates stem cell enrichment and promotes chemoresistance



1. Getu AA *et al., Mol Cancer* 2023; 22(43).

ADCs targeting B7-H3 (CD276)

- ADCs in development for indications in multiple solid tumors, primarily lung and colorectal cancers
- Preclinical data has demonstrated efficacy in breast cancer cell lines

Molecule	Stage	Cohorts
	Preclinical	
ITC-6102RO	Preclinical	
MGC026	Phase I NCT06242470	Multiple solid tumors
HS-20093	Phase II multiple	Multiple solid tumors
Vobramitamab duocarmazine	Phase II multiple	mCPRC, NSLC, SCLC, melanoma, SCCHN, anal
Ifinatamab deruxtecan	Phase I/II NCT04145622 NCT05280470	SCLC, sqNSCLC, mCPRC

B7-H4

B7-H4: Suppressor of antitumor immunity

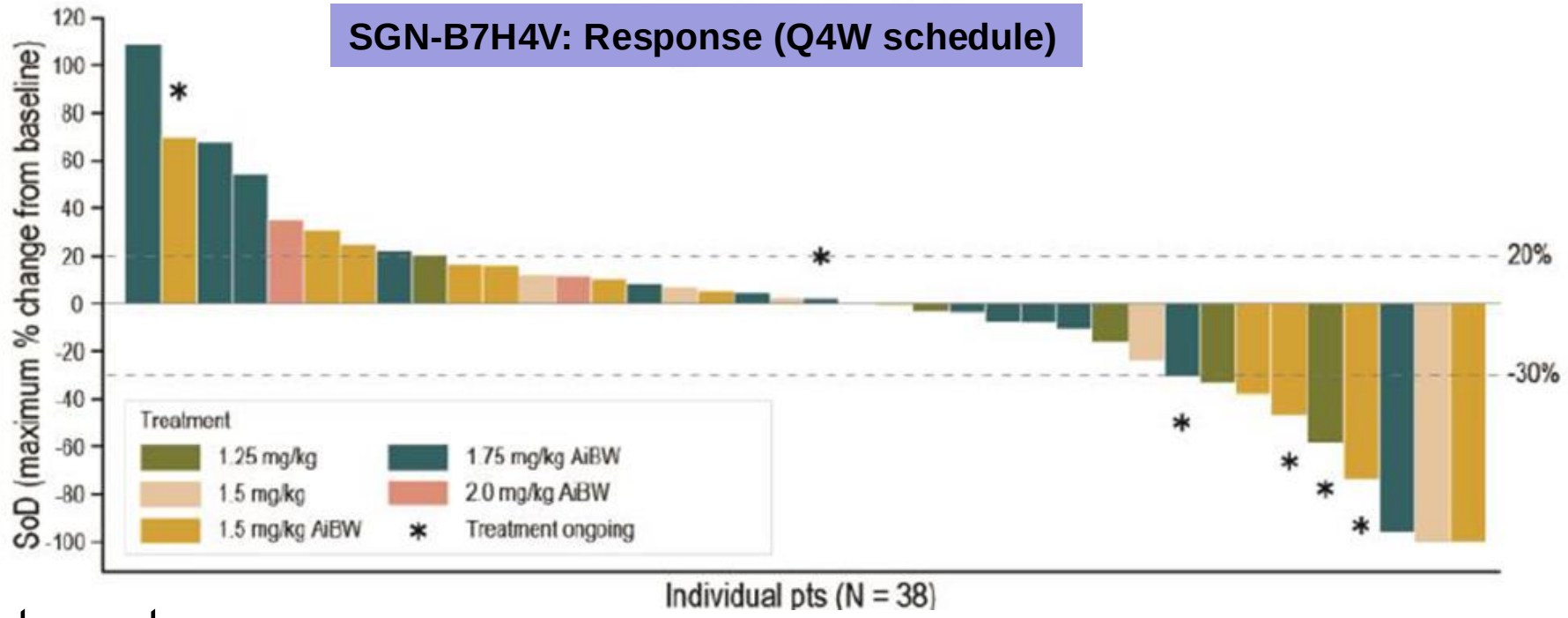
- B7-H4 (VCTN1) is a member of the CD28/B7 family of cell surface proteins that promotes tumorigenesis by suppressing anti-tumor immunity
- Overexpressed in multiple tumor types including breast, endometrial, and ovarian[1,2]
- B7-H4 can function as a co-inhibitory factor inhibiting CD4+ and CD8+ T-cell proliferation, cytokine production etc.
- ADCs in development for indications in multiple solid tumors, including HR+/HER2- BC and TNBC

Molecule	Stage	Cohorts
LNCB74	Preclinical	
BG-C9074	Phase I NCT06233942 (planned)	Multiple solid tumors
HS-20089	Phase I NCT05263479	Breast, ovarian, endometrial
XMT-1660	Phase I NCT05377996	Breast, ovarian, endometrial
SGN-B7H4V	Phase I NCT05194072	Multiple solid tumors
AZD8205	Phase I/II NCT05123482	Biliary, ovarian, breast, endometrial

1. Podojil JR and Miller SD. *Immunol Rev* 2017; 276(1): 40-51. 2. Sachdev JS et. Al J Clin Oncol 37, 2019 (suppl; abstr 2529) 3. Prasad DV et al. Immunity 18, 863–873 (2003).

B7-H4 ADCs

SGN-B7H4V comprised of B7-H4 directed MAb conjugated to MMAE via a protease-cleavable linker



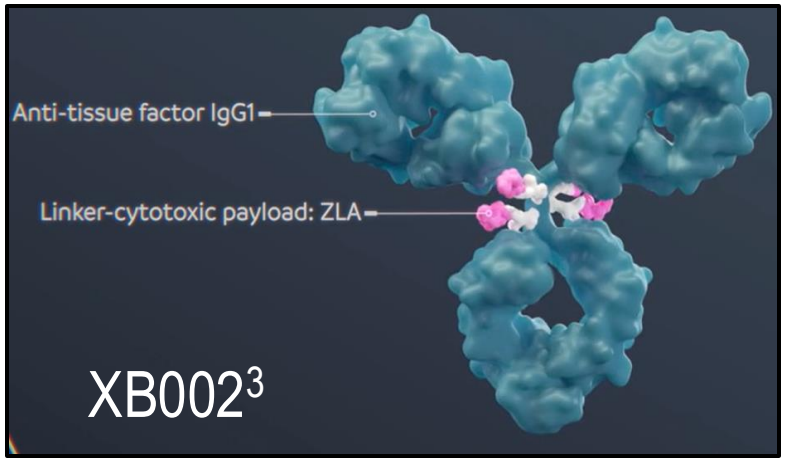
- activity across tumor types
- including confirmed responses in **7/28 patients with advanced ER+ and TNBC**[1]

1. Perez CA *et al*., ESMO 2023. NCT05194072 2. Mersana Corporate Presentation 2024. NCT05377996

Tissue factor

ADCs targeting Tissue Factor

- High expression in multiple cancers, promoting angiogenesis, invasion, and metastasis[1]
- Tisotumab vedotin was recently approved for metastatic cervical cancer[2]



Molecule	Stage	Cohorts
STRO-004	Preclinical	
XB002	Phase I/II NCT04925284	Multiple solid tumors
XNW28012	Phase I/II CTR20233056	Multiple solid tumors
MRG004A	Phase I/II NCT04843709	Multiple solid tumors
Tisotumab vedotin	Approved for cervical cancer; Phase II for other indications NCT03485209	Multiple solid tumors

1. Unruh D and Horbinski C. *J Hematol Oncol* 2020; 13(93). 2. Bogani G *et al.,* Curr Probl Cancer 2023; 47(3). 3. Exelixis Pipeline 2024.

Nectin -4

ADCs targeting Nectin-4 (PVRL4)

- Cell adhesion molecule
  - Not expressed in normal adult tissue
- Overexpressed in multiple tumor types including TNBC and basal subtypes of BC[1]
- Preclinical data showed efficacy in breast cancer patient-derived xenografts
- Phase I/II trials ongoing

Molecule	Stage	Cohorts
ADRX-0706	Phase I NCT06036121	Multiple solid tumors
LY4101174	Phase I NCT06238479	Multiple solid tumors including TNBC
Enfortumab vedotin	Approved for urothelial cancer; Phase II for other indications NCT04225117 (completed)	Multiple solid tumors including HER2- BC and TNBC

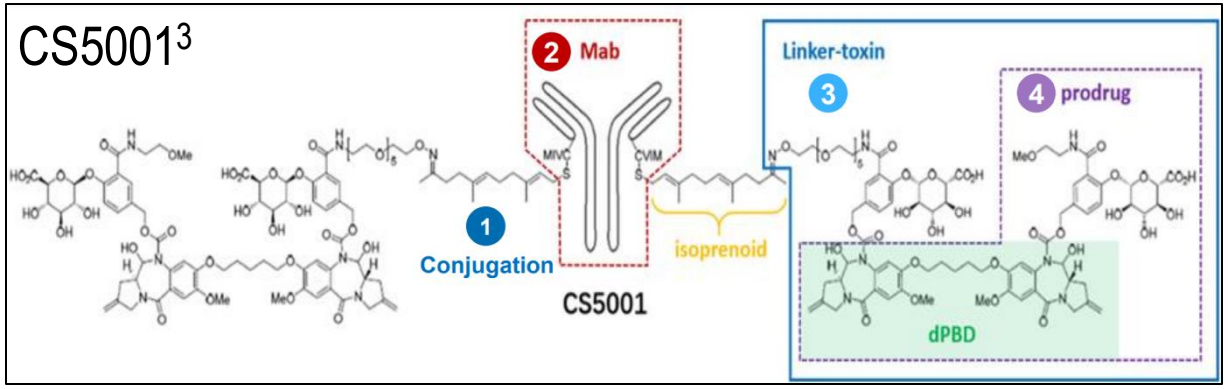
1. M-Rabet M *et al., Ann Oncol* 2017; 28(4): 769-776.

ROR 1 & 2

ADCs targeting ROR1 and ROR2

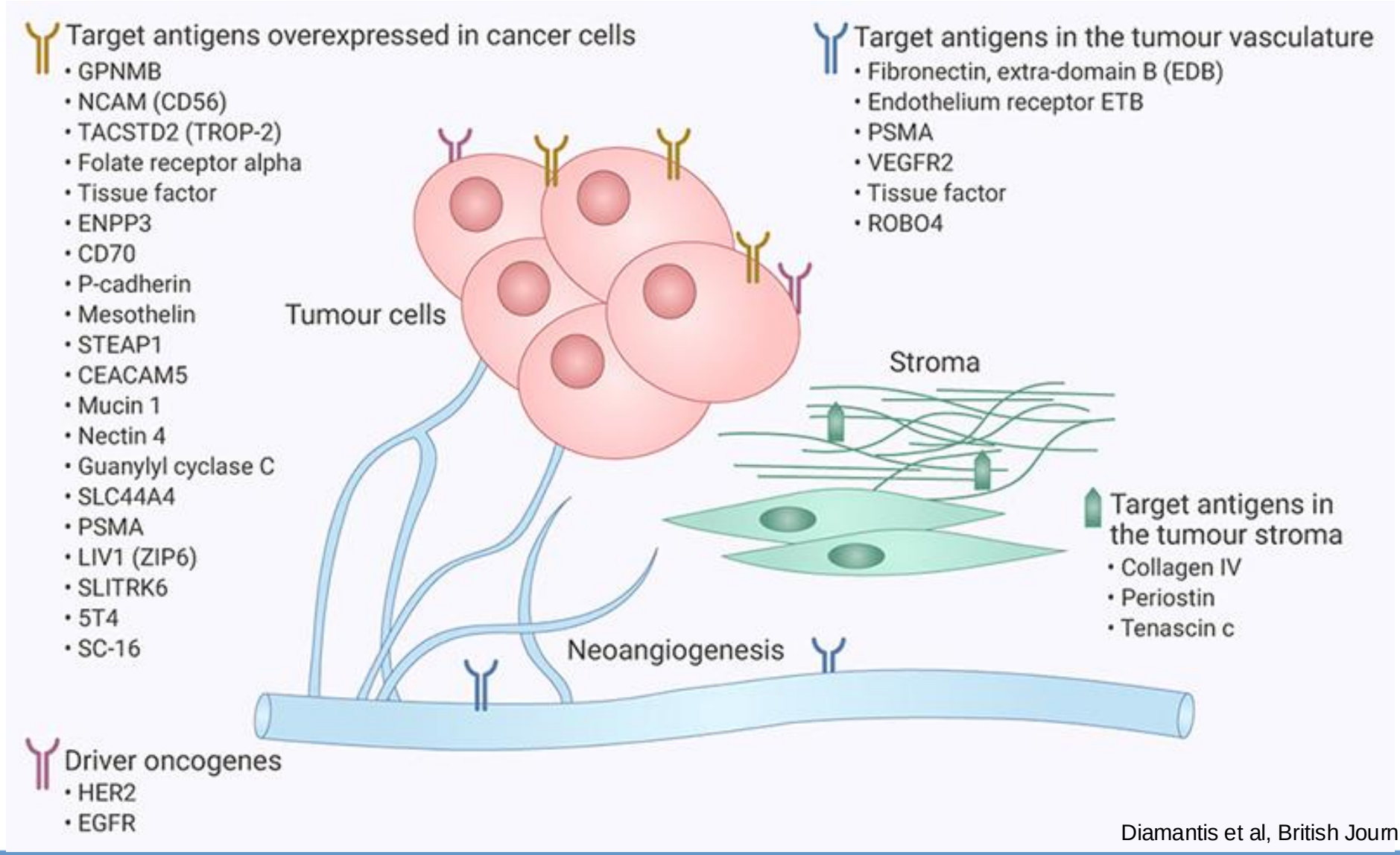
- Receptor tyrosine kinase-like orphan receptors (ROR1 and ROR2) now known to signal through the WNT pathway[1,2]
- Have roles in cell migration and cell invasiveness
- Highly expressed in development, but normally repressed in adult tissue

Molecule	Stage	Cohorts
STRO-003 (ROR1)	Preclinical	
CS5001 (ROR1)	Phase I NCT05279300	Multiple solid tumors including TNBC
Ozuriftamab vedotin (ROR2)	Phase I/II NCT03504488	Multiple solid tumors including TNBC
Zilovertamab vedotin (ROR1)	Phase II NCT04504916 (completed)	Multiple solid tumors including HER2- BC and TNBC

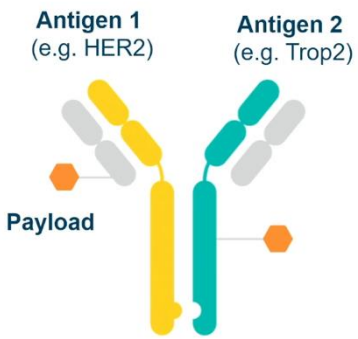


1. Zhao Y *et al., Front Oncol* 2021; 11. 2. Menck K *et al.,* J Exp Clin Cancer Res 2021: 40(395). 3. CStone Annual Results Presentation 2024.

ADC Novel Targets



Diamantis et al, British Journal of Cancer (2016), 1–6

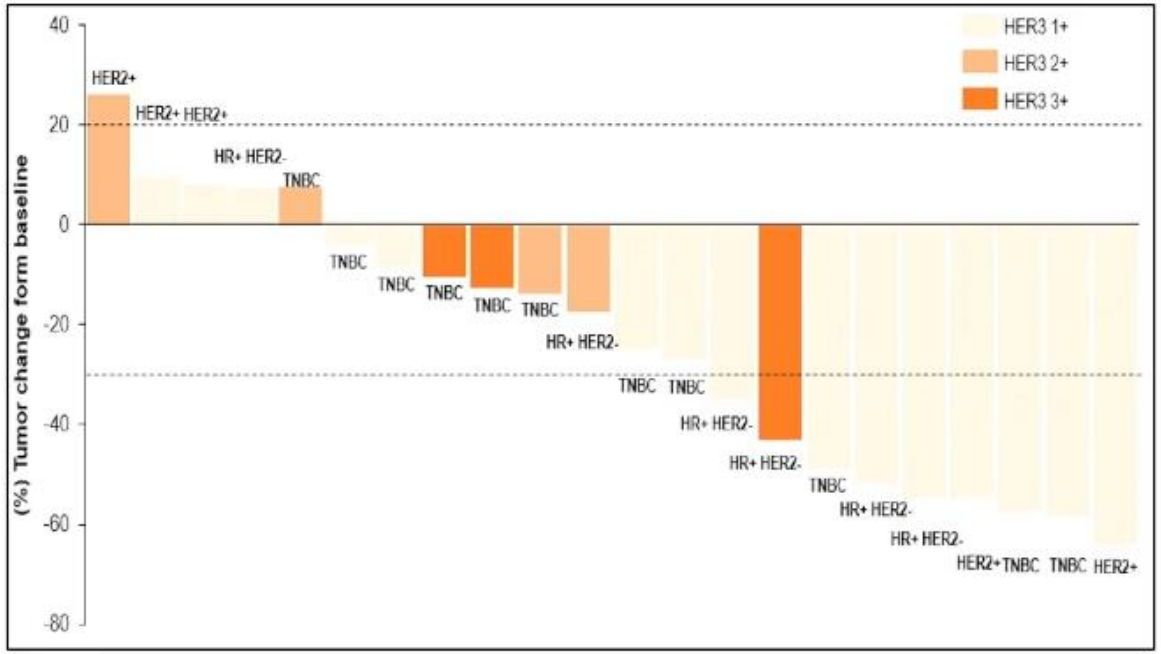


Bispecific and Biparatopic Antibodies

BL-B01D1

EGFRxHER3 bsADC

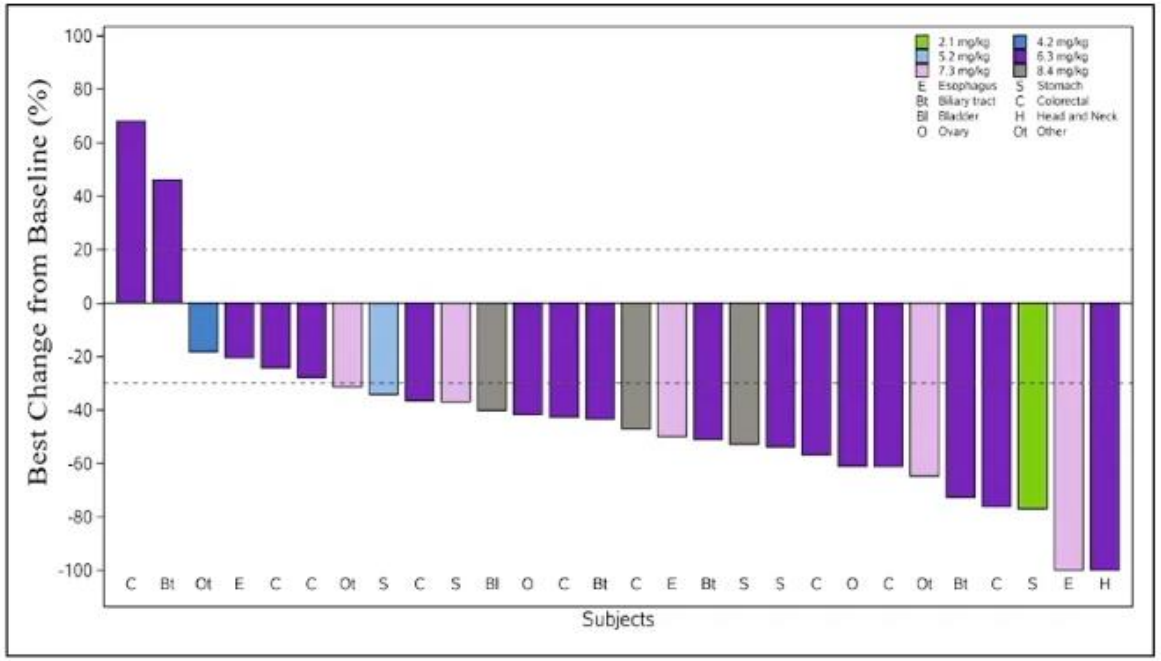
ORR 31-44% (MBC)



JSKN003

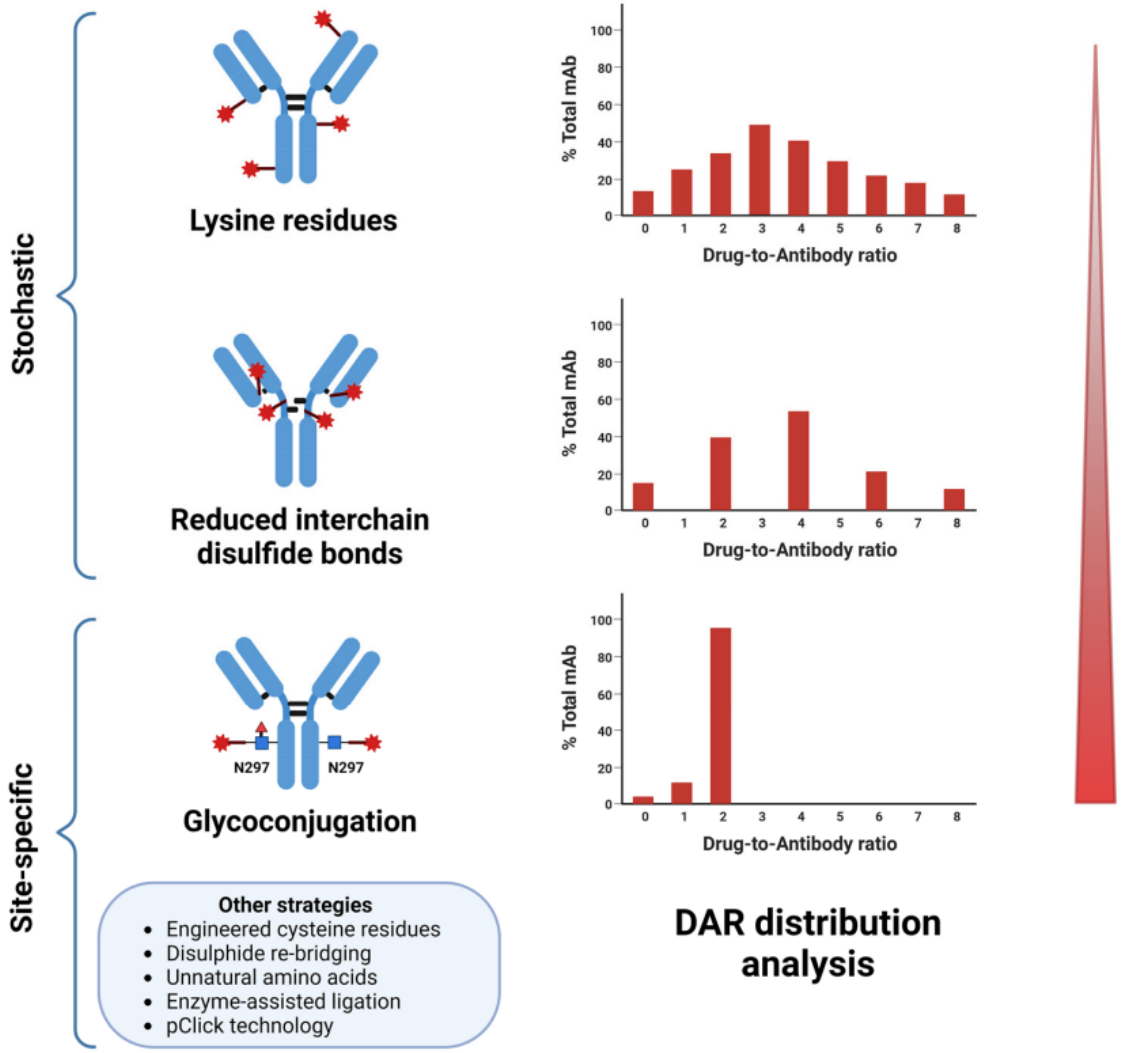
HER2 bsADC (biparatopic)

ORR 75% (HER2+ cancers)



Jiong Wu et al SABCS 2023; Shen L. et al ESMO 2024

Site-specific Linker



- All the currently approved ADCs utilize a stochastic conjugation process
- The random linking of payload leads to high heterogeneity in PK
- Site-specific linking improves homogeneity in drug to antibody ratio, leading to more predictable PK, and efficiency compared to conventionally coupled agents.

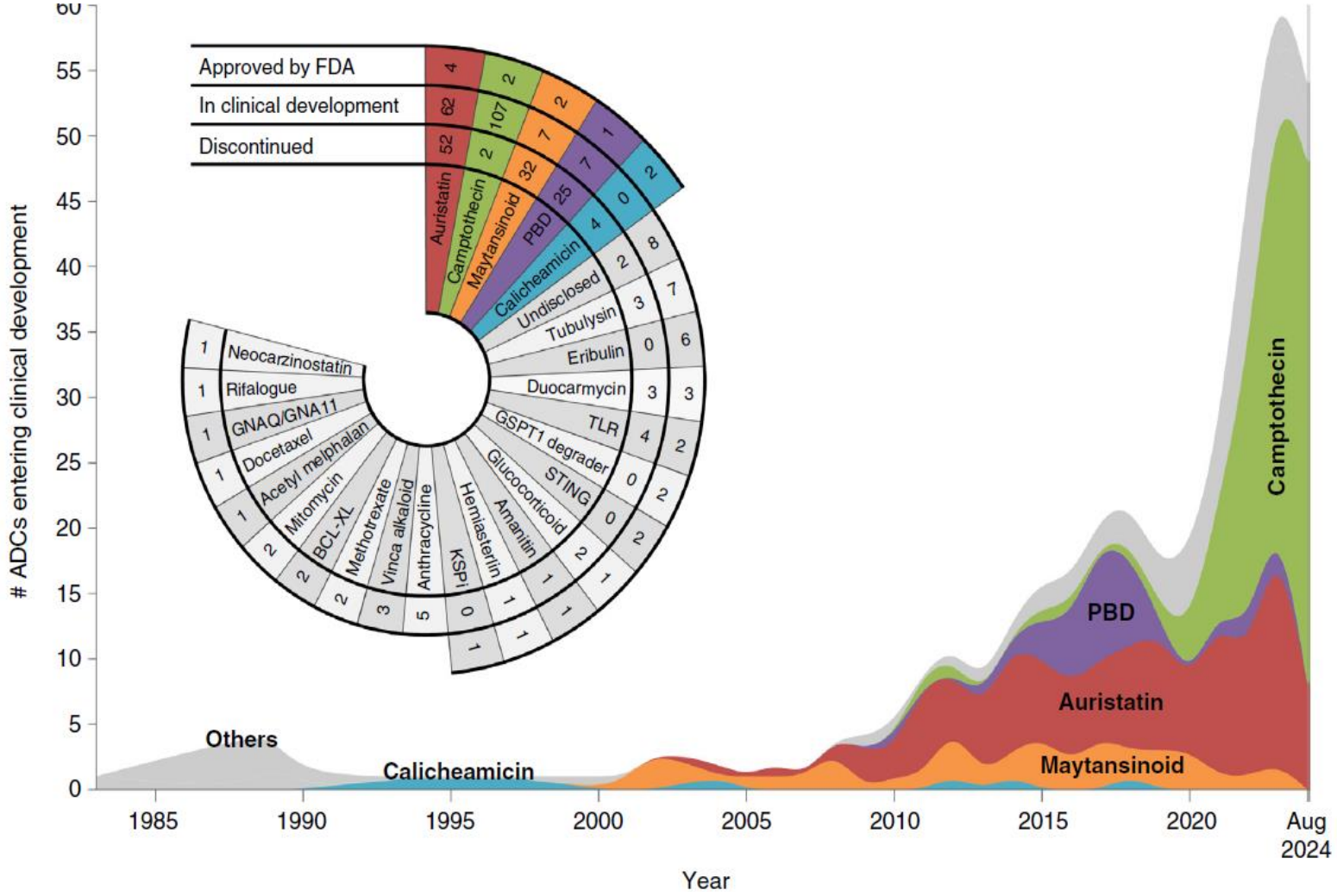
Metrangolo V. et al, Cancers 2024, 16, 447

ADC payload

Of the over 200 ADCs in clinical development

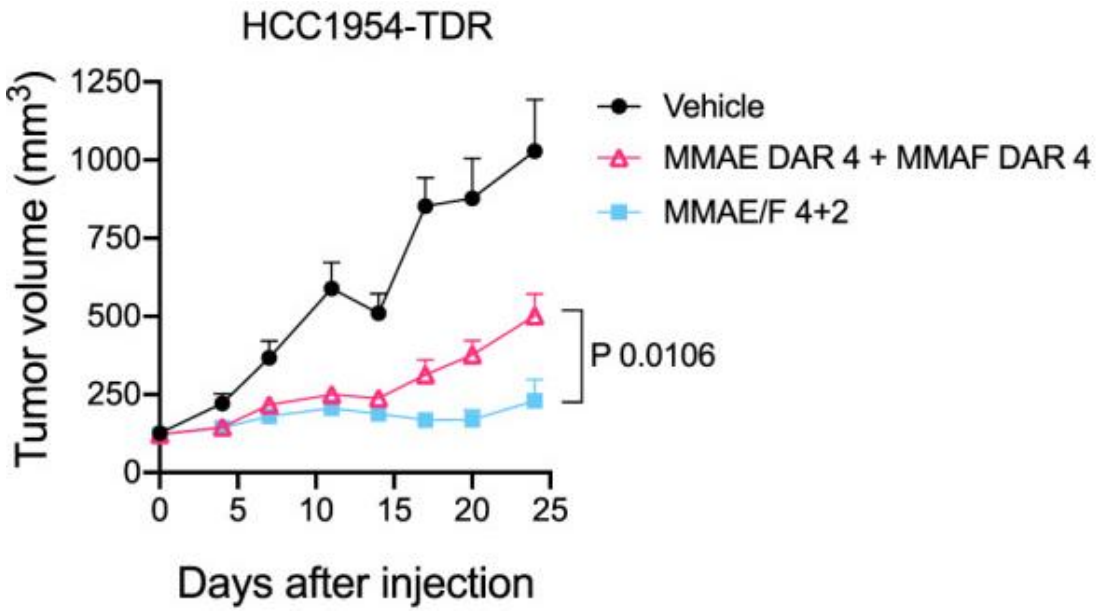
- Vast majority (n=107) have Topo 1 inhibitor payload

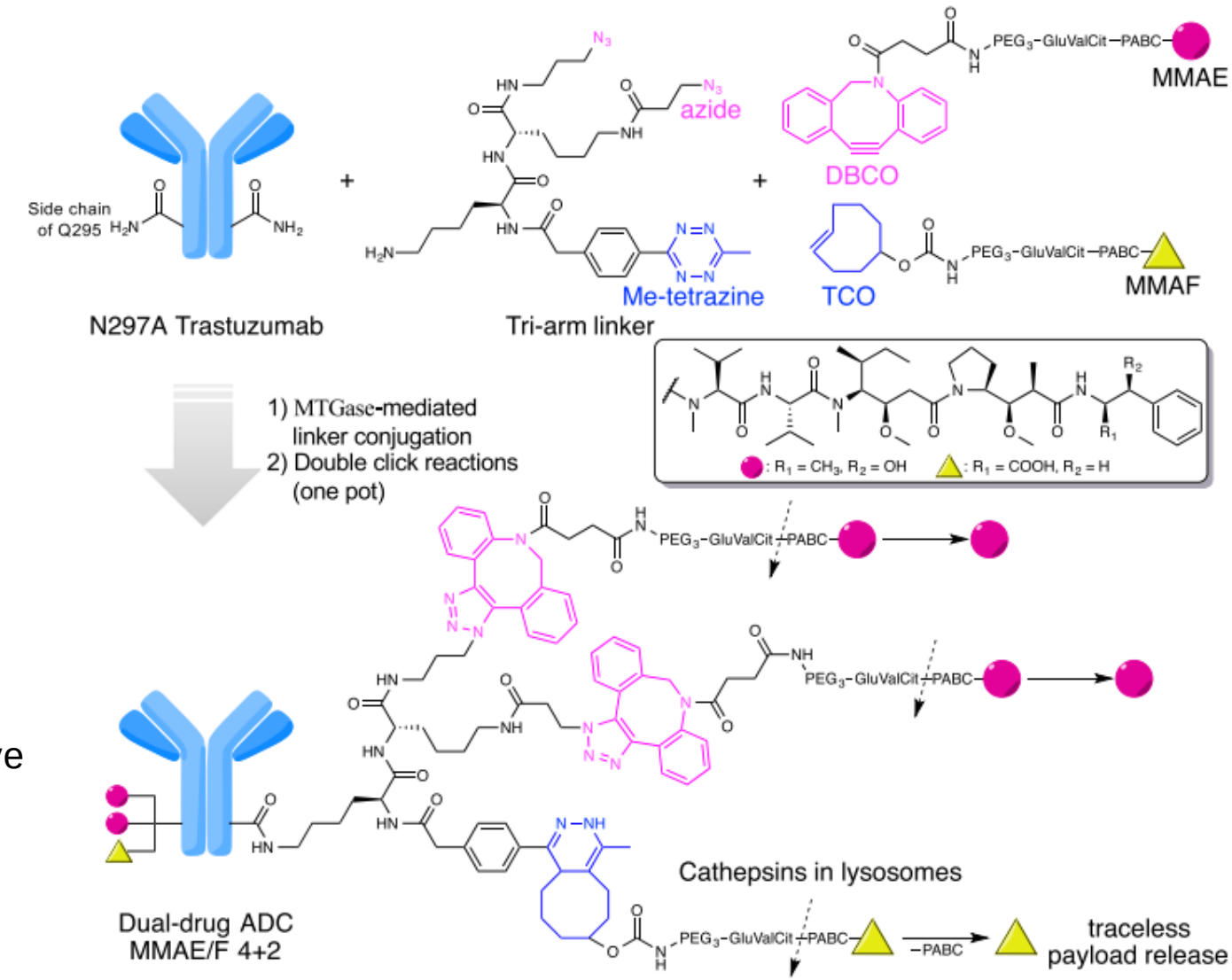
- 62 has auristatin payload



Colombo et al,

Dual Payload ADCs



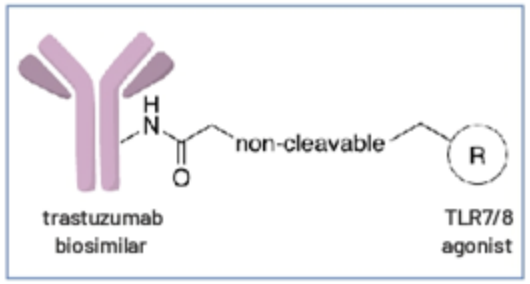


- Branched linkers that enable site-specific and quantitative installation of payloads
- MMAE: cell membrane permeable, but subject to MDR1 efflux
- MMAF: cell membrane impermeable but can not be pumped out

Yamazaki CM et al, Nat Commun (2021), 12 (1):3528

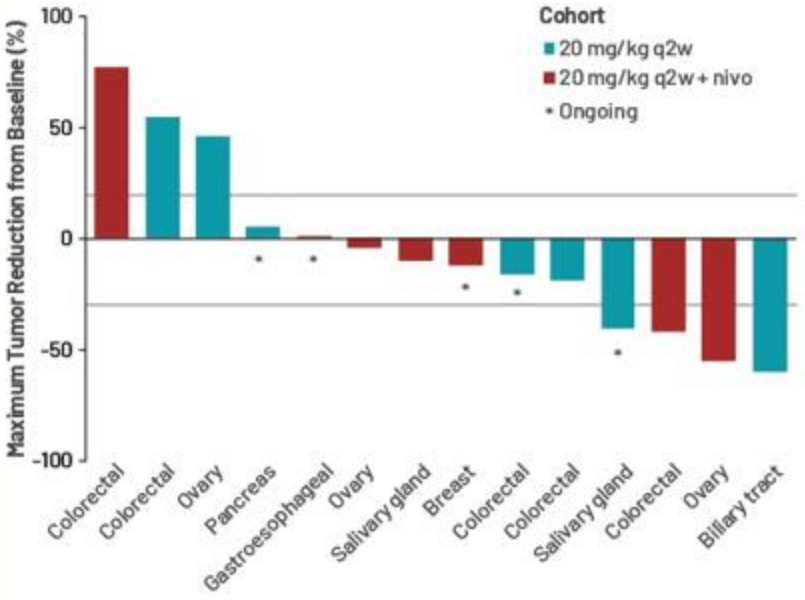
Immune Stimulating Antibody Conjugates (ISACs)

- BDC-1001 consists of
  - Trastuzumab biosimilar
  - Payload: TLR7/8 agonist
  - Linker: non-cleavable
- BDC-1001 linker-payload is cell membrane-impermeable



Meaningful Anti-tumor Activity in Evaluable Heterogeneous HER2+ Tumor Population at 20 mg/kg q2w (RP2D)

BDC-1001 Monotherapy and Combination with Nivolumab



Monotherapy (n=7)

- 29% achieved PR
- 43% had disease control ≥24w
- 57% achieved tumor shrinkage
  - Tumor types: colorectal, salivary gland, and biliary tract

Combination with Nivolumab (n=7)

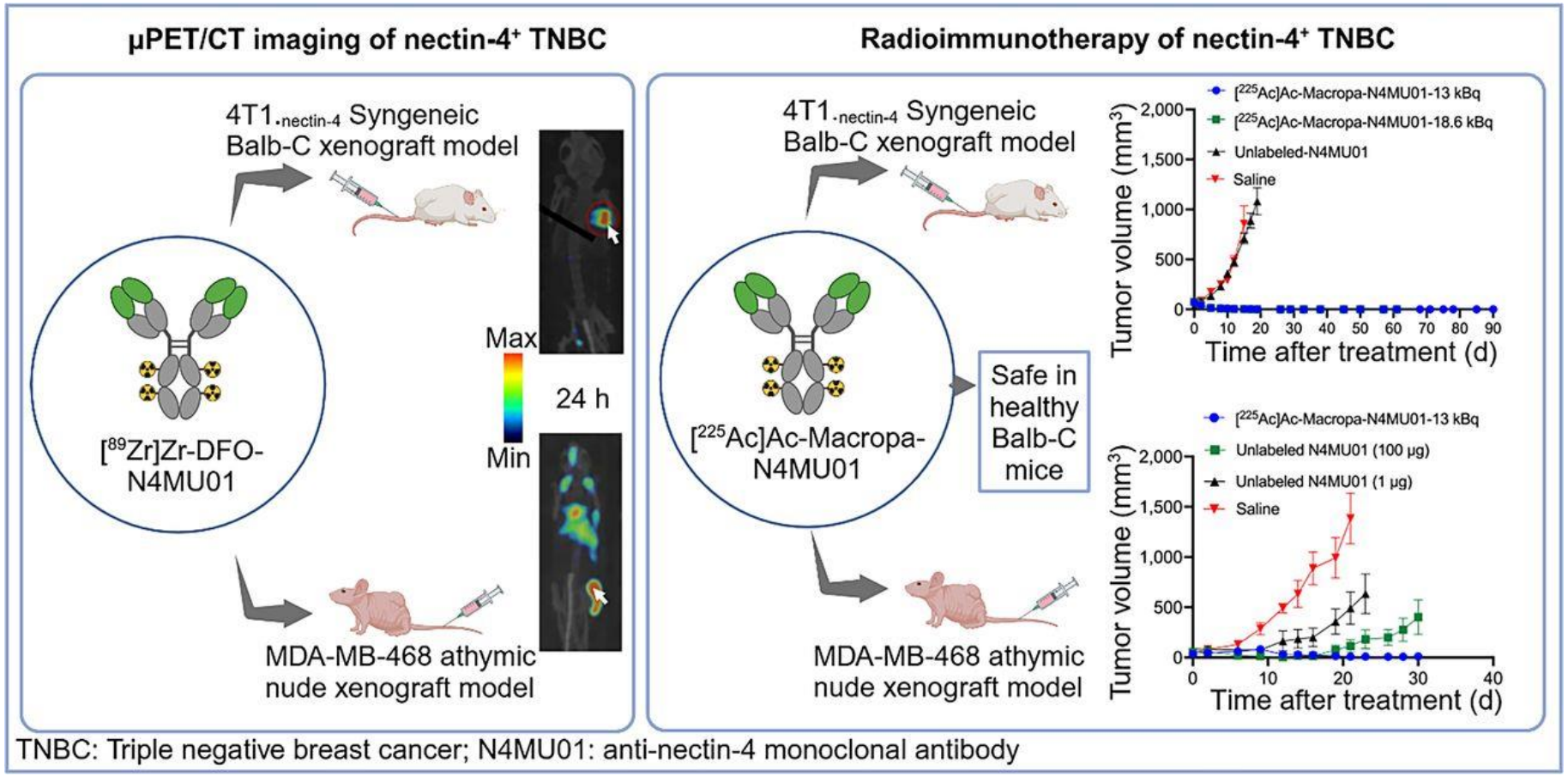
- 29% achieved PR
- 57% had disease control ≥24w
- 71% achieved tumor shrinkage
  - Tumor types: breast, colorectal, ovary, and salivary gland

HER2+ either assessed by protein or gene analysis determined at enrollment
RECIST v1.1 assessment criteria

Data cut-off: March 24, 2023

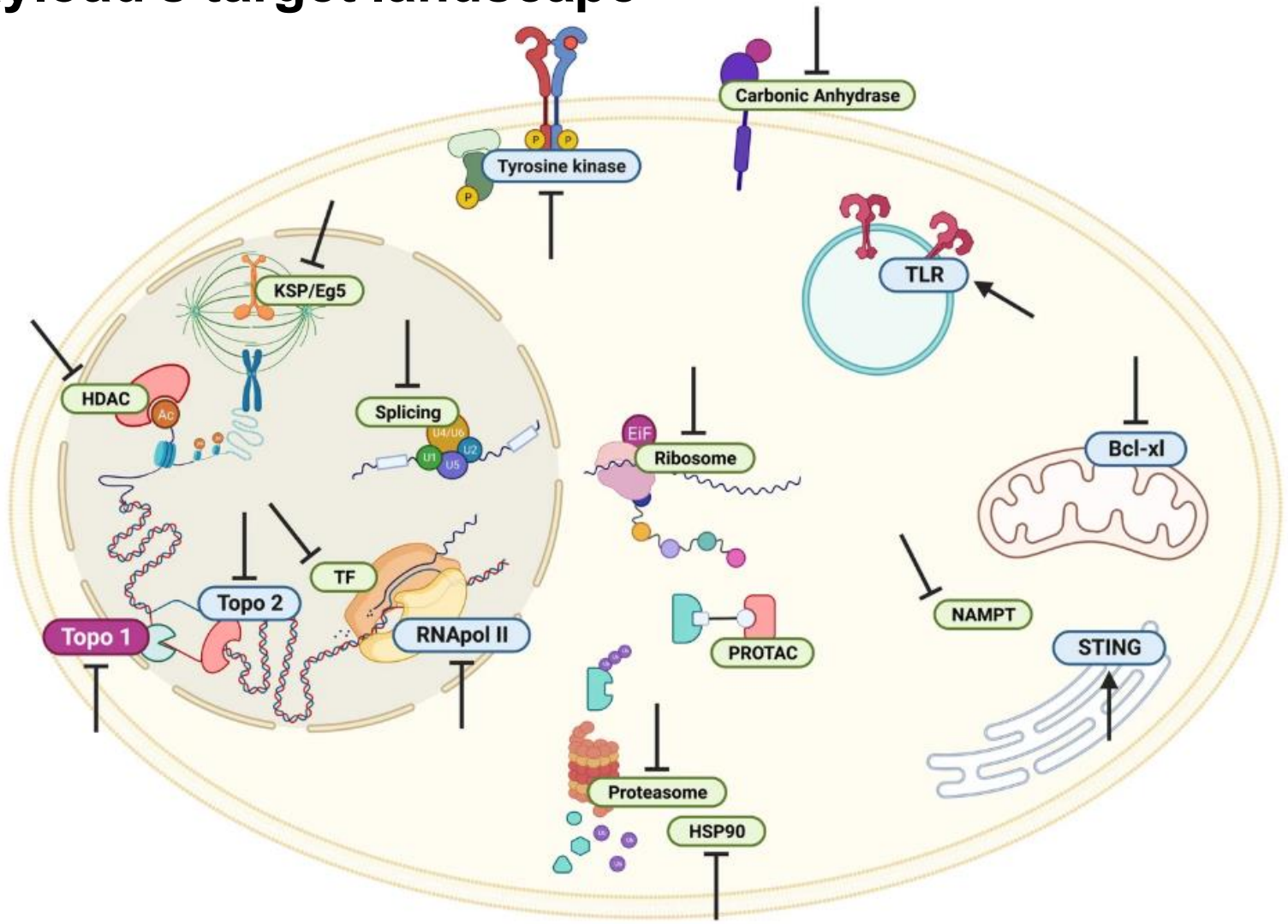
Li, B, et al, ASCO 2023

Radioimmunoconjugates



Hanan Babeker et al. J Nucl Med 2025;jnumed.124.268387

ADC payload's target landscape



Topo 1
Ds-8201a, IMMU-132
U3-1402, Ds-1062a, Ds-700a, Ds-6157a, IMMU-130, AZD8205, SKB264
IMMU-140, SGN-CD30c, PRO1102, PRO1160, PRO1184

Topo 2
SGN-15, IMMU-110, NBE-002, SOT102

RNApol II
HDP-101

Bcl-xl
ABBV-115

Tyrosine kinase
B43 Genistein

TLR
NJH395, BDC-1001, SBT6050
BDC-2034, HE-S2

STING
TAK-500
CRD5500, XMT-2056

FDA-aproved
clinical trials
pre-clinical investigation
inhibitor
agonist

Conilh et al. Journal of Hematology & Oncology (2023) 16:3

Conclusion

- ADCs are a rapidly evolving class of cancer therapeutics, combining the specificity of monoclonal antibodies with anti-cancer potency of therapeutic payload.
- Advances in linker technology, payload diversity, and antibody engineering have the promise to improve the stability, efficacy and safety profile of ADCs.
- “Most” newer ADCs have antitumor activity irrespective of the levels of target expression (TROP2, HER3)
- Correlative science will be integral to define resistance mechanisms to ADCs and ultimately, how to sequence ADCs for patients

Acknowledgement

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- Erika Hamilton, MD
- Paolo Tarantino, MD